

BMJ Open Acupuncture for retinitis pigmentosa: study protocol for a randomised, sham-controlled trial

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ABSTRACT

Introduction Primary retinitis pigmentosa (RP) is a common hereditary retinal disease in ophthalmology that has a considerable impact on quality of life, but there are few effective therapeutic strategies. This trial aims to determine the efficacy and safety of acupuncture versus sham acupuncture (SA) for RP.

Methods and analysis This is a study protocol for a randomised, participant-blind, sham-controlled trial. 64 eligible patients with RP will randomly be divided into acupuncture group and SA group. All groups will receive 48 sessions over 3 months. Participants will complete the trial by visiting the research centre in month 6/9 for a follow-up assessment. The primary outcome is visual field mean sensitivity and visual field mean deviation at month 3/6/9 compared with baseline. Secondary outcomes include the best-corrected visual acuity, central macular thickness, subfoveal choroidal thickness, traditional Chinese medicine syndrome score and the scale of life quality for diseases with visual impairment at month 3/6/9 compared with baseline. Adverse events and safety indexes will be recorded throughout the study. SPSS V.25.0 statistical software was used for analysis, and measurement data were expressed as mean±SD.

Ethics and dissemination Ethics approval was obtained from the Ethics Committee of the Chinese Clinical Trial Registry (approval no: ChiECRCT20200460). The results of this study will be published in a peer-reviewed journal, and trial participants will be informed via email and/or phone calls.

Trial registration number ChiCTR2000041090.

BACKGROUND

Primary retinitis pigmentosa (RP) is a group of diseases where a large number of mutations cause the rod type photoreceptors to die. After the rod type dies, the cone type photoreceptors gradually degenerate in a unique pattern.¹ RP is mainly manifested as visual field defects and progressive night blindness,² specialty examination showed abnormal electroretinogram (ERG), with typical triple signs of optic nerve waxy atrophy, vascular thinning and osteocellular pigmentation.³ It is a common hereditary retinal disease in ophthalmology, with an incidence of about 1/4000 of the world.⁴ The factors influencing the development of RP have not

Strengths and limitations of this study

- The statistical analysis will be carried out by an independent statistician who is not aware of group allocation.
- The results of this feasibility study will provide data for an adequately powerful pragmatic trial.
- Both the full analysis set and the conforming protocol set were used in the efficacy evaluation, which could enhance the credibility of the test results.
- One of the limitations is that this study is implemented in only one centre in Chinese subjects, without long-term treatment and follow-up.
- Though widely accepted and used, the rationality of sham acupuncture still has been questioned.

been fully defined, but it is generally believed that genetics is the most important factor. From the perspective of genetics, there are mainly autosomal dominant RP, autosomal recessive RP and X-linked inheritance RP.⁵ There are also a few RP genetic patterns that are mainly inherited by mitochondria and double genes.⁶

Because RP has a high degree of genetic and clinical heterogeneity,⁷ as well as a variety of complex clinical subtypes, it has a high rate of blindness and a poor prognosis. Currently, there is no effective method to cure RP, which seriously affects the quality of life of the affected population. At present, the research on the treatment of RP focuses on retinal transplantation and gene therapy,⁸ but retinal transplantation has many complications,⁹ and gene therapy is mostly still in the experimental stage, which has not been used in clinical practice. No matter what kind of modern medical treatment means can not cure RP, so it is urgent to actively explore and develop a safe and effective treatment for RP. The study has shown that acupuncture has a positive effect on the repair of the function of optic nerve cells in inhibition and partial injury, and the regeneration capacity of the central nervous system is greater than generally believed. If nerve fibres are placed in



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a suitable environment, it can accelerate the repair of the optic nerve.¹⁰ Acupuncture can improve the microcirculation of local ocular tissues and shorten the pathological reaction, which plays a good role in RP. Bittner *et al*¹¹ compared transcorneal electrical stimulation (TES) at 6 weekly half-hour sessions, electroacupuncture or inactive laser acupuncture (sham control) at 10 half-hour sessions over 2 weeks for RP patients by RCT. Both the central retinal artery mean flow velocity of the TES and the electroacupuncture group were significantly improved compared with sham controls. Xu *et al*¹² choose acupuncture treated from 1998 to 2017, a total of 26 patients with primary RP (51 eyes), adopt the method of before-after study in the same patient, and observe the patient's visual acuity and ERG, visual function damage, eye retina patients quality of life scale score index in acupuncture treatment after 3 months, and the change of the acupuncture treatment up to now, and assessed the clinical curative effect, it is concluded that the clinical total effective rate was 69.6%. Xie¹³ *et al* observed the effect of traditional Chinese medicine (TCM) combined with acupuncture on RP. The experimental group was treated with TCM combined with acupuncture. After treatment, the indicators of intraocular pressure, vision, visual field mean sensitivity (MS) and visual field mean deviation (MD) of the experimental group were superior to the control group ($p < 0.05$), and the total effective rate of the experimental group was higher than that of the control group ($p < 0.05$). However, most of the domestic studies are based on the combination of acupuncture and medicine, or single-arm clinical trials, and the main observation indicators are visual acuity and visual field MS and MD. Visual acuity and visual field examination is a subjective examination with many influencing factors. Therefore, central macular thickness (CMT)^{14 15} and subfoveal choroidal thickness (SFCT)¹⁶ were added as the indicators in this clinical trial. The non-meridian points were used as the control group, and a strict randomised controlled trial was conducted to evaluate the efficacy and safety of acupuncture alone in the treatment of primary retinal pigment degeneration, in order to provide effective methods and research ideas for the treatment of this disease with TCM.

Objectives

The purpose of this randomised, sham-controlled clinical trial is to evaluate the efficacy and safety of acupuncture in the treatment of RP. Since there is currently no cure for RP, this may provide an additional treatment option for patients with RP.

METHODS

Study design

This randomised, single-blind, sham-controlled trial will be conducted in the Hospital of Chengdu University of Traditional Chinese Medicine, China. The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist¹⁷: defining standard protocol items for clinical trials (online supplemental file 1 SPIRIT

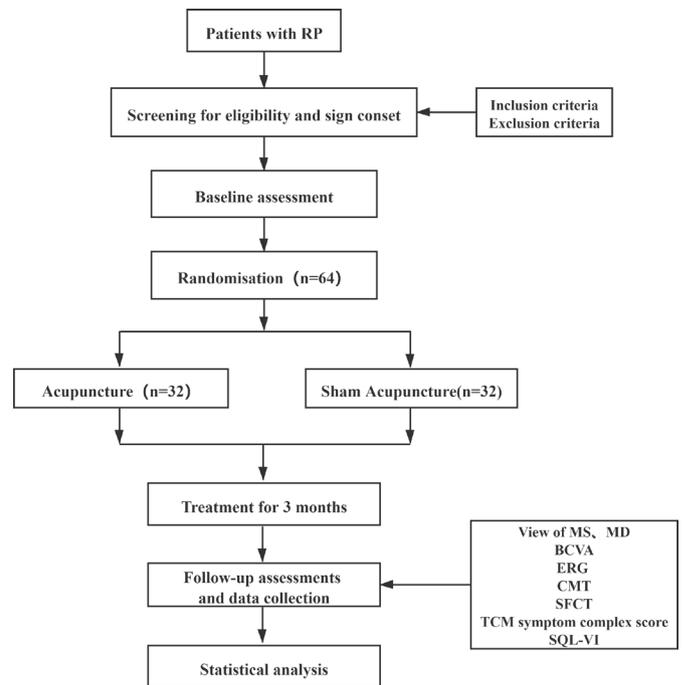


Figure 1 Flow diagram. BCVA, best-corrected visual acuity; CMT, central macular thickness; ERG, electroretinogram; MD, mean deviation; MS, mean sensitivity; RP, retinitis pigmentosa; SFCT, subfoveal choroidal thickness; SQL-VI, scale of life quality for diseases with visual impairment; TCM, traditional Chinese medicine.

Checklist). The study has been approved by the Ethics Committee of the Chinese Clinical Trial Registry (Ethical approval number: ChiECRCT20200460). A flow diagram of the trial is shown in figure 1. The schedule of enrolment, interventions and assessments are presented in figure 2. In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale in each section.

Patient recruitment

This study intends to recruit 64 patients with primary RP who meet the diagnostic criteria¹⁸ starting from January 2021, all from the outpatient department of the Hospital of Chengdu University of Traditional Chinese Medicine. The researcher took the initiative to introduce the study, and the subjects volunteered to participate in this study. After the clinician conducted screening according to the inclusion and exclusion criteria, the subjects could be included if they met the criteria. Before randomisation, all patients were required to provide written informed consent (online supplemental file 2 Informed Consent).

Inclusion criteria

- ▶ Patients who meet the diagnostic criteria for primary RP.¹⁸
- ▶ Aged 14–80 years (either sex), the course of the disease is not limited.
- ▶ Written informed consent. The process of obtaining informed consent conforms to the requirements of clinical trial management standards.

TIMEPOINT	STUDY PERIOD						
	Enrolment	Allocation	Treatment period (month)			Follow-up period (month)	
	-2 days	0	1	2	3	6	9
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Acupuncture group			←————→				
Sham acupuncture group			←————→				
ASSESSMENTS:							
View of MS, MD		X			X	X	X
BCVA		X			X	X	X
ERG		X			X	X	X
CMT		X			X	X	X
SFCT		X			X	X	X
TCM symptom score		X			X	X	X
SQL-VI		X			X	X	X
ERG		X			X	X	X
Adverse events ^[1]					X		
Assessment of safety ^[2]		X			X		

[1] AEs: Treatment-related symptoms include local subcutaneous hematoma, pruritus at the acupuncture site, persistent pain after acupuncture, dizziness, etc.

[2] Assessment of safety include routine blood tests, urine tests, faecal tests, liver function tests, renal function tests, and electrocardiogram.

Figure 2 The schedule of enrolment, interventions and assessments are presented. BCVA, best-corrected visual acuity; CMT, central macular thickness; ERG, electroretinogram; MD, mean deviation; MS, mean sensitivity; SFCT, subfoveal choroidal thickness; SQL-VI, scale of life quality for diseases with visual impairment; TCM, traditional Chinese medicine.

Exclusion criteria

- ▶ Best-corrected visual acuity (BCVA) is less than 0.1.
- ▶ Patients suffering from ophthalmic diseases such as amblyopia, diabetic retinopathy, glaucoma, severe cataract, etc, which affect vision or other blindness diseases.
- ▶ Patients with severe primary diseases such as cardiovascular and cerebrovascular, liver, kidney and haematopoietic system, as well as psychiatric patients.
- ▶ Patients who have received other related drugs or treatment for primary RP within 2 weeks.
- ▶ Poor compliance or participating in other clinical trials.

Randomisation and allocation concealment

A random sequence is generated by SAS V.9.4 (SAS Institute) and performed by the TCM Good Clinical Practice Centre, Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, China), through the online version of the central randomisation system. Participants will be randomly allocated to an intervention group (acupuncture) or control group (sham acupuncture (SA)) at a ratio of 1:1 with block randomisation. The

subject and investigator could not foresee the grouping information of the subjects. The random number is managed by TCM Good Clinical Practice Centre. Until the end of the study, neither the subjects nor the outcome measure knew how the subjects were grouped.

Masking

Due to the nature of acupuncture, masking by acupuncturists is quite difficult to achieve. Patients, outcome assessors and statisticians who perform the statistical analyses will be blinded to group assignment. The treatments subjects received will be not revealed until the statistical analysis is completed. In addition, all patients will be asked to guess which treatment they have received to test the patient-blinding effects at month 3.

Interventions

Treatment will be performed by licensed acupuncturists who have at least 5 years of experience in acupuncture. All the acupuncturists will be trained how to locate acupoints, puncture and manipulate needles before trials. Follow the prescribed treatment regimen four times a week. The baseline time is the day before treatment began. One month is a course of treatment, a total of three courses of treatment. Acupuncture will be discontinued if patients suffer from any serious adverse events (AEs).

Acupuncture

The patients in the acupuncture group were placed in the sitting or supine position. The selected acupoints around the eye were Taiyang (EX-HN5), Cuanzhu (BL2), Yuyao (EX-HN4), Qiuhou (EX-HN7), Jingming (BL1) and the full body acupoints were Baihui (GV20), Hegu (LI4), Taichong (LR3), Sanyinjiao (SP6), Zusanli (ST36). All acupoints are localised according to the WHO Standard Acupuncture Locations and are exhibited in [table 1](#) and [figure 3](#). After the local skin of the patient and the hands of the physician were routinely disinfected with 75% ethanol, both hands were used for needle insertion, and disposable acupuncture needles (0.25 mm×25 mm) were inserted into the acupoint skin except BL1 and EX-HN7 (approximately 10–20 mm depth), and then manipulations of twirling, lifting, and thrusting will be performed on all needles for at least 10s to reach De qi (a compositional sensation including soreness, numbness, distention, and heaviness), which is believed to be an essential component for acupuncture efficacy. BL1 and EX-HN7 should be the slight twists, do not lift and insert, and press the pinhole after pulling the needle for a moment to prevent bleeding. Needles will be retained in these acupoints for 20–30 min.

The above treatment was performed four times a week. One month is a course of treatment, a total of 3 courses of treatment.

Sham acupuncture

Participants in the SA group will receive the non-meridian and non-acupoint treatment,^{19 20} and the selected sham acupoint was at the midpoint of the line between the adjacent meridian acupoints (Xiaguan, Meichong, Touwei,

Table 1 Locations and manipulations of acupoints

	Acupoint	Location	Manipulation
Acupoints around the eye	Taiyang (EX-HN5)	Flat part at each side of the forehead	Puncture perpendicularly to a depth of 0.3–0.5 cun*
	Cuanzhu (BL2)	On the medial end of the eyebrow	Puncture horizontally or obliquely to a depth of 0.5–0.8 cun toward the middle of the eyebrows
	Yuyao (EX-HN4)	Directly above the pupil, in the centre of the eyebrow	Puncture horizontally or obliquely to a depth of 0.3–0.5 cun
	Qiuhou (EX-HN7)	In the face and the outer quarter of the lower orbital margin meets the inner three-quarters	Gently push the eye up, puncture slowly and perpendicularly to a depth of 0.5–1.5 cun toward the orbital rim
	Jingming (BL1)	In the depression and 0.1 cun above the inner canthus	Puncture perpendicularly to a depth of 0.3–0.5 cun close to the orbital rim
Body acupoints	Baihui (GV20)	On the midline of the head, 7 cun directly above the midpoint of the posterior hairline	Puncture horizontally to a depth of 0.5–0.8 cun
	Hegu (LI4)	Between the first and second metacarpal bones, and in the midpoint of the radial side of the second metacarpal bone	Puncture perpendicularly to a depth of 0.5–0.8 cun
	Taichong (LR3)	In the depression anterior to the junction of first and second metatarsal bones	Puncture perpendicularly to a depth of 0.5–1 cun
	Sanyinjiao (SP6)	Three cun superior to the prominence of the medial malleolus, posterior to the medial border of the tibia	Puncture perpendicularly to a depth of 1–1.5 cun
	Zusanli (ST36)	Three cun directly below Dubi†, and one finger-breadth lateral to the anterior border of the tibia	Puncture perpendicularly to a depth of 1–2 cun

*1 cun (≈20 mm) is defined as the width of the interphalangeal joint of patient's thumb.

†Dubi is in the lateral depression of the patellar ligament, when the knee is flexed.

Juliao, Yingxiang, etc). After skin disinfection, disposable acupuncture needles (0.25 mm×25 mm) were inserted into the sham acupoint skin without twist, lift or push all needles to achieve De Qi. This kind of SA with pierce the skin is relatively simple in clinical operation, and participants are not easy to distinguish. and the acupoint. Needles will be retained in these acupoints for 20–30 min.

The above treatment was performed four times a week. One month is a course of treatment, a total of three courses of treatment.

Concurrent treatments

Participants will not receive any other medical treatment for RP other than acupuncture.

Follow-Up

After 3 months of treatment, all participants entered an additional follow-up period. the follow-up time is the third and sixth month after treatment (ie, month 6 and month

9). During this time, they will receive routine healthcare as provided to all other patients with RP. However, acupuncture treatment will not be allowed during follow-up.

OUTCOMES

Primary outcome

Visual field MS and visual field MD of the patients. (All main indicators will be measured at each time point). The measurement time points are: the baseline time (month 0), end of treatment (month 3) and the follow-up time (month 6, 9).

Secondary outcomes

The BCVA, ERG waveform changes, CMT, SFCT, TCM syndrome score and the scale of life quality for diseases with visual impairment²¹ at the baseline time (month 0), end of treatment (month 3) and the follow-up time (month 6, 9).

Blinding assessment

To test the patient-blinding effects, all patients will be asked to guess their group assignment allocation within 2 min after the last treatment session in the third month as following: 'Which group do you think you are in?' (A) traditional acupuncture; (B) modified acupuncture or (C) not sure.

Adverse events

AEs data will document the occurrence, duration and severity of adverse reactions (symptoms and signs), and how the event was resolved (or not) during the treatment.

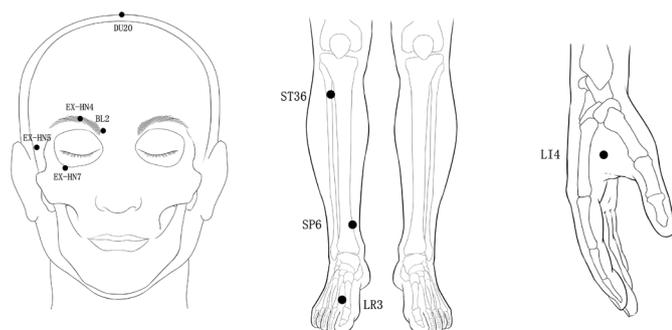


Figure 3 Locations of acupoints.

Based on their potential association with the acupuncture needling procedure, AEs will be categorised by acupuncturists and related specialists as treatment related or not within 24 hours after the occurrence. Common treatment-related AEs include local subcutaneous haematoma, itching at the sites of needle insertion, continuous postneedling pain, dizziness and so on. For patients with bleeding or severe haematoma, an ice compress or cold compress should be immediately applied to the local swelling area, during which dressing can be replaced several times, which is beneficial to stop bleeding and haematoma subsidence.

All participants will undergo routine blood tests, urine tests, faecal tests, liver function (alanine aminotransferase and aspartate aminotransferase), renal function tests (serum creatinine and blood urea nitrogen) and ECG. These trials will be conducted before treatment and at the end of treatment (3 months). Serious AEs will be reported to Medical Ethics Committee and the participant will be treated with relevant conventional therapy or hospitalisation if necessary (the participant's allocated intervention will be revealed).

Assessment of safety

All participants will undergo routine blood tests, urine tests, faecal tests, liver function (alanine aminotransferase and aspartate aminotransferase), renal function tests (serum creatinine and blood urea nitrogen) and ECG. We will evaluate the safety of the treatment based on the results of these tests.

Sensation during the treatment

Patients will be asked about their sensations during each treatment period as following: 'What sensation do you feel during the treatment? (A) soreness; (B) distention; (C) pain; (D) no feeling; (E) else, please specify____.'

Data collection, management and monitoring

All researchers including acupuncturists, outcome assessors and statisticians will receive training regarding data management. Case report forms will be completed and double entered into the electronic data capture system by two independent investigators to ensure the accuracy of data. All research documents, including both paper files and electronic documents, will be preserved for at least 5 years after publication. If reviewers or readers have any questions regarding our published data, they can contact the corresponding author for access to original data or visit ResMan (<http://www.medresman.org/uc/index.aspx>). Private information of patients including name, telephone number and ID number will be anonymous to ensure participant confidentiality. The safety of this study will be monitored by a team of independent clinical experts and statisticians.

Statistical methods

Sample size

Sample size estimation for the full-scale trial is based on a clinical trial about acupuncture combined with oral Chinese

Medicine for RP.²² The MS and MD scores were used to calculate the sample size, and a larger sample was used. The assumption is that using oral Chinese Medicine is more effective than SA. Accordingly, the MS and MD scores of control group was refer to baseline data. Sample size was estimated using PASS V.15.0 (NCSS), with a significance level ($\alpha=0.05$) of a two-sided two-sample t-test and 80% power to detect a difference between the two groups. Allowing for a drop-out of 20% at the end treatment time point, the recruitment goal of RP participants was 64 subjects (32 per group). Prior to formal trial, a pilot study of 10 participants will be conducted to test the feasibility of the trial protocol and adjust the final sample size.

Statistical analysis

Statistical analysis will be performed by an independent statistician who is not aware of group allocation. SPSS V.25.0 statistical software (IBM SPSS Statistics) was used for analysis, and measurement data were expressed as mean \pm SD. For those with normal distribution, the paired t-test was used for comparison before and after treatment, and the t-test was used for comparison between groups (homogeneity test of variance was performed, with 0.05 as the test standard). If the variance is not uniform or does not conform to a normal distribution, the rank-sum test is used. The χ^2 test was used for counting data, and the rank-sum test was used for grading data. Bilateral tests were used for all tests, with $p<0.05$ indicating a significant difference.

The baseline data were analysed using the full analysis set (including completed cases and exfoliated cases, excluding excluded cases). Both the full analysis set and the conforming protocol set (PP set, including completed cases, excluding exfoliated cases and excluded cases) were used in the efficacy evaluation. When the conclusions of the two analyses were consistent, the credibility of the test results could be enhanced. When there is inconsistency, the differences should be fully discussed and explained. In the analysis of the full analysis set, the missing data is replaced by the method of sequence mean value. In order to investigate the stability of the results, we will conduct sensitivity analysis, including converting data or changing primary outcomes to perform a hypothesis analysis.

Ethics and dissemination

The study protocol which follows the principles of the Declaration of Helsinki has been approved by the Ethics Committee of the Chinese Clinical Trial Registry (Ethical approval number: ChiECRCT20200460). Results will be disseminated through peer-reviewed publications, a master's thesis, or conference presentations. Data will be anonymised before publication to prevent the identification of individual participants.

Availability of data and materials

All unidentified data collected during the trial will be provided to anyone who wishes to access 6 months after publication in accordance with Findable, Accessible, Interoperable, Reusable (FAIR) principles.



DISCUSSION

RP is a serious blinding eye disease, characterised by progressive impairment of photoreceptor cells and pigment epithelial cells that leads to visual dysfunction.²³ Acupuncture has been widely used in the clinical practice of RP treatment in China. However, to date, no properly designed RCT or enough sample size has provided clear evidence for the effectiveness of acupuncture for RP at home and abroad. Most of them were self-controlled single-arm clinical trials, or compared the advantages and disadvantages of two acupuncture methods.²⁴ In this study, the inclusion criteria ranged from 14 to 80 years old, and were chosen to cover the widest possible age range. During the study period, the subjects will not receive any medical treatment for RP other than acupuncture. We believe that such strategies can reflect real-world practices and better fulfil moral obligations. Standardised treatment regimens will be used to ensure reproducibility. In this trial, the treatment regimen was based on the traditional acupuncture theory and the consensus of ophthalmologists and acupuncturists in the affiliated Hospital of Chengdu University of Traditional Chinese Medicine. Manually stimulate the needle at each acupoint for at least 10s and keep it in place for 20–30 min. Treatment was given four times a week, with a course of treatment of 1 month, and a total of three courses of treatment.

The right control group is essential to a well-designed clinical trial. This study selected the most commonly used virtual acupuncture device in the clinic.^{25–26} Patients who had received related drugs, acupuncture or other treatments for primary RP in the past 2 weeks and were able to distinguish SA from MA were excluded. In addition, all patients will be asked to guess which treatment they received in March to test the blinding effect of the patient.

The severity of RP is assessed depending on the outcome of the patient's visual field examination. visual field MS²⁷ and visual field MD²⁸ are relatively valuable indicators to evaluate the pathological status of patients in RP study. Therefore, visual field MS and visual field MD were measured as the main results in this study. The limitation of our trial is that the acupuncturist will not be blind to the nature of the intervention. We hope that the results of this trial will provide more reliable evidence and clarify the value of acupuncture as a treatment for RP.

Even so, there are some limitations of this study. In the first place, the adherence of participants may be poor because the treatment period lasts 3 months. The study size is calculated on the hypothesis of a 20% loss rate, it will be necessary to ascertain that there is no bias between the two intervention groups. In another, due to the lack of accurate efficacy estimation, the calculation of sample size has some deviation. Pilot study before full-scale trial are necessary to help adjust the final sample size. What's more, SA and placebo acupuncture were considered an inappropriate choice for control for several reasons in some studies.^{29–31} The ideal method of SA must have the same appearance and feeling as the real acupuncture, but cannot produce specific curative effect. Currently, none

of the SA control settings meet the standard requirements of the traditional placebo group. Therefore, in the actual operation process, the implementation conditions of SA should be the same as that of real acupuncture, so as to ensure the minimum non-specific effect (placebo benefit), minimise the bias to the greatest extent, and accurately evaluate the specific effect of treatment acupuncture.

In summary, the trial met the methodological requirements of full randomisation and allocation concealment, patient blindness, outcome evaluator and statistician. The findings of this pilot study will provide a high-quality basis for evaluating the efficacy and safety of acupuncture and moxibustion in the treatment of RP.

Contributors HH, JW and HL contributed equally to this work and are co-first authors. HH and YZ contributed to the conception of the study. The manuscript protocol was drafted by HH, and was revised by YZ, JW and HL. HH and RL developed the search strategies, and QH and NG will implement them. RL and WZ will extract data of included studies, assess the risk of bias and complete the data synthesis. YZ will arbitrate the disagreements and ensure that no errors are introduced during the study. All authors approved the publication of the protocol.

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