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Efficacy and safety of Suanzaoren decoction, a classical herbal prescription, for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial

Running title: Suanzaoren decoction for adult chronic insomnia disorder

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Abstract

Background Insomnia disorder is defined as a combination of both dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. The chronic insomnia disorder referred to clinical symptoms of persistent insomnia at least three nights per week for at least 3 months. Prevalence estimates of insomnia disorder range from 12% to 20% in the adult population, with approximately 50% having a chronic course. However, the potential side effects of hypnotic medications hinder their clinical application. Thus, traditional Chinese medicine (TCM) is considered as an alternative option for treating insomnia. The objective of the study is to evaluate the efficacy and safety of Suanzaoren decoction (SZRD), a classical Chinese herbal prescription, for adult chronic insomnia disorder.

Methods/analysis This is a randomized, double-blind, double-dummy, placebo-controlled clinical trial. A total of 150 patients with chronic insomnia disorder are randomized allocated in a ratio of 1:1:1 to three groups: intervention group, control group and placebo group. The intervention group receives SZRD granule plus zolpidem tartrate (ZT) placebo; the control group receives ZT tablet plus SZRD granule placebo; and the placebo group receives ZT placebo and SZRD granule placebo. The patients receive medicine or placebo for 5 weeks and follow-up 20 weeks. The primary outcome measures are Polysomnography (PSG) and Pittsburgh Sleep Quality Index (PSQI). Secondary outcome measures are the Insomnia Severity Index (ISI), sleep dairy and safety assessment. Outcomes will be assessed at baseline and post-treatment.

Ethics and dissemination the protocol has been approved by Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (NO. 201656). The trial will help to demonstrate if SZRD is an effective and safety therapy to the patients with chronic insomnia disorder.

Trial registration number ChiCTR-IOR-16009198; Pre-results.

Keywords Suanzaoren decoction; chronic insomnia disorder; study protocol

Strengths and limitations of this study

This is the first well-designed study to assess the efficacy and safety of Suanzaoren decoction, a classical herbal prescription, for chronic insomnia disorder in adults. This study will provide the project of herbal prescription for adult chronic insomnia disorder after cognitive and behaviors therapy for insomnia based on the guideline from the American College of Physicians recommendation.

Potential limitations include the need for further validation studies from other center.

Introduction

Insomnia disorder is defined as a combination of both dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. Based on the Diagnostic and Statistical Manual (DSM)-5 of the American Psychiatric Association, insomnia is present with one or more of the following persistent symptoms: difficulty initiating sleep, difficulty maintaining sleep, and early-morning awakening with inability to return to sleep.[1] Chronic insomnia disorder referred to these symptoms that must cause clinically significant functional distress or impairment at least three nights per week for at least 3 months, excluding other sleep, medical, or mental disorders.[2] Insomnia is a highly prevalent in the general population, and is commonly encountered in medical practices. Prevalence estimates of insomnia disorder range from 12% to 20% in the adult population, with approximately 50% having a chronic course.[3] A latest guideline from the American College of Physicians (ACP) recommends that cognitive and behaviors therapy for insomnia (CBT-I) should be the initial treatment for chronic insomnia disorder in all patients.[2] If CBT-I alone was unsuccessful for the patients, ACP advises that clinicians discuss with patients to decide whether to combine with pharmacological therapy, including benzodiazepines and non-benzodiazepine hypnotics.[2] However, the hypnotic medication have a pool of undesirable side-effects such as memory and performance impairment, residual sedation, undesired behaviors during sleep, falls, somatic symptoms and drug interactions.[4, 5] Thus, there are rising number of patients with insomnia resort to various kinds of complementary and/or alternative medicine (CAM) worldwide, including acupuncture, meditation, massage and Chinese herbal medicine.[6-9] Traditional Chinese medicine (TCM), a form of CAM, has been widely used to treat insomnia in China for thousand years.[10] In modern time, it is still commonly utilized for the patients suffering from insomnia disorder in China and elsewhere around the world.[11 12] Suanzaoren decoction (SZRD) has also a long history of use as a classical herbal prescription for combating insomnia, and is first documented in the classical Chinese text *Jingui Yaolue* (*Synopsis of Prescriptions of the Golden Chamber*) by Zhong-Jing Zhang (AD 152-219).[13] It is composed of 5 kinds of CHMs (Table 1): Suanzaoren (Semen Ziziphi Spinosae, seed of wild jujube), Fuling (Hoelen, Poria), Chuanxiong (Ligusticum, Rhizoma Chuanxiong), Zhimu (Rhizoma Anemarrhenae, Anemarrhena), and Gancao (Licorice, Radix Glycyrrhizae), all of which are recorded in the Chinese Pharmacopoeia (Version 2015). The National Health Insurance

program in Taiwan has found that SZRD was the most frequently prescribed Chinese herbal formula for treating insomnia.[14] A meta-analysis in our group has demonstrated that the current evidence is insufficient to support the efficacy and safety of SZRD for insomnia due to lack of high-quality RCTs.[15] In 2015, a randomized, double-blind, placebo-controlled trial was conducted by Chan et al.,[16] indicating that SZRD is effective for improving sleep quality and quantity in methadone–maintained patients with sleep disturbances. However, it was specifically focused on the methadone–maintained sleep disturbances. Therefore, the objective of present study is to evaluate effectiveness and safety of SZRD for adult chronic insomnia by using rigorous RCT.

Method

Trial design

This is a double-blind, double dummy, placebo-controlled trial. The study will be conducted in the Second Affiliated Hospital of Wenzhou Medical University, a teaching hospital in China. Patients with sleep dissatisfaction undergo a standardized baseline evaluation before treatment consisted of detailed history taking, physical examination and laboratory testing. The scale will be assessed by a professional psychological evaluator. The hospital clinical laboratory and the sleep monitoring room are responsible for biochemical and sleep quality indicator detection, respectively. All included patients are randomly divided into three groups, every patient will receive CBT-I treatment as an initial therapy. Additional, three groups are designed to receive SZRD granule plus ZT placebo, ZT tablet plus SZRD granule placebo or both of the two placebos treatment, respectively. The efficacy and safety of SZRD granule was assessed after 5 weeks treatment and at 20 weeks follow-up after drug withdrawal. The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and China's regulations and guidelines on good clinical practice. Ethical clearance for the trial was obtained from the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University. Written informed consent was obtained from all subjects. The study design is shown in Figure1.

Sample size

The trial aims to detect if SZRD is as effective as ZT for treating sleep disorder. We deem a clinically significant difference of an average two-point reduction on the PSQI scores in the intervention group when comparing to the control group.

According to a previously study written by Ming-Shi et al.[17], the global score of PSQI after 12 weeks treatment is 4.52±3.218 in the intervention group and 10.42±3.214 in the control group, respectively. On the basis of 0.9 power to detect a significant difference (α=0.01, two-sided), 44 participants will be required for the two groups, and as 1:1:1 ratio, we enrolled 44 patients in the placebo group. Allowing for a 10% withdrawal rate, we plan to include 150 patients in the whole trial.

Participants and recruitment

Inclusion criteria: Subjects were included in the study if they met the following criteria: (i) over 18 and under 80 years old; (ii) chronic insomnia disorder diagnosed by two clinical attending doctors according to the DSM-5 criteria;[1] the symptoms must be present for at least 3 nights per week for at least 3 months; (iii) after a shared decision-making, clinicians decide to add pharmacological therapy while the CBT-I[18] alone is unsuccessful; (iv) having good compliance and willing to accept the test; (v) no mental disease or using psychoactive medications; (vi) signed the written informed consent form for the clinical trial.

Exclusion criteria: Individuals were excluded if one of the following criteria were met: (i) diagnoses of severe hepatic, renal or thyroid dysfunction or cardiovascular diseases; (ii) having a severe psychiatric disorder or a history of major psychiatric disorder (for example, depression, anxiety, autism, schizophrenia and so on); (iii) diagnoses of other sleep disorders such as narcolepsy, obstructive sleep apnea syndrome or restless legs syndrome; (iv) taking sleep medications, psychotherapy or acupuncture for insomnia within a month; (v) taking part in other clinical trial; (vi) diagnosed with severe, life-threatening chronic sleep disorders; (vii) not suitable for the study by a physician's evaluation; (viii) pregnancy, breast-feeding or juvenile.

Exit criteria: Patients will exit the trial when one of the following criteria was met: (i) having bad compliance or being pregnancy; (ii) insomnia aggravates during trial, occurring severe problems which need emergency interventions such as severe depression, mania and suicidal tendency; (iii) other appearances need to be terminated. Participants may withdraw from the study at any time for any reason.

Randomization and allocation concealment

The randomization will be performed by an independent statistician. The randomization sequence is generated by the use of SAS software. Randomization numbers will be kept in a predetermined computer-made randomization opaque sealed

envelope. The random numbers are divided into three groups sequentially; the group numbers will be printed inside the envelopes. The sealed opaque envelopes will be properly preserved by the designer and the statistician until the end of the trial. All envelopes will be numbered consecutively and connected. Clinicians who screen the eligible patients will open the envelopes according to the patients' screening sequence numbers, and then assign the patients to treatment group, control group or placebo group in accordance with the group number inside.

Blinding

This is a triple-blind (with patients, clinicians and statistics blinded) trial. The evaluation of participants and analysis of results will be performed by professionals. Treatment assignments will not be revealed until the whole process complete. To achieve blinding, all three groups will use the same kind of packing to encase the drug or placebo. The aspects of size, color, shape, taste, smell and package of placebo are made identical to that of corresponding medicine by adding artificial pigment.

Intervention

Participants in the intervention group will receive SZRD granule plus ZT placebo twice a day for 5 weeks. Patient visits were required as frequent as once a week. Participants in the control group will take ZT tablet plus SZRD granule placebo twice a day for 5 weeks. The SZRD granule placebo is similar to the SZRD granule in the aspects of size, color, shape, taste, smell and package. Participants in the placebo group are about to receive ZT placebo and SZRD granule placebo twice a day for 5 weeks.

Follow-up

All included patients will be re-evaluated at 4-, 8-, 12-, and 20-week follow-ups through phone calls or as an outpatient. Patients who developing a worsen sleep quality will receive relevant medicine supply and a written withdrawal schedule.

Outcome measures

Primary outcome

Polysomnography (PSG): PSG is the gold standard for sleep assessment, and is the only instrument that objectively evaluates sleep using quantifiable data, such as total sleep time, sleep onset latency, wake after sleep onset, the rapid eye movement and non-rapid eye movement sleep.[19] All included patients will be assessed for two nights (1 night at baseline and 1 night after treatment phase) in a sound-attenuated, light-controlled sleep laboratory. During the assessment, patients are allowed to sleep

voluntarily based upon their habitual sleep time. Sleep will be recorded with standard equipment range from 22:00 to 7:00 every time.[20] All PSG data will be further collected and processed using an E-Series digital system (Compumedics, Abbotsford, Australia) by an experienced PSG technologist blinded to the treatment assignment.

Pittsburgh Sleep Quality Index (PSQI): PSQI is a self-report questionnaire measuring sleep quality and disturbance over a 1-month time interval.[21] The items are divided into seven 'component' scores: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. A lower global score reflects a better quality of sleep.

Secondary outcome

The Insomnia Severity Index (ISI): ISI is a seven-item self-rated instrument that was used to assess the nature, severity and impact of insomnia during the previous one month.[22, 23] The ISI contains seven items, which are sleep onset, sleep maintenance, early morning awakenings, and satisfaction with current sleep pattern, interference of sleep difficulties with daytime functioning, ability to notice sleep problems, and distress caused by sleep disorder. The total score ranges from 0 to 28, with higher scores indicate more severe levels of insomnia. Each item is rated on 0 to 4 scale (0=none, 4=very). Insomnia severity is classified as: no clinically significant insomnia (total score: 0 to 7), sub-threshold insomnia (total score: 8 to 14), moderate clinical insomnia (total score: 15 to 21), and severe clinical insomnia (total score: 22 to 28).

Sleep dairy: Estimates of wake and sleep times are obtained daily by using a sleep diary. Participants report the information about their night's sleep, includes bedtime, wake time, sleep onset latency, total sleep time, number and length of nocturnal awakenings, subjective rating of sleep quality, and other factors that may influence sleep. Participants with missing data are contacted by phone to remind them to fill out the diary daily. Sleep diaries are obtained for one week at baseline and at each subsequent assessment period, as well as for the entire treatment period.

Safety assessment

The safety will be assessed by the changes of blood, urine, stool routine and electrocardiogram comparing before with after five weeks treatments. Adverse events were defined as all deaths, suicide attempts, unexpected signs or symptoms, and any physical changes. The occurrence of any adverse events in trial participants will be recorded in the case report form during each patient visit. If the adverse event is

associated with the trial and severe, the patient will be withdrawn from the trial and given relevant medical care.

Discussion

To our knowledge, this project is the first study protocol of randomized, double-blinded, double-dummy, placebo-controlled trial testing SZRD for chronic insomnia disorder in adult. This trial aims to evaluate the efficacy and safety of SZRD when compared with ZT or placebo. To facilitate high validity and reliability, a strict quality control and high-quality methodology is indispensable. We in detail describe the method of allocation concealment, recruitment, randomization and data collection. Additionally, objective sleep measurement, such as PSG, is used to assess insomnia remission. Currently, the ACP recommended that patients suffering from insomnia should receive CBT-I as first-line therapy. Thus, we provide every patient with CBT-I at the beginning, and only include the subject who is insensitive to CBT-I alone. The results from this trial may highlight evidence on the effectiveness and safety of SZRD. The trial has also been registered with the Chinese Clinical Trial Registry.

Our study has some limitations and strengths. One weakness is the participant self-rating scales that have a possibility to exaggerate the severity of sleep. Another limitation is that the trial is only implementing in one hospital. Notwithstanding these limitations, the results from this study will provide novel evidence about the SZRD available from a well-designed trial. In addition, this study will provide the project of herbal prescription for adult chronic insomnia disorder after CBT-I based on the guideline from the ACP recommendation.

Acknowledgments

We thank all study participants and staff who devoted their time and efforts to the study.

Footnotes

Contributors YL and GQZ contributed as the senior authors and the principal investigator (PI) of this study. QHZ, HLW, XLZ and MBX wrote the first draft of the manuscript and contributed to the design of the study. GQZ and YL refined the protocol. HFZ and LBH, as the medical statistician for the study, contributed to the statistical design, acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics Committee, the Second Affiliated Hospital of Wenzhou Medical University, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The study results will be available after publication in peer reviewed medical journal.

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Table 1. Overview of Suanzaoren decoction

Chinese name	English name	Latin name	Family	Amount(%)
Suanzaoren	Spine date seed	Semen Ziziphi Spinosae	The dried ripe seeds of Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou	15g (41%)
Gancao	Liquoriceroot	Radix Glycyrrhizae	The dried roots or rhizome of G uralensis Fisch. or G inflata Bat. or G glabra L.	6g (17%)
Zhimu	Common anemarrhena rhizome	Rhizoma Anemarrhenae	The dried rhizome of Anemarrhena asphodeloides Bge.	3g (8%)
Fuling	Indian bread	Poria	The dried sclerotia of P cocos (Schw.) Wolf	6g (17%)
Chuanxiong	Sichuan lovage rhizome	Rhizoma Ligustici Chuanxiong	The dried rhizome of L chuanxiong Hort.	6g (17%)

Figure legend

Figure 1. Flow diagram

Note: SZRD, Suanzaoren decoction; ZT, zolpidem tartrate

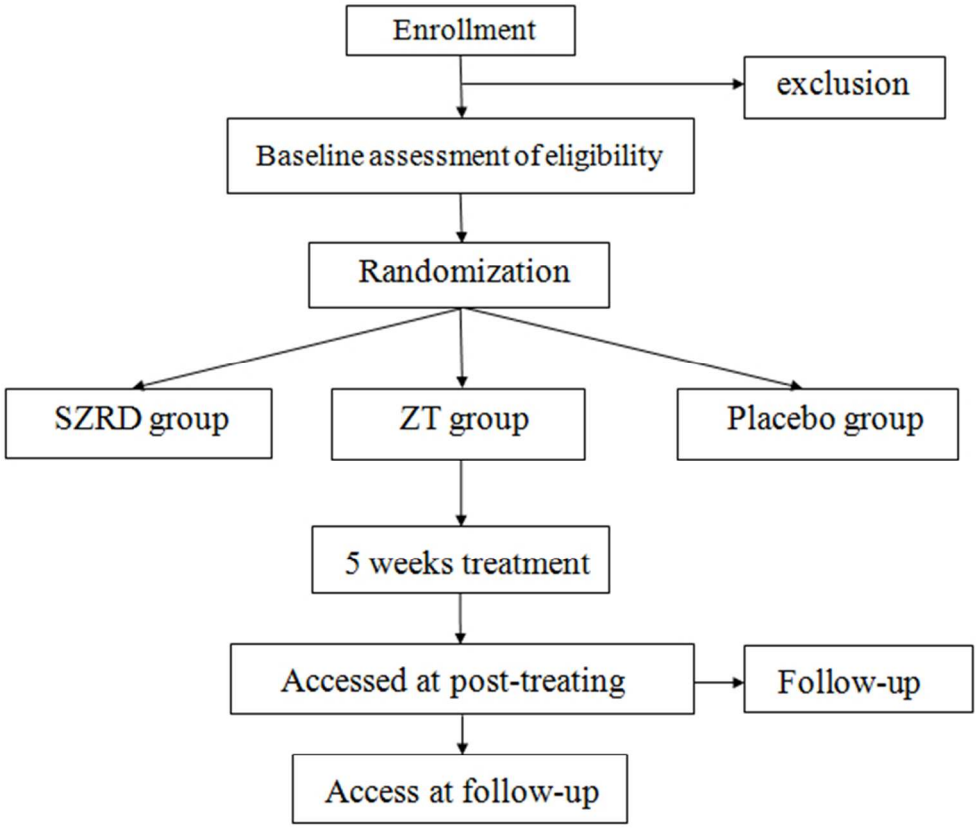

Figure 1. Flow diagram

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Abstract

Background Insomnia disorder is defined as a combination of both dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. The chronic insomnia disorder referred to clinical symptoms of persistent insomnia at least three nights per week for at least 3 months. Prevalence estimates of insomnia disorder range from 12% to 20% in the adult population, with approximately 50% having a chronic course. However, the potential side effects of hypnotic medications hinder their clinical application. Thus, traditional Chinese medicine (TCM) is considered as an alternative option for treating insomnia. The objective of the study is to evaluate the efficacy and safety of Suanzaoren decoction (SZRD), a classical Chinese herbal prescription, for adult chronic insomnia disorder.

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Ethics and dissemination The protocol has been approved by Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (NO. 201656). The trial will help to demonstrate if SZRD is an effective and safety therapy to the patients with chronic insomnia disorder.

Trial registration number ChiCTR-IOR-16009198; Pre-results.

Keywords Suanzaoren decoction; chronic insomnia disorder; study protocol

Strengths and limitations of this study

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Potential limitations include the need for further validation studies from other center. Additionally, the study may limit the generalisability since the other populations are not evaluated.

Introduction

Insomnia disorder is defined as a combination of both dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. Based on the International Classification of Sleep Disorder (ICSD)-3 of the American Academy of Sleep Medicine, insomnia is present with one or more of the following persistent symptoms: difficulty initiating sleep, difficulty maintaining sleep, and early-morning awakening with inability to return to sleep.[1] Chronic insomnia disorder referred to these symptoms that must cause clinically significant functional distress or impairment at least three nights per week for at least 3 months, excluding other sleep, medical, or mental disorders.[2] Insomnia is highly prevalent in the general population, and is commonly encountered in medical practices. Prevalence estimates of insomnia disorder range from 12% to 20% in the adult population, with approximately 50% having a chronic course.[3] A latest guideline from the American College of Physicians (ACP) recommends that cognitive and behavioral therapy for insomnia (CBT-I) should be the initial treatment for chronic insomnia disorder in all patients.[2] If CBT-I alone was unsuccessful for the patients, ACP advises that clinicians discuss with patients to decide whether to combine with pharmacological therapy, including benzodiazepines and non-benzodiazepine hypnotics.[2] However, the hypnotic medication have a pool of undesirable side-effects such as memory and performance impairment, residual sedation, undesired behaviors during sleep, falls, somatic symptoms and drug interactions.[4, 5] Thus, there are rising number of patients with insomnia resort to various kinds of complementary and/or alternative medicine (CAM) worldwide, including acupuncture, meditation, massage and Chinese herbal medicine.[6-9] Traditional Chinese medicine (TCM), a form of CAM, has been widely used to treat insomnia in China for thousand years.[10] In modern time, it is still commonly utilized for the patients suffering from insomnia disorder in China and elsewhere around the world.[11 12] Suanzaoren decoction (SZRD) has also a long history of use as a classical herbal prescription for combating insomnia, and is first documented in the classical Chinese text *Jingui Yaolue* (*Synopsis of Prescriptions of the Golden Chamber*) by Zhong-Jing Zhang (AD 152-219).[13] It is composed of 5 kinds of CHMs (Table 1): Suanzaoren (Semen Ziziphi Spinosae, seed of wild jujube), Fuling (Poria, Hoelen), Chuanxiong (Ligusticum, Chuanxiong Rhizoma), Zhimu (Anemarrhena aspodeloidea, Anemarrhena), and Gancao (Glycyrrhiza glabra L.,

Radix Glycyrrhizae), all of which are recorded in the Chinese Pharmacopoeia (Version 2015). Experimental studies have detected that SZRD increases spontaneous sleep activity and its implicit mechanisms is considered mediated through the serotonergic system.[14-16] Spinosin and jujubosides are the main active compounds of Semen ziziphi spinosae contributing its sedative and hypnotic effects on insomnia.[17-19] The National Health Insurance program in Taiwan has found that SZRD was the most frequently prescribed Chinese herbal formula for treating insomnia.[20] A meta-analysis in our group has demonstrated that the current evidence is insufficient to support the efficacy and safety of SZRD for insomnia due to lack of high-quality RCTs.[21] In 2015, a randomized, double-blind, placebo-controlled trial was conducted by Chan et al.,[22] indicating that SZRD is effective for improving sleep quality and quantity in methadone–maintained patients with sleep disturbances. However, it was specifically focused on the methadone–maintained sleep disturbances. Therefore, the objective of present study is to evaluate effectiveness and safety of SZRD for adult chronic insomnia by using rigorous RCT.

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fully explanation by the clinicians, written informed consent will be obtained from the included subjects before intervention. The trial has been registered at Chinese Clinical Trial Registry (ChiCTR-IOR-16009198) on 13 September 2016 and will be executed from January 2017 to December 2017. The study design is shown in Figure1.

Sample size

The trial aims to detect if SZRD is as effective as ZT for treating sleep disorder. We deem a clinically significant difference of an average two-point reduction on the PSQI scores in the intervention group when comparing to the control group. According to a previously study written by Ming-Shi et al.[23], the global score of PSQI after 12 weeks treatment is 4.52±3.218 in the intervention group and 10.42±3.214 in the control group, respectively. On the basis of 0.9 power to detect a significant difference (α=0.01, two-sided), 44 participants will be required for the two groups, and as 1:1:1 ratio, we enrolled 44 patients in the placebo group. Allowing for a 10% withdrawal rate, we plan to include 150 patients in the whole trial.

Participants and recruitment

Inclusion criteria: Subjects are included in the study if they met the following criteria: (i) over 18 and under 80 years old; (ii) chronic insomnia disorder diagnosed by two clinical attending doctors according to the ICSD-3 criteria;[1] the symptoms must be present for at least 3 nights per week for at least 3 months; (iii) after a shared decision-making, clinicians decide to add pharmacological therapy while the CBT-I[24] alone is unsuccessful; (iv) having good compliance and willing to accept the test; (v) no mental disease or using psychoactive medications; (vi) signing the written informed consent form for the clinical trial.

Exclusion criteria: Individuals are excluded if one of the following criteria were met: (i) diagnoses of severe hepatic, renal or thyroid dysfunction or cardiovascular diseases; (ii) having a severe psychiatric disorder or a history of major psychiatric disorder (for example, depression, anxiety, autism, schizophrenia and so on); (iii) diagnoses of other sleep disorders such as narcolepsy, obstructive sleep apnea syndrome or restless legs syndrome; (iv) taking sleep medications, psychotherapy or acupuncture for insomnia within a month; (v) taking part in other clinical trial; (vi) diagnosing with severe, life-threatening chronic sleep disorders; (vii) not suitable for the study by a physician's evaluation; (viii) pregnancy, breast-feeding or juvenile.

Exit criteria: Patients will exit the trial when one of the following criteria was met: (i) having bad compliance or being pregnancy; (ii) insomnia aggravates during trial, occurring severe problems which need emergency interventions such as severe depression, mania and suicidal tendency; (iii) other appearances need to be terminated. Participants may withdraw from the study at any time for any reason.

Concomitant treatments and forbidden drugs

It is forbidden to combine with other sleep medications in the study. Acupuncture therapy, psychotherapy and any drugs and diet such as psychopharmacological drugs, opioids, anxiolytics, coffee and alcohol that may induce sedative or hypnotic effects are also not allowed in this trial. It is acceptable if patients had already taken medicine that did not act upon the central nervous system before the trial. Yet, all combined administration should be recorded in case report form (CRF).

Randomization and allocation concealment

The randomization will be performed by an independent statistician. The randomization sequence is generated by the use of SAS software. Randomization numbers are kept in a predetermined computer-made randomization opaque sealed envelope. The random numbers are divided into three groups sequentially; the group numbers are printed inside the envelopes. The sealed opaque envelopes are properly preserved by the designer and the statistician until the end of the trial. All envelopes will be numbered consecutively and connected. Clinicians who screen the eligible patients will open the envelopes according to the patients' screening sequence numbers, and then assign the patients to treatment group, control group or placebo group in accordance with the group number inside.

Blinding

This is a triple-blind (with patients, clinicians and statistics blinded) trial. The evaluation of participants and analysis of results will be performed by professionals. Treatment assignments will not be revealed until the whole process complete. If patients had severe adverse events, clinicians will unblind patients emergently and provide relevant treatment in time. To achieve blinding, all three groups will use the same kind of packing to encase the drug or placebo. The aspects of size, color, shape, taste, smell and package of placebo are made identical to that of corresponding medicine by adding artificial pigment.

Intervention

All researchers are the certificated clinical doctors in neurology for at least 3 years, receive a standardized training for the diagnostic interview before trial beginning. Two clinicians make the diagnosis of chronic insomnia disorder. Participants in the intervention group will receive SZRD granule plus ZT placebo orally twice a day for 5 weeks. Participants in the control group will take ZT tablet plus SZRD granule placebo twice a day for 5 weeks. Participants in the placebo group are about to receive ZT placebo and SZRD granule placebo twice a day for 5 weeks. Patient visits are required as frequent as once a week. The SZRD granule placebo is composed by 98% maltodextrin, 2% caramel and very little bitterant. ZT placebo is made of starch. SZRD granule and its placebo are produced by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd and can be preserved for 2 years. ZT tablet is provided by Senofi (Hangzhou) Pharmaceutical Co., Ltd and the dosage strength is 10mg. The SZRD granule placebo and ZT placebo are similar to the SZRD granule and ZT in the aspects of size, color, shape, taste, smell and package, respectively.

Follow-up

All included patients will be re-evaluated at 4-, 8-, 12-, 16- and 20- week follow-ups through phone calls or as an outpatient. Patients who developing a worsen sleep quality will receive relevant medicine supply and a written withdrawal schedule.

Outcome measures

Primary outcomes

Polysomnography (PSG): PSG is the gold standard for sleep assessment, and is the only instrument that objectively evaluates sleep using quantifiable data, such as total sleep time, sleep onset latency, wake after sleep onset, the rapid eye movement and non-rapid eye movement sleep.[25] All included patients will be assessed for two nights (1 night at baseline and 1 night after treatment phase) in a sound-attenuated, light-controlled sleep laboratory. During the assessment, patients are allowed to sleep voluntarily based upon their habitual sleep time. Sleep will be recorded with standard equipment range from 22:00 to 7:00 every time. All PSG data will be further collected and processed using an E-Series digital system (Compumedics, Abbotsford, Australia) by an experienced PSG technologist blinded to the treatment assignment.

Pittsburgh Sleep Quality Index (PSQI): PSQI is a self-report questionnaire measuring sleep quality and disturbance over a 1-month time interval.[26] The items are divided into seven ‘component' scores, and a lower global score reflects a better

quality of sleep. As the sleeping medication applied in intervention and control group rather than placebo group, we delete the item of "use of sleeping medication" for comparability of three groups. There are six remaining items to rate the sleep quality containing sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction.

Secondary outcomes

The Insomnia Severity Index (ISI): ISI is a seven-item self-rated instrument that is used to assess the nature, severity and impact of insomnia during the previous one month.[27, 28] The ISI contains seven items, which are sleep onset, sleep maintenance, early morning awakenings, and satisfaction with current sleep pattern, interference of sleep difficulties with daytime functioning, ability to notice sleep problems, and distress caused by sleep disorder. The total score ranges from 0 to 28, with higher scores indicate more severe levels of insomnia. Each item is rated on 0 to 4 scale (0=none, 4=very). Insomnia severity is classified as: no clinically significant insomnia (total score: 0 to 7), sub-threshold insomnia (total score: 8 to 14), moderate clinical insomnia (total score: 15 to 21), and severe clinical insomnia (total score: 22 to 28).

Sleep diary: Estimates of wake and sleep times are obtained daily by using a sleep diary. Participants report the information about their night's sleep, includes bedtime, wake time, sleep onset latency, total sleep time, number and length of nocturnal awakenings, subjective rating of sleep quality, and other factors that may influence sleep. Participants with missing data are contacted by phone to remind them to fill out the diary daily. Sleep diaries are obtained for one week at baseline and at each subsequent assessment period, as well as for the entire treatment period.

Safety assessments

The safety will be assessed by renal function test, liver function test, routine blood test, routine urine test, routine stool test and electrocardiogram. These indicators are detected during the period of screening and after 5 weeks treatment. Adverse events are defined as all deaths, suicide attempts, unexpected signs or symptoms, and any physical changes. The occurrence of any adverse events in trial participants will be recorded in the CRFs during each patient visit. We will withdraw the patients who have severe adverse events, as it is unsafe for them to continue the trail. Meanwhile, we will give them relevant medical care and follow them until the reaction has terminated.

Data analyses

Data analysis will be performed by professional statisticians using the SPSS software. An intent-to-analysis (ITT) will be conducted for the patients who have received treatment at least once. We will perform sensitivity analysis by using various imputation methods to detect if the results were robust for different assumptions about the missing data. The per-protocol analysis will be restricted to patients who do not violate the protocol and complete the program. We use Mean±SD for continuous variables and percentages for categorical variables. Analysis of variance is performed on categorical variables and Pearson's chi-square test on continuous variables. The study will set alpha level of 0.05 two sided for all statistical tests. 95% CI will be used regarding continuous variables.

Discussion

To our knowledge, this project is the first study protocol of randomized, double-blinded, double-dummy, placebo-controlled trial testing SZRD for chronic insomnia disorder in adult. This trial aims to evaluate the efficacy and safety of SZRD when compared with ZT or placebo. To facilitate high validity and reliability, a strict quality control and high-quality methodology is indispensable. We in detail describe the method of allocation concealment, recruitment, randomization and data collection. Additionally, objective sleep measurement, such as PSG, is used to assess insomnia remission. Currently, the ACP recommends that patients suffering from insomnia should receive CBT-I as first-line therapy. Thus, we provide every patient with CBT-I at the beginning, and only include the subject who is insensitive to CBT-I alone. The results from this trial may highlight evidence on the effectiveness and safety of SZRD. The trial has also been registered with the Chinese Clinical Trial Registry.

Our study has some limitations and strengths. One weakness is the participant self-rating scales that have a possibility to exaggerate the severity of sleep. Another limitation is that the trial is only implementing in one hospital. Notwithstanding these limitations, the results from this study will provide novel evidence about the SZRD available from a well-designed trial. In addition, this study will provide the project of herbal prescription for adult chronic insomnia disorder after CBT-I based on the guideline from the ACP recommendation.

Acknowledgments

We thank all staff who devoted their time and efforts to the study.

Footnotes

Contributors YL and GQZ contribute as the senior authors and the principal investigator (PI) of this study. QHZ, HLW, XLZ and MBX write the first draft of the manuscript and contribute to the design of the study. GQZ and YL refine the protocol. HFZ and LBH, as the medical statistician for the study, contribute to the statistical design, acquisition and analysis of data for the work. All authors revise the protocol critically for important intellectual content and approve the final manuscript.

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Competing interests None declared.

Patient consent Will be obtained.

Ethics approval Ethics Committee, the Second Affiliated Hospital of Wenzhou Medical University, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The study results will be available after publication in peer reviewed medical journal.

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Table 1. Overview of Suanzaoren decoction

Chinese name	Common name	Latin name	Species/Family	Amount(%)
Suanzaoren	Spine date seed	*Semen Ziziphi Spinosae*	The dried ripe seeds of Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou/ Rhamnaceae	20g (41%)
Gancao	Liquorice root	*Glycyrrhiza glabra L.*	The dried roots or rhizome of G uralensis Fisch. or G inflata Bat. or G glabra L./ Leguminosae	3g (6%)
Zhimu	Common anemarrhena rhizome	*Anemarrhena aspodeloidea*	The dried rhizome of Anemarrhena asphodeloides Bge./ Liliaceae	10g (20%)
Fuling	Indian buead	*Poria*	The dried sclerotia of P cocos (Schw.) Wolf/Polyporaceae	10g (20%)
Chuanxiong	Chuanxiong Rhizoma	*Rhizoma Ligustici Chuanxiong*	The dried rhizome of L chuanxiong Hort./Umbelliferae	6g (13%)

Figure legend

Figure 1. Flow diagram

Note: SZRD, Suanzaoren decoction; ZT, zolpidem tartrate

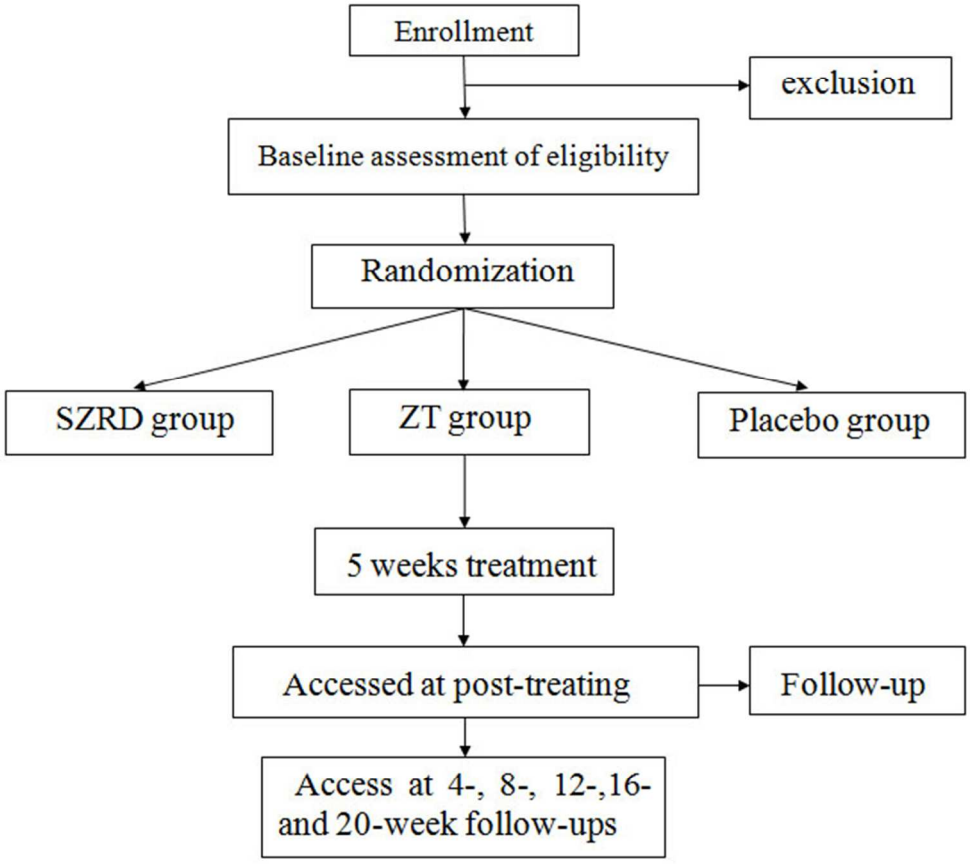

Figure 1. Flow diagram

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

Section/item	Item No.	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**P1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**P2**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	**P11**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
	5b	Name and contact information for the trial sponsor	
	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	
	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)	
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	**P4-5**
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	**P5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**P5-6**
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	**P5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**P6-7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**P7-8**
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**P7**
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	**P8-9**
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)	
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	**P6**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	
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	**P7**
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	**P7**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**P7**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**P7**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	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	**P10**
	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	
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	**P10**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**P10**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	

	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)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	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	
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	**P9**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
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)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**P5-6**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**P5-6**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	

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
Dissemination policy	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
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of Suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial

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Secondary Subject Heading:	Neurology
Keywords:	Suanzaoren decoction, chronic insomnia disorder, study protocol

Efficacy and safety of Suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial

Running title: Suanzaoren decoction for adult chronic insomnia disorder

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Abstract

Background Insomnia disorder is defined as a combination of both dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. The chronic insomnia disorder referred to clinical symptoms of persistent insomnia at least three nights per week for at least 3 months. Prevalence estimates of insomnia disorder range from 12% to 20% in the adult population, with approximately 50% having a chronic course. However, the potential side effects of hypnotic medications hinder their clinical application. Thus, traditional Chinese medicine is considered as an alternative option for treating insomnia. The objective of the study is to evaluate the efficacy and safety of Suanzaoren decoction (SZRD), a classical Chinese herbal prescription, for adult chronic insomnia disorder.

Methods/analysis This is a randomized, double-blind, double-dummy, placebo-controlled clinical trial. A total of 150 patients with chronic insomnia disorder are randomized allocated in a ratio of 1:1:1 to three groups: intervention group, control group and placebo group. The intervention group receives SZRD granule plus zolpidem tartrate (ZT) placebo; the control group receives ZT tablet plus SZRD granule placebo; and the placebo group receives ZT placebo and SZRD granule placebo. The patients receive medicine or placebo for 5 weeks and follow-up 20 weeks. The primary outcome measures are Polysomnography and Pittsburgh Sleep Quality Index. Secondary outcome measures are the Insomnia Severity Index, sleep diary and safety assessment. Outcomes will be assessed at baseline and post-treatment.

Ethics and dissemination The protocol has been approved by Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (NO. 201656). The trial will help to demonstrate if SZRD is an effective and safety therapy to the patients with chronic insomnia disorder. We will publish the results of this study in peer-reviewed journals to have widespread dissemination.

Trial registration number ChiCTR-IOR-16009198; Pre-results.

Keywords Suanzaoren decoction; chronic insomnia disorder; study protocol

Strengths and limitations of this study

- This is the well-designed study to assess the efficacy and safety of suanzaoren decoction for chronic insomnia disorder in adults.
- The results from this randomized, double-blind, double-dummy, placebo-controlled clinical trial will provide novel evidence of the suanzaoren decoction for insomnia.
- This study will provide the project of herbal prescription for adult chronic insomnia disorder after cognitive and behavioral therapy for insomnia based on the guideline from the American College of Physicians recommendation.
- One weakness is the participant self-rating scales that have a possibility to exaggerate the severity of sleep.
- Another limitation is that the trial is only implementing in one hospital in Chinese subjects. It may limit the generalisability.

Introduction

Insomnia disorder is defined as a combination of both dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. Based on the International Classification of Sleep Disorder (ICSD)-3 of the American Academy of Sleep Medicine, insomnia is present with one or more of the following persistent symptoms: difficulty initiating sleep, difficulty maintaining sleep, and early-morning awakening with inability to return to sleep.[1] Chronic insomnia disorder referred to these symptoms that must cause clinically significant functional distress or impairment at least three nights per week for at least 3 months, excluding other sleep, medical, or mental disorders.[2] Insomnia is highly prevalent in the general population, and is commonly encountered in medical practices. Prevalence estimates of insomnia disorder range from 12% to 20% in the adult population, with approximately 50% having a chronic course.[3] A latest guideline from the American College of Physicians (ACP) recommends that cognitive and behavioral therapy for insomnia (CBT-I) should be the initial treatment for chronic insomnia disorder in all patients.[2] If CBT-I alone was unsuccessful for the patients, ACP advises that clinicians discuss with patients to decide whether to combine with pharmacological therapy, including benzodiazepines and non-benzodiazepine hypnotics.[2] However, the hypnotic medication have a pool of undesirable side-effects such as memory and performance impairment, residual sedation, undesired behaviors during sleep, falls, somatic symptoms and drug interactions.[4, 5] Thus, there are rising number of patients with insomnia resort to various kinds of complementary and/or alternative medicine (CAM) worldwide, including acupuncture, meditation, massage and Chinese herbal medicine.[6-9] Traditional Chinese medicine (TCM), a form of CAM, has been widely used to treat insomnia in China for thousand years.[10] In modern time, it is still commonly being utilized for the patients suffering from insomnia disorder in China and elsewhere around the world.[11 12] Suanzaoren decoction (SZRD) has also a long history of use as a classical herbal prescription for combating insomnia, and is first documented in the classical Chinese text *Jingui Yaolue* (*Synopsis of Prescriptions of the Golden Chamber*) by Zhong-Jing Zhang (AD 152-219).[13] It is composed of 5 kinds of CHMs (Table 1): Suanzaoren (*Semen Ziziphi Spinosae,* seed of wild jujube), Fuling (*Poria,* Hoelen), Chuanxiong (*Ligusticum,* Chuanxiong Rhizoma), Zhimu (*Anemarrhena aspodeloidea,* Anemarrhena), and Gancao (*Glycyrrhiza glabra L.,*

Radix Glycyrrhizae), all of which are recorded in the Chinese Pharmacopoeia (Version 2015). Experimental studies have detected that SZRD increases spontaneous sleep activity and its implicit mechanisms is considered mediated through the serotonergic system.[14-16] Spinosin and jujubosides are the main active compounds of Semen ziziphi spinosae contributing its sedative and hypnotic effects on insomnia.[17-19] The National Health Insurance program in Taiwan has found that SZRD was the most frequently prescribed Chinese herbal formula for treating insomnia.[20] A meta-analysis in our group has demonstrated that the current evidence is insufficient to support the efficacy and safety of SZRD for insomnia due to lack of high-quality RCTs.[21] In 2015, a randomized, double-blind, placebo-controlled trial was conducted by Chan *et al*.,[22] indicating that SZRD is effective for improving sleep quality and quantity in methadone–maintained patients with sleep disturbances. However, it was specifically focused on the methadone–maintained sleep disturbances. Therefore, the objective of present study is to evaluate effectiveness and safety of SZRD for adult chronic insomnia by using rigorous RCT.

Method

Trial design

This is a double-blind, double dummy, placebo-controlled trial. The study will be conducted in the Second Affiliated Hospital of Wenzhou Medical University, a teaching hospital in China. Patients with sleep dissatisfaction undergo a standardized baseline evaluation before treatment consisted of detailed history taking, physical examination and laboratory testing. The scale will be assessed by a professional psychological evaluator. The hospital clinical laboratory and the sleep monitoring room are responsible for biochemical and sleep quality indicator detection, respectively. All included patients are randomly divided into three groups, every patient will receive CBT-I treatment as an initial therapy. Additional, three groups are designed to receive SZRD granule plus ZT placebo, ZT tablet plus SZRD granule placebo or both of the two placebos treatment, respectively. The efficacy and safety of SZRD granule is assessed after 5-weeks treatment and at 20-weeks follow-up after drug withdrawal. The trial is conducted in accordance with the World Medical Association Declaration of Helsinki and China's regulations and guidelines on good clinical practice. Ethical clearance for the trial was obtained from the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University. After a

fully explanation by the clinicians, written informed consent will be obtained from the included subjects before intervention. The trial has been registered at Chinese Clinical Trial Registry (ChiCTR-IOR-16009198) on 13 September 2016 and will be executed from January 2017 to December 2017. The study design is shown in Figure1.

Sample size

The trial aims to detect if SZRD is as effective as ZT for treating sleep disorder. We deem a clinically significant difference of an average two-point reduction on the PSQI scores in the intervention group when comparing to the control group. According to a previously study written by Ming-Shi *et al*.[23], the global score of PSQI after 12 weeks' treatment is 4.52±3.218 in the intervention group and 10.42±3.214 in the control group, respectively. On the basis of 0.9 power to detect a significant difference (α=0.01, two-sided), 44 participants will be required for the two groups, and as 1:1:1 ratio, we enrolled 44 patients in the placebo group. Allowing for a 10% withdrawal rate, we plan to include 150 patients in the whole trial.

Participants and recruitment

Inclusion criteria: Subjects are included in the study if they met the following criteria: (i) over 18 and under 80 years old; (ii) chronic insomnia disorder diagnosed by two clinical attending doctors according to the ICSD-3 criteria;[1] the symptoms must be present for at least 3 nights per week for at least 3 months; (iii) after a shared decision-making, clinicians decide to add pharmacological therapy while the CBT-I[24] alone is unsuccessful; (iv) having good compliance and willing to accept the test; (v) no mental disease or using psychoactive medications; (vi) signing the written informed consent form for the clinical trial.

Exclusion criteria: Individuals are excluded if one of the following criteria were met: (i) diagnoses of severe hepatic, renal or thyroid dysfunction or cardiovascular diseases; (ii) having a severe psychiatric disorder or a history of major psychiatric disorder (for example, depression, anxiety, autism, schizophrenia and so on); (iii) diagnoses of other sleep disorders such as narcolepsy, obstructive sleep apnea syndrome or restless legs syndrome; (iv) taking sleep medications, psychotherapy or acupuncture for insomnia within a month; (v) taking part in other clinical trial; (vi) diagnosing with severe, life-threatening chronic sleep disorders; (vii) not suitable for the study by a physician's evaluation; (viii) pregnancy, breast-feeding or juvenile.

Exit criteria: Patients will exit the trial when one of the following criteria was met: (i) having bad compliance or being pregnancy; (ii) insomnia aggravates during trial, occurring severe problems which need emergency interventions such as severe depression, mania and suicidal tendency; (iii) other appearances need to be terminated. Participants may withdraw from the study at any time for any reason.

Concomitant treatments and forbidden drugs

It is forbidden to combine with other sleep medications in the study. Acupuncture therapy, psychotherapy and any drugs and diet such as psychopharmacological drugs, opioids, anxiolytics, coffee and alcohol that may induce sedative or hypnotic effects are also not allowed in this trial. It is acceptable if patients had already taken medicine that did not act upon the central nervous system before the trial. Yet, all combined administration should be recorded in case report form.

Randomization and allocation concealment

The randomization will be performed by an independent statistician. The randomization sequence is generated by the use of SAS software. Randomization numbers are kept in a predetermined computer-made randomization opaque sealed envelope. The random numbers are divided into three groups sequentially; the group numbers are printed inside the envelopes. The sealed opaque envelopes are properly preserved by the designer and the statistician until the end of the trial. All envelopes will be numbered consecutively and connected. Clinicians who screen the eligible patients will open the envelopes according to the patients' screening sequence numbers, and then assign the patients to group A, B or C in accordance with the group number inside.

Blinding

This is a double-blind (with patients and clinicians blinded) trial. The evaluation of participants and analysis of results will be performed by professionals. Treatment assignments will not be revealed until the whole process complete. If patients had severe adverse events, clinicians will unblind patients emergently and provide relevant treatment in time. To achieve blinding, all three groups will use the same kind of packing to encase the drug or placebo. The aspects of size, color, shape, taste, smell and package of placebo are made identical to that of corresponding medicine by adding artificial pigment.

Intervention

All researchers are the certificated clinical doctors in neurology for at least 3 years, receive a standardized training for the diagnostic interview before trial beginning. Two clinicians make the diagnosis of chronic insomnia disorder. Participants in the intervention group will receive SZRD granule plus ZT placebo orally twice a day for 5 weeks. Participants in the control group will take ZT tablet plus SZRD granule placebo twice a day for 5 weeks. Participants in the placebo group are about to receive ZT placebo and SZRD granule placebo twice a day for 5 weeks. Patient visits are required as frequent as once a week. The SZRD granule placebo is composed by 98% maltodextrin, 2% caramel and very little bitterant. ZT placebo is made of starch. SZRD granule and its placebo are produced by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd and can be preserved for 2 years. ZT tablet is provided by Senofi (Hangzhou) Pharmaceutical Co., Ltd and the dosage strength is 10mg. The SZRD granule placebo and ZT placebo are similar to the SZRD granule and ZT in the aspects of size, color, shape, taste, smell and package, respectively.

Follow-up

All included patients will be re-evaluated at 4-, 8-, 12-, 16- and 20- week follow-ups through phone calls or as an outpatient. Patients who developing a worsen sleep quality will receive relevant medicine supply and a written withdrawal schedule.

Outcome measures

Primary outcomes

Polysomnography (PSG): PSG is the gold standard for sleep assessment, and is the only instrument that objectively evaluates sleep using quantifiable data, such as total sleep time, sleep onset latency, wake after sleep onset, the rapid eye movement and non-rapid eye movement sleep.[25] All included patients will be assessed for two nights (1 night at baseline and 1 night after treatment phase) in a sound-attenuated, light-controlled sleep laboratory. During the assessment, patients are allowed to sleep voluntarily based upon their habitual sleep time. Sleep will be recorded with standard equipment range from 22:00 to 7:00 every time. All PSG data will be further collected and processed using an E-Series digital system (Compumedics, Abbotsford, Australia) by an experienced PSG technologist blinded to the treatment assignment.

Pittsburgh Sleep Quality Index (PSQI): PSQI is a self-report questionnaire measuring sleep quality and disturbance over a 1-month time interval.[26] The items are divided into seven ‘component’ scores, and a lower global score reflects a better

quality of sleep. As the sleeping medication applied in intervention and control group rather than placebo group, we delete the item of "use of sleeping medication" for comparability of three groups. There are six remaining items to rate the sleep quality containing sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances and daytime dysfunction.

Secondary outcomes

The Insomnia Severity Index (ISI): ISI is a seven-item self-rated instrument that is used to assess the nature, severity and impact of insomnia during the previous one month.[27, 28] The ISI contains seven items, which are sleep onset, sleep maintenance, early morning awakenings, and satisfaction with current sleep pattern, interference of sleep difficulties with daytime functioning, ability to notice sleep problems, and distress caused by sleep disorder. The total score ranges from 0 to 28, with higher scores indicate more severe levels of insomnia. Each item is rated on 0 to 4 scale (0=none, 4=very). Insomnia severity is classified as: no clinically significant insomnia (total score: 0 to 7), sub-threshold insomnia (total score: 8 to 14), moderate clinical insomnia (total score: 15 to 21), and severe clinical insomnia (total score: 22 to 28).

Sleep diary: Estimates of wake and sleep times are obtained daily by using a sleep diary. Participants report the information about their night's sleep, includes bedtime, wake time, sleep onset latency, total sleep time, number and length of nocturnal awakenings, subjective rating of sleep quality, and other factors that may influence sleep. Participants with missing data are contacted by phone to remind them to fill out the diary daily. Sleep diaries are obtained for one week at baseline and at each subsequent assessment period, as well as for the entire treatment period.

Safety assessments

The safety will be assessed by renal function test, liver function test, routine blood test, routine urine test, routine stool test and electrocardiogram. These indicators are detected during the period of screening and after 5-weeks treatment. Adverse events are defined as all deaths, suicide attempts, unexpected signs or symptoms, and any physical changes. The occurrence of any adverse events in trial participants will be recorded in the case report forms during each patient visit. We will withdraw the patients who have severe adverse events, as it is unsafe for them to continue the trail. Meanwhile, we will give them relevant medical care and follow them until the reaction has terminated.

Data analyses

Data analysis will be performed by professional statisticians using the SPSS software. An intent-to-treat analysis will be conducted for the patients who have received treatment at least once. We will perform sensitivity analysis by using various imputation methods to detect if the results were robust for different assumptions about the missing data. The per-protocol analysis will be restricted to patients who do not violate the protocol and complete the program. We use Mean±SD for continuous variables and percentages for categorical variables. Analysis of variance is performed on categorical variables and Pearson's chi-square test on continuous variables. The study will set alpha level of 0.05 two sided for all statistical tests. 95% CI will be used regarding continuous variables.

Ethics and dissemination

The protocol has been approved by Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (NO. 201656), and has been registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-16009198). The trial will help to demonstrate if SZRD is an effective and safety therapy to the patients with chronic insomnia disorder. We will publish the results of this study in peer-reviewed journals to have widespread dissemination.

Discussion

To our knowledge, this project is the first study protocol of randomized, double-blinded, double-dummy, placebo-controlled trial testing SZRD for chronic insomnia disorder in adult. This trial aims to evaluate the efficacy and safety of SZRD when compared with ZT or placebo. To facilitate high validity and reliability, a strict quality control and high-quality methodology is indispensable. We in detail describe the method of allocation concealment, recruitment, randomization and data collection. Additionally, objective sleep measurement, such as PSG, is used to assess insomnia remission. Currently, the ACP recommends that patients suffering from insomnia should receive CBT-I as first-line therapy. Thus, we provide every patient with CBT-I at the beginning, and only include the subject who is insensitive to CBT-I alone. The results from this trial may highlight evidence on the effectiveness and safety of SZRD.

Our study has some limitations and strengths. One weakness is the participant self-rating scales that have a possibility to exaggerate the severity of sleep. Another

limitation is that the trial is only implementing in one hospital. Notwithstanding these limitations, the results from this study will provide novel evidence about the SZRD available from a well-designed trial. In addition, this study will provide the project of herbal prescription for adult chronic insomnia disorder after CBT-I based on the guideline from the ACP recommendation.

Acknowledgments

We thank all staff who devoted their time and efforts to the study.

Footnotes

Contributors YL and GQZ contribute as the senior authors and the principal investigator (PI) of this study. QHZ, HLW, XLZ and MBX write the first draft of the manuscript and contribute to the design of the study. GQZ and YL refine the protocol. HFZ and LBH, as the medical statistician for the study, contribute to the statistical design, acquisition and analysis of data for the work. All authors revise the protocol critically for important intellectual content and approve the final manuscript.

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Competing interests None declared.

Patient consent Will be obtained.

Ethics approval Ethics Committee, the Second Affiliated Hospital of Wenzhou Medical University, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The study results will be available after publication in peer reviewed medical journal.

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Table 1. Overview of Suanzaoren decoction

Chinese name	Common name	Latin name	Species/Family	Amount (%)
Suanzaoren	Spine date seed	*Semen Ziziphi Spinosae*	The dried ripe seeds of Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou/ Rhamnaceae	20g (41%)
Gancao	Liquorice root	*Glycyrrhiza glabra L.*	The dried roots or rhizome of G uralensis Fisch. or G inflata Bat. or G glabra L./ Leguminosae	3g (6%)
Zhimu	Common anemarrhena rhizome	*Anemarrhena aspodeloidea*	The dried rhizome of Anemarrhena asphodeloides Bge./ Liliaceae	10g (20%)
Fuling	Indian buead	*Poria*	The dried sclerotia of P cocos (Schw.) Wolf/Polyporaceae	10g (20%)
Chuanxiong	Chuanxiong Rhizoma	*Rhizoma Ligustici Chuanxiong*	The dried rhizome of L chuanxiong Hort./Umbelliferae	6g (13%)

Figure legend

Figure 1. Flow diagram

Note: SZRD, Suanzaoren decoction; ZT, zolpidem tartrate

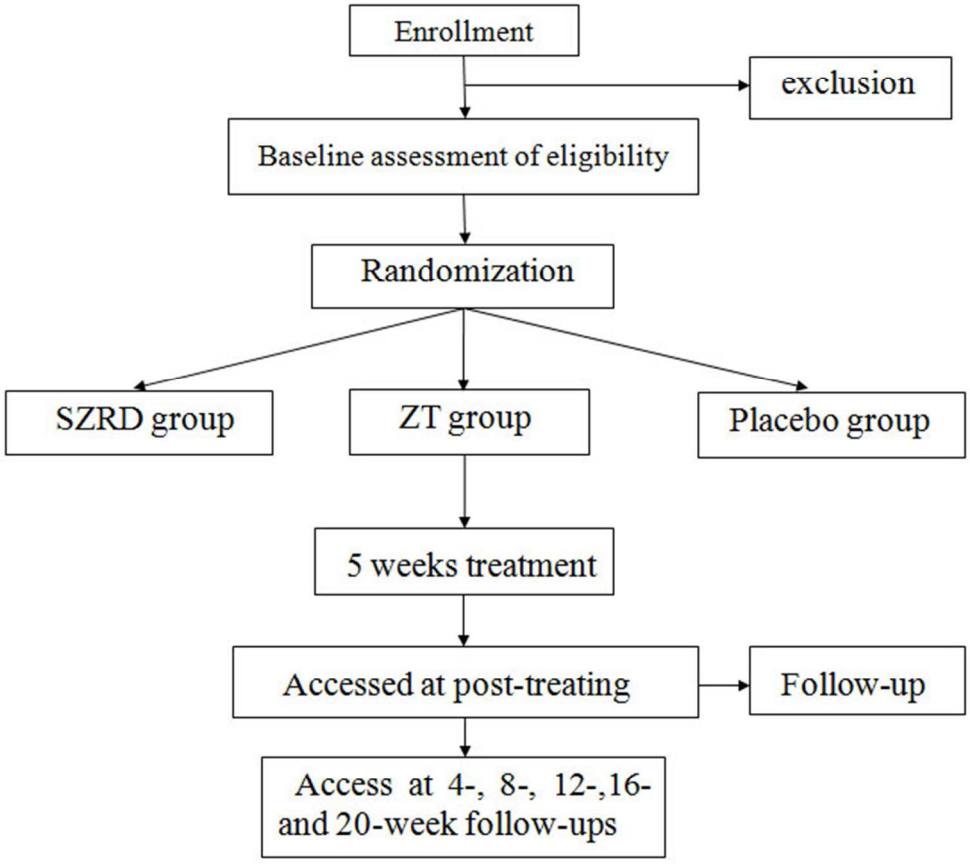

Figure 1. Flow diagram

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

Section/item	Item No.	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**P1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**P2**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	**P11**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
	5b	Name and contact information for the trial sponsor	
	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	
	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)	
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	**P4-5**
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	**P5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**P5-6**
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	**P5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**P6-7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**P7-8**
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**P7**
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	**P8-9**
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)	
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	**P6**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	
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	**P7**
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	**P7**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**P7**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**P7**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	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	**P10**
	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	
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	**P10**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**P10**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	

	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)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	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	
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	**P9**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
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)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**P5-6**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**P5-6**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	

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
Dissemination policy	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
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.