

Acupuncture Collaborative Care for Patients with Poststroke Cognitive Impairment: Protocol for a Randomized Controlled Trial

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Study protocol

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Abstract

Background: PSCI is a series of syndromes that meet the diagnostic criteria for cognitive impairment that appear after a stroke. The treatment of PSCI with oral drugs alone is not ideal and has obvious side effects. Therefore, complementary and alternative treatments are needed for patients with insufficient or significant side effects of oral medications. Therefore, we will evaluate the clinical effectiveness and safety of acupuncture in the treatment of PSCI.

Methods/design: In this study, patients will be randomly divided into two groups. Intervention group: Acupuncture combined with oral medication. Control group: Western medicine treatment plan. All participants will continue to receive conventional drug treatment. The selection of outcomes will be evaluated by Mini Mental State Examination Scale (MMSE) at week 12.

Discussion: This trial may provide evidence regarding the clinical effectiveness, safety, and cost-effectiveness of acupuncture for patients with PSCI.

Trial registration: Trial registration: ClinicalTrials.gov, ChiCTR2000029926, Registered on 17 February 2020 <http://www.chictr.org.cn/showproj.aspx?proj=49356>

Background

Cognitive function is composed of multiple cognitive areas such as memory, computing power, time orientation, space orientation, structural ability, execution ability, language understanding ability and expression application ability[1]. Cognitive impairment refers to a series of syndromes with varying degrees of cognitive impairment from mild cognitive impairment to dementia caused by various reasons. These behavioral and emotional disorders have become important diseases affecting the health and quality of life of middle-aged and elderly people, as well as important causes of disability for patients[2]. The disease places a heavy burden of care and economic burden on society and families. Stroke can cause multiple types and varying degrees of cognitive dysfunction. The definition of post-stroke cognitive impairment (PSCI) was also clarified in '*the 2016 Chinese Expert Consensus on Post-Stroke Cognitive Impairment Management*'. It points out that PSCI is a series of syndromes that meet the diagnostic criteria for cognitive impairment that appear after a stroke[3,4]. It highlights the potential causal relationship between stroke and cognitive impairment and the relevance of clinical management between the two. PSCI is a common and serious complication after stroke, with a high incidence, which seriously affects the quality of life and prognosis of patients. In addition, the survival time of patients is significantly reduced, and it can increase the risk of recurrent stroke, thereby placing a heavy burden on society and families[5]. The current treatments for PSCI are oral acetylcholinesterase inhibitors, anti-glutamate drugs, antioxidants, non-steroidal anti-inflammatory agents, and hormone replacement therapies. Recent studies have shown that the anticholinergic function of such drugs has certain limitations and can have a certain effect on patients' memory[6,7]. The treatment of PSCI with oral drugs alone is not ideal and has obvious side effects.

Acupuncture, as an important part of the appropriate technology of TCM, is currently the most commonly used complementary and alternative treatment.[8]. Acupuncture has a significant regulating effect on human psychology. Modern studies have found that acupuncture can improve cognitive function by affecting cerebral blood flow and hemorheology, protecting the internal structure of brain nerve cells[9,10]. The theory of TCM holds that acupuncture can regulate the balance of Qi and blood in the human body, it can improve human function. Acupuncture is becoming more and more popular with clinicians and patients for its unique advantages of simplicity, low cost, and significant efficacy. Based on the current needs of patients with PSCI who have poor response to conventional treatment and obvious adverse reactions, as well as the need for clinical research on the level of evidence for this effect, it is worthwhile to further explore the treatment model of acupuncture for PSCI. Therefore, we will evaluate the clinical effectiveness and safety of acupuncture in the treatment of PSCI. We hope that the results of this study can provide clinicians with acupuncture basis for PSCI and more treatment options. In this manuscript,we describe the rationale and the detailed methodology of

the trial. This protocol is guided by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Fig. 1 and Additional file 1: Table S1).

Methods/design

Study design and setting

In this study, patients will be randomly divided into two groups. Intervention group: Acupuncture combined with oral medication. Control group: Western medicine treatment plan. Patients who meet the inclusion and exclusion conditions first complete informed consent, are randomly divided into groups, and are randomly stratified according to the clinical treatment period of the "Plan". For specific stratification factors and reasons, see "Sample Estimation" of the statistical analysis plan. The intervention time was 12 weeks. The treatment was observed for 7 days, followed up for 28 days, and the evaluators will be evaluated blindly. During the observation period, patients who meet the criteria of the "Removal of Isolation and Discharge from the Plan" or those who have died and actively withdrew will be suspended from observation. After the observation period, patients who do not meet the "Resolution" of the Isolation and Discharge from the Hospital will still be hospitalized for standard treatment. In addition, we will implement a clinical surveillance system to ensure research quality.The trial work plan is summarized in Fig. 2.

Inclusion/exclusion criteria

We aim to recruit patients with PSCI who feel down in the dumps despite standard medical therapy.Patient inclusion criteria☒(1) A clear history of ischemic stroke or hemorrhagic stroke was confirmed by CT/MRI examination of the head; (2) Memory and/or cognitive and executive function impairments. Cognitive dysfunction has been determined after Mini Mental State Evaluation (MMSE) score; (3) Age will be limited to between 40-75 years of age, regardless of gender; (4) Stable condition,

clear awareness , No aphasia, can take drugs orally; (5) No severe comorbidities, no major depression; (6) Agree and sign the patient's informed consent.

Exclusion criteria:(1) Computer computed tomography (CT) or magnetic resonance imaging (MRI) shows that in addition to the responsible lesion, there are other lesions unrelated to the lesion or severe brain atrophy or white matter porosity; (2) with sensory Aphasia or motor aphasia that affects speech communication; (3) People with a previous history of mental retardation; (4) Patients with previous mental illness and/or with epilepsy; (5) Unstable vital signs, diabetes, blood Patients with disease or tumor; (6) Patients who have been taking sedatives for a long time; (7) People with a history of allergies to drugs and food; (8) People who have been identified with a cognitive impairment before a stroke.

Control group

Patients in the control group will receive conventional drug treatment, specifically, given donazepam hydrochloride tablets 5 mg orally once a night. If there are no adverse reactions, take 3 consecutive months. And they will be given symptomatic supportive treatments such as improving circulation, anti-free radicals, anti-platelet aggregation, lipid-lowering, and blood pressure. In addition, all patients underwent routine rehabilitation exercises after stroke.

Intervention group

In the intervention group, acupuncture will be added to the control group. We will select *Baihui*, *Shenting*, *Sishencong*, *Neiguan* and *Waiguan* as the main acupuncture points. After the doctor cleans his hands, he disinfects with an ethanol cotton ball. Wipe outward with a medical ethanol cotton ball or iodophor from the center of the patient's acupuncture site. We will use acupuncture needles with a size of 0.25 mm×40 mm. Acupuncture physicians start treatment with acupuncture on the inside, outside and outside points. The order of acupuncture at acupoints is left internal pass, right internal pass, left external pass, and right external pass. The needle point is inserted into the acupuncture point vertically downward, and the needle insertion speed should be fast. After the needle point penetrates the cortex, slowly insert the needle inward, the depth is about 15mm, until the Qi is obtained. The needle method mainly adopts the gentle lifting method, that is, after getting Qi, the patient does not aggravate the pain level as a standard, and the lifting method is used to puncture slowly. Secondly, acupuncture the *Baihui* acupoint on the head, keep the needle tip at an angle of 20 ° with the plane of the scalp, and quickly pierce the needle tip into the scalp. After penetrating the cortex, the needle points back into the needle along the vein, and the needle is inserted about 15mm. Until the Qi is obtained, the needle method is still used to gently lift. Finally, acupuncture *Sishencong*, pick up the local skin at the acupuncture point, and quickly pierce the needle tip to gain anger. At the same time, with the method of air-conduction, the patient closed his eyes, closed his lips lightly, snorted, and breathed slowly until the acupuncture needle will be pulled out. The indwelling time of acupuncture needles in each acupuncture point is 30 minutes. After pulling out the acupuncture needle, sterilize the cotton ball and press the area for 30s without bleeding. The above treatment will be performed once a day, followed by a rest day after 6 consecutive days of treatment for a total of 12 weeks.

Primary outcomes

The selection of outcomes will be evaluated by Mini Mental State Examination Scale (MMSE). This scale will be conducted by two trained assessors who performed a combined MMSE examination of the patient, using conversation and observation. After the MMSE test has been over, the two raters independently scored and took the average of the two as the final score. According to the international agreement MMSE score, The scale includes the following 7 aspects: time-oriented force, place-oriented force, immediate memory, attention and computing power, delayed memory, language, and spatial perception. A total of 30 items, each answer is worth 1 point, the answer is wrong or do not know the answer 0 points, the total scale of the scale is 0-30 points. The test results are closely related to cultural level. Scoring reference: scores 27-30: normal; scores <27 can be considered cognitive impairment; scores 21-26 are mild cognitive dysfunction; scores 10-20 are moderate cognitive dysfunction ; A score of 0-9 is considered severe cognitive impairment. The primary and secondary outcome measures are shown in Table 1.

Secondary outcomes

For the secondary outcomes, we will use the Montreal Cognitive Assessment Scale (MOCA). It is an assessment tool for rapid screening of cognitive abnormalities. It includes 11 inspection items in 8 cognitive areas including attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, computing and orientation. The total score is 30 points and ≥ 26 points are normal. It has high sensitivity, covers important cognitive areas, and has a short test time, which is suitable for clinical application. However, it is also affected by education level, differences in cultural background, the examiner's skills and experience in using MoCA, the environment of the examination and the emotional and mental state of the testee will all affect the score, and for mild cognitive function Obstacles are more sensitive. As education level is considered to be the most independent factor affecting the MOCA score. In order to correct the bias caused by education level, the total score is increased by 1 point for subjects with less than 12 years of education. For subjects with 4-9 years of education, the total score is increased by 2 points, and for those with 10-12 years of education, the score is increased by 1 point. This can better correct the bias caused by low education levels. □

Instruments and definitions

The MMSE compiled by Foistein and others in 1975 is one of the most influential and widely used screening scales at home and abroad. The scientific and rationality of this scale in predicting the progress of cognitive function in stroke patients has been fully confirmed. MMSE is a screening scale that mainly evaluates cognitive areas such as orientation, instantaneous memory, calculated attention, delayed recall, ability to understand and use, and language function. This scale is generally used for preliminary screening tests for cognitive function. In clinical practice, the MMSE scale is simple, time-saving and easy to operate. The scale has high sensitivity and specificity for detecting dementia, and has good validity and reliability. However, it also has the disadvantages of rough scores and incomplete evaluation. Because the education level of patients will affect their assessment results, false positive

results may be clinically obtained. Other studies have shown that the MMSE scale scoring method is too simple and leads to poor sensitivity. The sensitivity for screening for mild cognitive impairment (MCI) is only 1% -9%, and there is a "ceiling effect". Therefore, other scales need to be further improved and supplemented.

The Montreal Cognitive Assessment Scale (MoCA) was developed by Canadian Nasreddine and others based on clinical experience and with reference to MMSE (Concise Mental State Examination) cognitive items and scores. The Montreal Cognitive Assessment Scale adds assessments of functions such as executive function, visual spatial function, fluency of words, digital forward and backward. As early as 2006, MOCA has been recommended by international organizations as a 5-minute rapid screening PSCI scale. In 2007, the "Expert Consensus of Vascular Cognitive Impairment in China" listed it as the preferred test scale. In the same year, the 3rd Canadian Consensus Diagnosis and Treatment Conference and the Cardiovascular Society Consensus Conference also recommended MOCA for MCI testing. Where MMSE cannot detect cognitive impairment, MOCA can be an effective and simple screening tool. In addition, the patient's early MOCA score can predict the risk of cognitive impairment and risk in the future, and has certain predictive validity. It has certain guiding value for clinical judgment of patients' cognitive prognosis.

Safety

Adverse reaction (AE) refers to the occurrence of harmful reactions unrelated to the purpose of treatment during the process of preventing, diagnosing or treating diseases by applying drugs according to normal usage and dosage. Its specific occurrence condition is to use the medicine in the normal dosage and normal usage, and exclude the reaction caused by the drug abuse, excessive misuse, use of the medicine in accordance with the prescribed method and quality problems. Efficacy indicators reflect the effectiveness of interventions, while adverse events reflect intervention safety. In this study, adverse events refer to "adverse medical events that occur after a patient or subject in a clinical trial receive an intervention, but are not necessarily causally related to the intervention. Adverse events and adverse reactions The concept is different. Adverse reactions are directly related to the intervention, and the scope of adverse events covers adverse reactions.

Sample size justification

According to clinical experience, the effective rate of PSCI in the intervention group was $P_1 = 0.80$. The PSCI effective rate of the control group was $P_2 = 0.65$ [(two-sided type I error rate of 0.05, $\alpha = 0.05$); (one-sided type I error rate of 0.10, $\beta = 0.10$)]. Substituting $f(\alpha, \beta)$ into the formula is as follows: $n_1 = n_2 = 10.5 \times (0.8 \times 0.2 + 0.65 \times 0.35) \div 0.152 = 75$. The lost follow-up rate of patients will be controlled at 10%, so an additional 8 cases are added to each group. $n_1 = n_2 = 83$, that is, 83 cases will be taken from each of the intervention group and the control group. According to Cohen, this effect size is considered "moderate".

Data collection and management

The case report form (CRF) is a paper version, and the CRF is a carbonless copy, in duplicate, to be completed by the investigator. The inspector (CRA) shall conduct an on-site inspection of the CRF, and the problems discovered shall be verified and signed by the researcher after verification. After the completed paper version of the CRF is reviewed and signed by the CRA and the main investigator, the first copy is submitted to the data management unit. After the CRF is submitted, a logical data review is performed by the data management team. If there is any doubt about the data, the data administrator will send an "electronic data inquiry" to the CRA and the researcher, and send the inquiry to the researcher through the CRA. The researcher should answer and return as soon as possible, confirm. All error content and modification results shall be recorded and kept properly. Paper CRFs should be properly recorded and kept between researchers, CRAs, and data stewards.

Statistical analysis

Statistical analysis will be performed using SPSS 25.0 software for statistical analysis. The normality of the measurement data is tested. The data obeying the normal distribution is Student's t test, which is expressed by mean \pm standard deviation. The data not obeying the normal distribution is rank sum test. And marginal homogeneity test; count data are expressed by rate and composition ratio, and comparison is performed by chi-square test; repeated measurement data are expressed by mean \pm standard deviation, intra-group comparison is performed by analysis of variance of repeated measurement data, and inter-group comparison is by multivariate analysis of variance (MANOVA). $P\leq 0.05$ indicates that the difference is statistically significant.

Ethics and dissemination

This study has been approved by the Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (Reference number DZMEC-KY-2019-26). Independent clinicians and biostatisticians with extensive research experience in clinical trials will serve as the Data and Safety Monitoring Committee. The Ethics Committee of Dongzhimen Hospital Office may perform random audits to ensure that relevant regulations and guidelines are met. Study participation is voluntary and can be discontinued at any time, and deciding not to take part will not affect a patient's care. Protocol amendments, adverse effects reporting, and annual review will be overseen by the Ethics Committee of Dongzhimen Hospital. The information provided by the patients will only be shared with members of the research team. Every effort will be made to keep patient information confidential. All research-related paper documents will be kept in a locked cabinet. All patient information will be kept strictly confidential.

Discussion

The main symptoms of PSCI are related to the location of brain injury after stroke, which mainly involves calculation, memory, attention, space, and orientation[11,12]. Current research holds that the most important factor in the occurrence of cognitive impairment after stroke is the joint damage and interaction of blood vessels and nerves[13,14]. Ischemic stroke can cause a series of diseases such as hypoperfusion of cerebral blood flow, oxidative stress response, damage to free radicals, and reduction of

neurotransmitters in the brain, leading to damage to the structure or area that controls the corresponding cognitive function in the brain[15,16]. According to the degree of damage to the area or structure, the lesions with different severity in each cognitive field are displayed. Based on the pathogenesis of PSCI, cholinergic neurotransmitter function is low[17,18]. Therefore, enhancing central cholinergic transmitter system function can effectively treat cognitive dysfunction after cerebral infarction. Donepezil hydrochloride can improve the memory function and improve the living ability of patients with cognitive impairment after cerebral infarction by enhancing the cerebral cholinergic system. However, some studies have pointed out that the clinical efficacy of donepezil hydrochloride may be related to individual differences in patients, and further research is needed to confirm its effectiveness[19]. There have been many reports of acupuncture treatment of PSCI in recent years. The possible mechanism is to affect cerebral blood flow and hemorheology and protect the internal structure of brain nerve cells, thereby improving cognitive function[20]. Studies have also shown that the possible mechanism of acupuncture for PSCI is to improve brain protein synthesis and resist free radical damage, thereby protecting brain cells[21].

Modern research shows that acupuncture, like medicine, can improve the body's immunity and maintain the homeostasis of the cellular environment, thereby maintaining the body's normal physiological functions and maintaining body fluid balance, in order to achieve the purpose of controlling and eliminating diseases[22]. At the same time, both acupuncture and medicine have side effects, but acupuncture is still relatively safe. The side effects of acupuncture are mostly halo needles that appear after acupuncture, but these side effects disappear quickly after the needle is stopped, and the impact on the body is much smaller than the adverse reactions of drugs. Therefore, it is necessary to further explore the diagnosis and treatment model of acupuncture for PSCI. In this study, we will evaluate the clinical effectiveness and safety of acupuncture in the treatment of PSCI through the research method of randomized controlled trials. We hope that the results of this study can provide clinicians with acupuncture basis for PSCI and more treatment options.

Trial Status

Approval documents: The vision of study protocol(V1.0 2018.12.20); informed consent (V2.0 2019.03.26); case report form; recruitment advertisement; copy of the main researcher GCP training certificate. At the time of submission of the manuscript, the study had not yet begun to recruit subjects. We expect to start in June 2020 and complete the recruitment of subjects on December 31 of the same year.

Abbreviations

AE: Adverse reaction; CRF: case report form; MANOVA: multivariate analysis of variance; MOCA Montreal Cognitive Assessment Scale; MBI Modified Barthel Index Rating Scale; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination Scale; PSCI: post-stroke cognitive impairment; PRECIS-2: Pragmatic Explanatory Continuum Indicator Summary Framework-2; Recommendations for

Interventional Trials; SOP:standard operation procedures;SS-QOL Stroke-specific quality of life scale;;SPIRIT:Standard Protocol Items: Recommendations for Interventional Trials;TCM: Traditional Chinese medicine;

Declarations

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Availability of data and materials

Not applicable.

Author contributions

RJL designed the protocol for this clinical study and completed the writing of the manuscript. XDY designed interventions and controls for this study. JSW and YL is responsible for data collection and statistical analysis for this study. BWL and XWL is mainly responsible for the design and coordination of research. HWY completed the review of the first draft of the manuscript. TYC and YW completed the production of clinical research related scales.

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (Reference number DZMEC-KY-2019-26). Written informed consent is required for participation. Protocol amendments, adverse event reporting and annual review will be overseen by the Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine.

Consent for publication

Consent to published de-identified information is included in the written informed consent process. However, no data is being published at this time.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1

Treatment schedule and outcome measures.

Items	Before Treatment	Treatment period, twice a week, 8 times in total (treatment starts within one week after registration)				Post observation Period
	Registration	Week 1-4	Week 6	Week 8	Week 12	2 week later Treatment completion
Inclusion criteria	✓					
Exclusion criteria	✓					
Informed consent	✓					
Confirmation of subjective symptoms	✓	✓	✓	✓	✓	✓
Mini Mental State Examination Scale	✓		✓		✓	✓
Traditional Chinese Medicine Syndrome Score	✓		✓		✓	✓
Observation of adverse events		✓	✓	✓	✓	✓

Figures

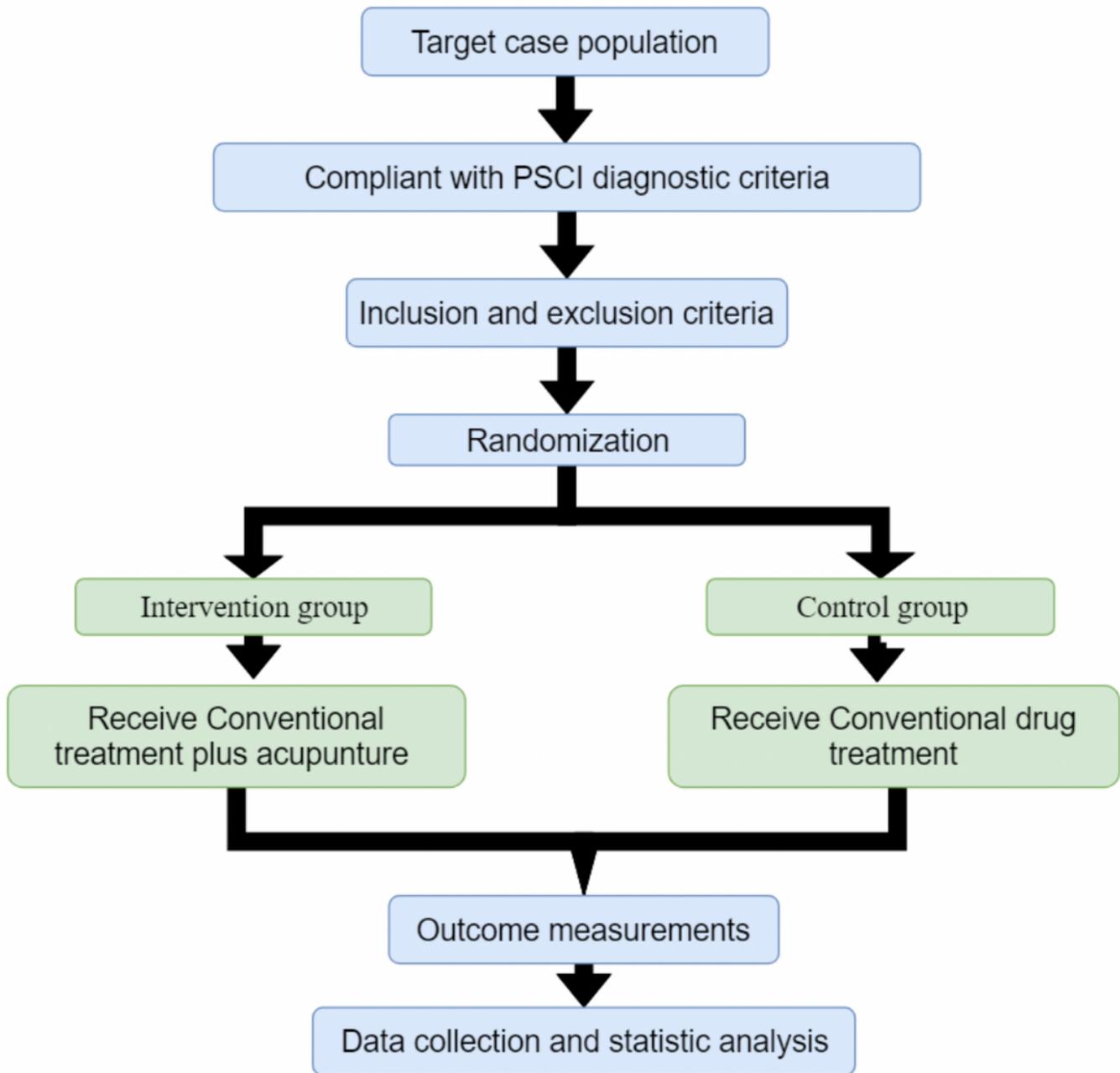


Figure 2

Study design flow chart