Acupuncture for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Study Protocol with Statistical Analysis Plan (SAP) and Informed Consent Form (ICF)

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2. Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) refers to the presence of bothersome pelvic pain symptoms without an identifiable cause[1]. Table 1 illustrates the 4 categories of prostatitis per the National Institutes of Health (NIH) classification of prostatitis syndromes. CP/CPPS affects approximately 10–16% of men worldwide[1-4]. Men of all ages can be impacted, among whom those aged 36–50 years are the most commonly affected[5]. There is no apparent racial predisposition to this disease.

Common symptoms of CP/CPPS include discomfort in the perineum, suprapubic region, and lower urinary tract symptoms[6]. Patients with CP/CPPS also frequently experience a wide array of sexual dysfunctions, including erectile dysfunction (ED), painful ejaculation and premature ejaculation (PE)[7-11], on top of symptoms suggestive of negative cognition or emotional consequences[12]. The aforementioned symptoms negatively impact upon the patient's quality of life (QoL) to a similar degree or worse than those of congestive heart failure, Crohn's disease, diabetes mellitus or angina[13, 14]. Because of its high prevalence and lack of effective therapies, direct and indirect costs associated with CP/CPPS are substantial[15]. Approximately 25% of men experience loss of work and approximately 50% have reduced leisure time at some point due to CP/CPPS[16]. The direct and indirect cost of care in China approaches 8059 CNY per person in 2009[17], and data indicate that in the USA, the total annual cost for patients with prostatitis was US$4387 in 2006[15].

Unlike acute/chronic bacterial prostatitis, the cause of CP/CPPS is unknown and no well-conducted epidemiologic studies are available to support any particular risk factors[18]. The diagnosis of CP/CPPS is mainly based on symptoms. Treatments for CP/CPPS usually include alpha-blockers, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and phytotherapy. Alpha-blockers and antibiotics have moderate effects on pain, voiding and QoL[19]. Both alpha-blockers and antibiotics are recommended for patients with CP/CPPS for less than 1 year, but only antibiotics are recommended in treatment-naïve patients. NSAIDs and phytotherapy are less commonly used, because of lack of research evidence[19]. Although advances have been made in research and developing novel treatment options, definitive treatments for CP/CPPS are still lacking[19]. Besides, pharmacological interventions are accompanied with adverse effects such as dizziness, nausea, and postural hypotension, which also reduce patients' compliance to treatments[20]. Previous studies suggest that acupuncture may be a potential treatment for CP/CPPS [21-25]. However, owing to small sample sizes and other methodological limitations of clinical trials, the efficacy of acupuncture in CP/CPPS remains inconclusive [19, 26]. In addition, the durable efficacy of the acupuncture is still unclear.[27]

NIH consensus classification of prostatitis	Definition
(I) Acute bacterial prostatitis	Acute infection of the prostate
(II) Chronic bacterial prostatitis	Chronic or recurrent infection of the prostate
(III) Chronic prostatitis/chronic pelvic pain syndrome	No demonstrated infection
A. Inflammatory	Leukocytes in expressed prostatic secretions, post prostate massage urine, or semen
B. Noninflammatory	No evidence of inflammation
(IV) Asymptomatic inflammatory prostatitis	No subjective symptoms detected, inflammation shown either by prostate biopsy or the presence of leukocytes in EPS/semen during evaluation for infertility or other disorders

NIH, National Institutes for Health

Table 1. NIH consensus classification and definition of 4 categories of prostatitis[1]

3. Study Design and Objective

3.1 Objective

The objective of this multi-center, randomized, sham acupuncture-controlled trial is to assess the effectiveness of acupuncture for relieving symptoms of CP/CPPS.

3.2 Primary Hypothesis

The primary study hypothesis is that acupuncture is more effective than sham acupuncture in relieving symptoms of CP/CPPS after treatment and 24 weeks after the cessation of treatment.

3.3 Study Design and Organizations

This is a multicenter, participants-blinded, parallel-group, randomized controlled study conducted in China.

The participants will be recruited in 10 clinical sites, which are Dongfang Hospital Beijing University of Chinese Medicine; Beijing Fengtai Hospital of Integrated Traditional and Western Medicine; West China Hospital of Sichuan University; The Third Affiliated Hospital of Zhejiang Chinese Medical University; The First Affiliated Hospital of Anhui University of Chinese Medicine; Hengyang Hospital Affiliated to Hunan University of Chinese Medicine; The First Hospital of Hunan University of Chinese Medicine; Guangdong Provincial Hospital of Traditional Chinese Medicine; Yantai Hospital of Traditional Chinese Medicine; and Shaanxi Provincial Hospital of Traditional Chinese Medicine. Guang'anmen Hospital, China Academy of Chinese Medical Sciences will be responsible for study design and organization. A data coordination center will be established at China Academy of Chinese Medical Sciences (CACMS) to monitor data management.

3.4 Study Time Frame

The duration of the study for each participant will be 34 weeks: 2 weeks before randomization as eligibility screening and baseline assessment, 8 weeks of treatment period, and 24 weeks of follow up period after the cessation of treatment (Figure 1. Study Design).

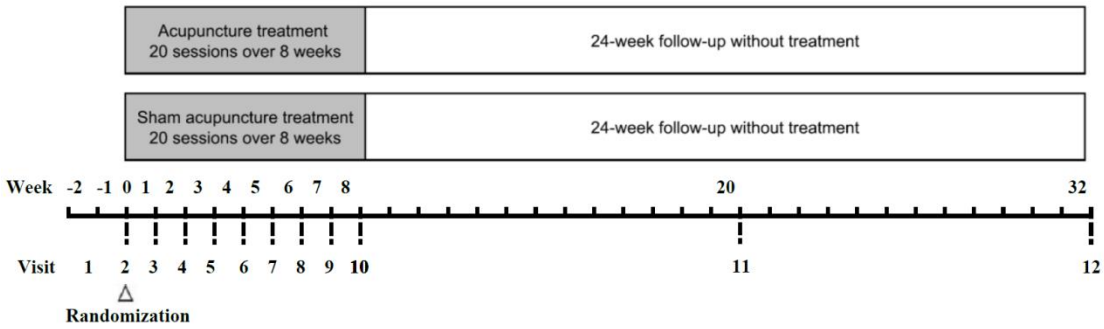

Figure 1. Study Design

There will be twelve clinical visits:

Visit 1 will be scheduled during weeks -1 and -2 as eligibility screening and baseline assessment;

Visit 2 will be scheduled for baseline assessment and randomization;

Visits 3-10 (20 sessions of treatments) will be scheduled for the 8-week treatment period;

Visits 11 and 12 will be scheduled at weeks 20 and 32, respectively, during 24-week follow-up period.

3.5 Trial Flow Chart

The trial flow chart is shown in Figure 2.

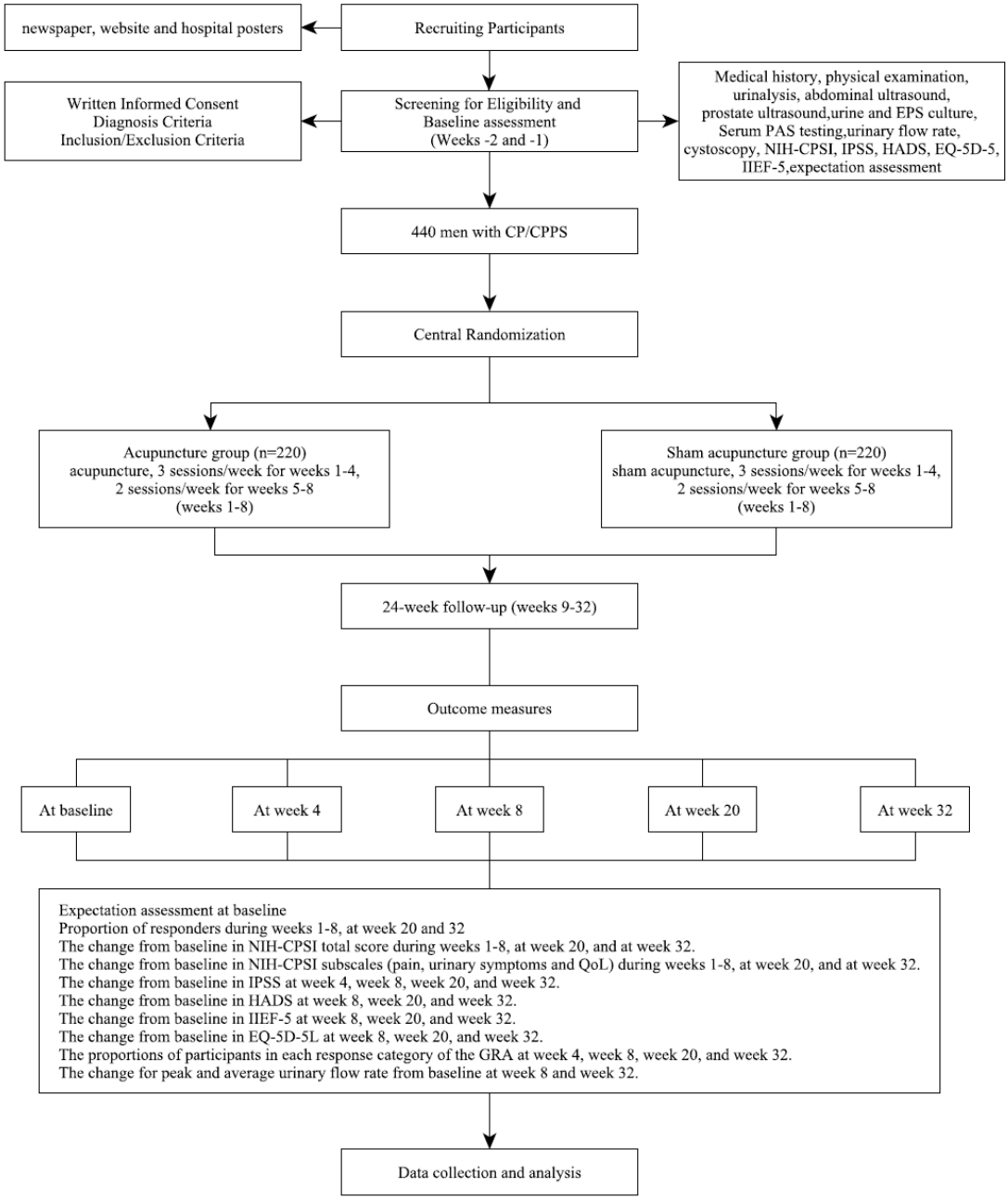

Figure 2. Trial Flow Chart

EPS, expressed prostatic secretion; PSA, prostate-specific antigen; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; IPSS, International Prostate Symptom Score; HADS, Hospital Anxiety and Depression Scale; IIEF-5, International Index of Erectile Function 5; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels.

4. Study Population

4.1 Diagnosis criteria

The diagnosis of CP/CPPS is made according to the NIH CP/CPPS consensus[1], based on medical history, physical examination and a process of exclusion. Urologists are responsible for diagnosis and the differential diagnosis of CP/CPPS.

Participants should have a medical history of persistent discomfort or pain in the pelvic region for at least 3 months in the previous 6 months and an absence of other lower urinary tract pathologies.

Physical examinations will be performed for each participant to detect abnormalities, which include an abdominal examination, digital rectal examination, external genital examination and perineal examination. Abdominal ultrasound will be conducted to assess the condition of other organ and the volume of post-void residual urine. Prostate ultrasound will be conducted to rule out prostatic hyperplasia.

Urinalysis will be performed to rule out urinary tract infections.

A screening "two-glass test"[28] will be performed to collect urine specimens and expressed prostatic secretion (EPS) for analysis and culture to rule out possible infection.

A urinary flow rate will be performed for all patients presenting with CP/CPPS to provide information about the function of the lower urinary tract.

Serum prostate-specific antigen (PSA) testing will be completed to screen for the possibility of prostate cancer.

Cystoscopy will be performed in selected patients (decided by urologists) with hematuria, suspicious cytology, irritative and obstructive voiding symptoms.

4.2 Eligibility criteria

Men will be included in the study if they meet the following criteria:

(1) History of pain perceived in the prostate region and absence of other lower urinary tract pathology for a minimum of three of the past 6 months. In addition, any associated lower urinary tract symptoms, sexual function, and psychological factors should be addressed. Physical examinations, urinary analyses, and urine cultures will be performed for all subjects;
(2) Age 18 to 50 years;
(3) NIH-CPSI total score≥15.

4.3 Exclusion criteria

Men will be excluded from the study if they meet one of the following criteria:

(1) Other types of prostatitis, such as acute bacterial prostatitis, chronic bacterial prostatitis, or asymptomatic inflammatory prostatitis;
(2) Urinary tract infection with a urine culture value >100,000 colony forming units (CFU)/mL, clinical evidence of urethritis, including urethral discharge or positive culture, diagnostic of sexually transmitted diseases (including gonorrhoea, chlamydia, mycoplasma or trichomonas, but not including HIV/AIDS), symptoms of acute or chronic epididymitis;
(3) Prostate, penile, testicular, bladder, or urethral cancer, seizure disorder in any medical history;
(4) Inflammatory bowel disease, active urethral stricture, bladder outlet obstruction, neurologic disease or disorder affecting the bladder, neurologic impairment or psychiatric disorder preventing understanding of consent and self-report scale;
(5) Overactive bladder, neurogenic bladder, interstitial cystitis, glandular cystitis;
(6) Organic disease of the urinary system;
(7) Severe cardiac, lung, cerebrum, liver or renal system disease, or hematopoietic system disease;

(8) Residual urine volume≥100 mL;

(9) Qmax≤15mL/s;

(10) During previous 4 weeks prior to study participation, used androgen hormone inhibitors (finasteride), alpha-blockers (terazosin, doxazosin mesylate. tamsulosin hydrochloride), antibiotics (ciprofloxacin hydrochloride), or any other prostatitis-specific medication (including herbal and Chinese medicine).

5. Subject Recruitment, Screening, Enrolment, and Group Assignment

5.1 Recruitment and Informed Consent

From October 2017 to December 2019, men with CP/CPPS will be recruited via newspaper, website and hospital posters in 10 centers over China. Patients who show interest in the study and meet the basic criteria of the study will sign the written informed consent form (see Appendix 1 Patient Inform Consent) before the formal screening process. The informed consent form will be reviewed and approved by institutional review boards at Guang'anmen Hospital, China Academy of Chinese Medical Sciences, and individual clinical site.

5.2 Screening and Baseline Assessment

On patients' official Visit 1 (screening visit) to hospital, they will sign the written informed consent form. Research assistants of each site will record their demographic information, course of disease and previous treatments. Urologists are responsible for the diagnosis and the differential diagnosis of CP/CPPS.

Patients will receive a series of procedures to screen for eligibility, which will take approximately two weeks (weeks -1 to -2). To use the funds rationally and for consideration of the convenience of participants, the procedures will be scheduled step by step (Figure 3. Subject Flow Chart), and the eligibility criteria will be verified timely during the process. Those fails in one step will not receive further screening. During the screening periods, participants will not receive any therapy for CP/CPPS.

The screening procedures include (in sequence):

(1) The medical history, demographic information and previous treatments;

(2) Chinese-version National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)[29, 30];

(3) Physical examinations (abdominal examination, digital rectal examination, external genital examination and perineal examination);

(4) Urinalysis

(5) Abdominal ultrasound and prostate ultrasound will be performed;

(6) Urine and EPS culture;

(7) Serum PAS testing;

(8) Urinary flow rate;

(9) Cystoscopy, if needed.

Participants who are still eligible after the examinations will complete the baseline outcome assessment questionnaires at home, which include International Prostate Symptom Score (IPSS)[31, 32], the Hospital Anxiety and Depression Scale (HADS)[33], International Index of Erectile Function 5 (IIEF-5)[34], European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)[35], and participants' expectation assessment. The NIH-CPSI will completed again.

To eliminate the possible influence of invasive examinations on baseline assessment as much as possible, participants should complete the baseline questionnaires several days after the examinations, preferably on the last day of the screening period. During participants' Visit 2 to hospital, research assistants will collect the questionnaires and verify the eligibility.

Note: Although the eligibility screening and baseline assessment are interpreted as Visit 1 and Visit 2, participants might need to visit the hospital more than twice during the process. The clinical site can arrange the procedures of examinations in accordance with the rapidity of each examination in their own hospital to save participants' time and visits to hospital.

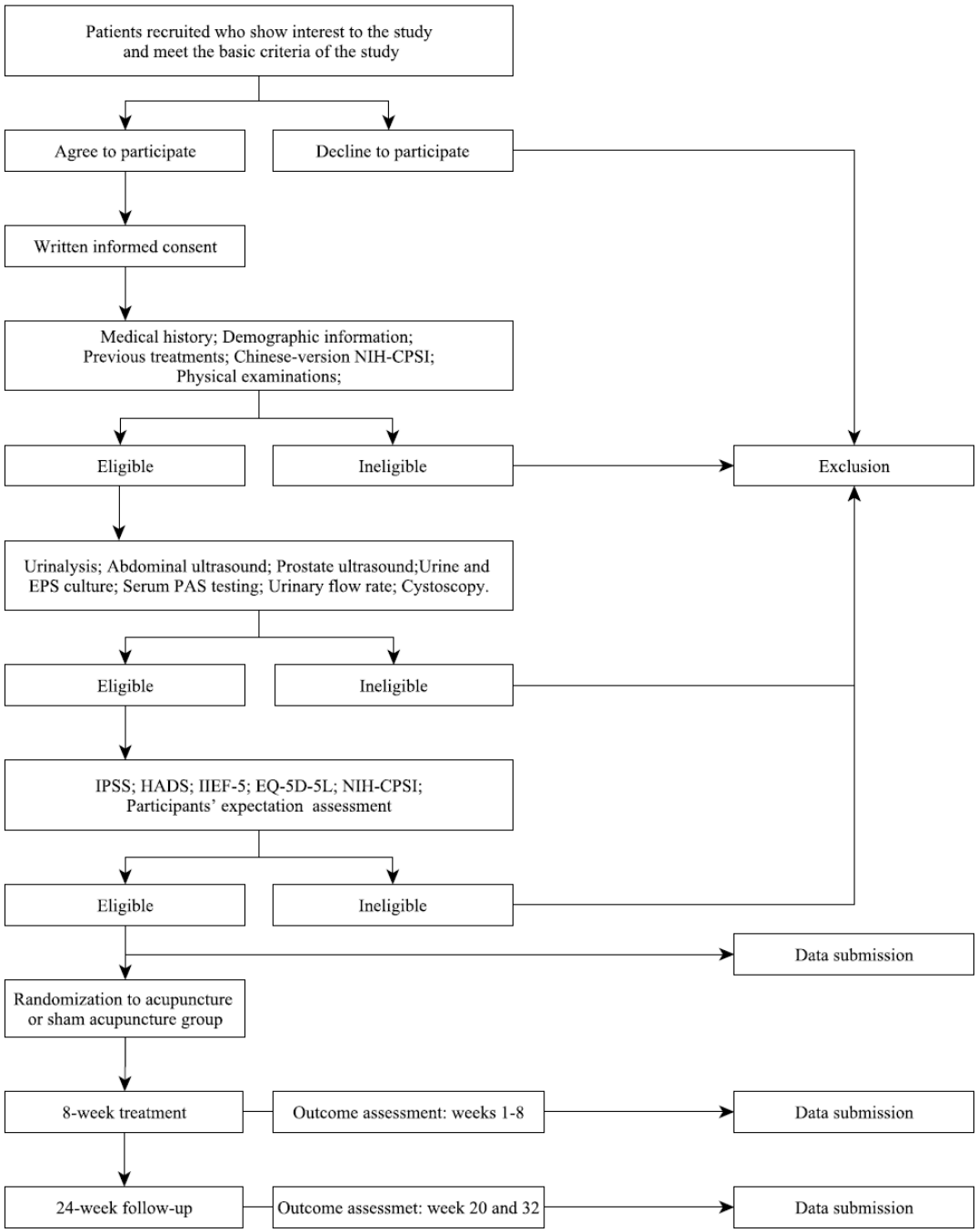

Figure 3. Subject Flow Chart

EPS, expressed prostatic secretion; PSA, prostate-specific antigen; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; IPSS, International Prostate Symptom Score; HADS, Hospital Anxiety and Depression Scale; IIEF-5, International Index of Erectile Function 5; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels.

5.3 Group Assignment

On patients' Visit 2 to hospital, eligible participants will be randomly assigned either to acupuncture group or sham acupuncture group. The randomization will be completed by Acupuncturists. The details of the central randomization will be described below.

6. Randomization and Blinding

6.1 Randomization

In this study, we will use permuted blocks randomization, stratified according to center. A web-response system of Central Randomization System for Clinical Research (designed by Clinical Evaluation Center, China Academy of Chinese Medical Sciences) will be applied in our trial. The allocation sequence will be generated by Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences using statistical analysis software SAS 9.4 with "proc plan" program. After production, the sequence will be signed and sealed by the staff who produce it and kept by other staff who take no part in this trial. It will not be allowed to be checked by anyone except the top system administrator.

Only acupuncturists in each center will have access to random numbers and group allocation prior to treatment through the web. Participants will be randomly assigned to the acupuncture or sham acupuncture group at 1:1 ratio.

6.2 Blinding

Research assistants, statisticians, participants, and outcome assessors will be blind to treatment allocations. Only acupuncturists are aware of the group allocation to administrate treatments.

Participants in the sham acupuncture group will receive minimally invasive, superficial needle insertion of 2-3mm at non-acupoints. Treatment protocol will be similar to that of the acupuncture group, and the acupuncturists will be trained to perform the same needling rituals in both groups.

To test the success of blinding, within 5 minutes after treatment (sessions 19 or 20) at week 8, participants will be told that there are two kinds of acupuncture methods, which are the traditional acupuncture where the insertion is relatively deep, and the minimal acupuncture at non-acupoints where the insertion is relatively shallow; and participants will be randomly assigned to receive traditional acupuncture or minimal acupuncture at non-acupoints at 50% chance respectively. Participants will then be asked to answer the question that "Do you think you have received traditional acupuncture in the past weeks?" The participants will be able to choose one of the following options as the answer: "Yes", "No" or "Unclear".

7. Interventions

The intervention scheme of this trial will be based on consensus meeting with acupuncturists and acupuncture experts from CACMS and result of prior study. Sanyinjiao (SP6), Zhongliao (BL33), Shenshu (BL23), and Huiyang (BL35) were selected for the acupuncture treatment group. Based on the theories of traditional Chinese medicine (TCM) and acupuncture, the spleen meridian (SP), kidney meridian (KI), and liver meridian (LI) intersect at Sanyinjiao (SP6), one of the most frequently used acupoints for urological disorders. The urinary bladder meridian (BL) is commonly used for urologic disorders, including pelvic pain, lower urinary tract symptoms, and sexual disorders in both male and female patients. SP6 locates slightly above the medial malleolus, posterior to the tibia where the tibial nerve innervates anatomical structures. Previous research supports the possible beneficial effects of sacral nerve stimulation and tibial nerve stimulation on the severity and frequency of chronic pelvic pain[36].

There will be two full-time acupuncturists per center responsible for administration of acupuncture

and sham acupuncture. In general, acupuncturists will be assigned to the same participants throughout the 8-week treatment schedule, except for vacation conflicts and staff turnover. All acupuncturists will be registered TCM practitioners with a clinical acupuncture experience of ⩾2 years. Disposable acupuncture needles (sizes 0.30 ×75, 0.30 ×40 mm and 0.30 ×25 mm, Hwato Brand, Suzhou Medical Appliance Factory, Suzhou, China) will be used in this trial.

Participants in both the acupuncture and the sham acupuncture groups will receive 20 sessions of treatment over an 8-week period after baseline (3 sessions in each of the first 4 weeks [ideally every other day], and 2 sessions in each of the remaining 4 weeks [ideally every two or three days]). Each session will last for 30 minutes.

7.1 Acupuncture

Acupoints of bilateral Zhongliao (BL33), Huiyang (BL35), Shenshu (BL23), and Sanyinjiao (SP6), which will be located according to the WHO Standardized Acupuncture Points Location[37] will be used. Zhongliao (BL33) is located in the sacral region, the third posterior sacral foramen. Huiyang (BL35) is located in the buttock region, 0.5 proportional bone (skeletal) cun (B-cun) lateral to the extremity of the coccyx. Shenshu (BL23) is located in the lumbar region, at the same level as the inferior border of the spinous process of the second lumbar vertebra (L2), 1.5 B-cun lateral to the posterior median line. Sanyinjiao (SP6) is located on the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun superiors to the prominence of the medial malleolus.

With patients in a prone position in relaxation, acupuncturists will use 75% alcohol pads to sterilize the skin around the acupuncture points and then insert Hwato-brand disposable acupuncture needles (sizes 0.30 ×75 and 0.30 ×40 mm) into the acupuncture points. For bilateral Zhongliao (BL33), the needle will be inserted approximately 50–60 mm with a 30°-45° angle in an inferomedial direction. For Huiyang (BL35), the needle will be inserted approximately 50–60 mm in a slightly superolateral direction. For Shenshu (BL23) and Sanyinjiao (SP6), the needles will be inserted vertically with a depth of 25–30 mm. For acupuncture at BL23, BL35 and SP6, needle insertion will be followed by acupuncture manipulation of lifting and thrusting combined with twirling and rotating to reach deqi, which is defined as the sensation of aches, soreness, swelling, heaviness or numbness in the needle location region[38]. Manipulations will be performed once every 10 minutes, 30 seconds each time. Immediately after needle removal, the acupuncturist will gently press the needled skin area with dry sterilized cotton balls to avoid bleeding.

7.2 Sham Acupuncture

The participants in the sham acupuncture group will receive minimally invasive, superficial needle insertion of 2-3mm at bilateral sham BL23, BL33, BL35 and SP6 (non-acupuncture points lateral to the corresponding acupoints, 15 mm to BL23, BL33 and BL35; 10 mm to SP6). Treatment protocol will be similar to that of the acupuncture group, but Hwato-brand disposable acupuncture needles (size 0.30 × 25 mm) will be inserted at sham acupoints with depths of 2–3 mm without manipulation[39].

7.3 Standardization of Treatment

Guang'anmen Hospital will supply single-use, sterile, and disposable acupuncture needles for each participating site.

Two certified acupuncturists will be needed in each site to perform all the treatments, while the 20 sessions of treatment for each participant should be completed by one specific acupuncturist. All acupuncturists in this trial are required to have completed their professional training in acupuncture in universities of Chinese medicine with more than 2 years clinical experience.

To improve the consistency of treatments, acupuncturists at each site will receive trial-specific

(standardized operation procedure) training at the project launching session. The training will include detailed acupuncture points locations and manipulation methods in both the acupuncture and sham acupuncture groups. A video showing detailed information on how to perform the acupuncture and sham acupuncture will also be provided.

To avoid the inadvertent unblinding, acupuncturists will not tell anyone else the treatment allocation. The contacts between acupuncturists and participants should be as short as possible.

The acupuncturists will be instructed to follow standardized operating procedure:

Step 1:

The participant is piloted by research assistant to hospital bed, which was screened-off separately one-by-one. Their companions will be guided to wait outside the clinic, if any. The specific acupuncturist accepts the patient and asks the participant to take a rest. After a short while, acupuncturist instructs the patient to lie prone on the bed, with lumbosacral and lower shin areas exposed, and tell the participant that a 30-minute treatment will be given.

Before the first session of treatment, participants will be told that they may receive either the traditional acupuncture or sham acupuncture group, and they may not have sensation during the 30-minute retention of acupuncture needles out of body adaptation.

Step 2:

After sterilization, the acupuncturist will start to conduct administration according to treatment protocol. The acupuncture group will receive deep insertion of needles at acupuncture points, while the sham acupuncture group will receive superficial insertion of needles at non-acupuncture points.

Step 3:

After insertion of needles at appropriate areas, acupuncturist will conduct the first needle manipulation in the acupuncture group for 30 seconds, while in the sham acupuncture group, acupuncturists will hold the handles of acupuncture needles gently for 30 seconds without manipulations.

Step 4:

After 10 minutes, acupuncturist will conduct the second needle manipulation in the acupuncture group for 30 seconds, while in the sham acupuncture group, acupuncturists will hold the handles of acupuncture needles gently for 30 seconds without manipulations.

Step 5:

After another 10 minutes, acupuncturist will conduct the third needle manipulation in the acupuncture group for 30 seconds, while in the sham acupuncture group, acupuncturists will hold the handles of acupuncture needles gently for 30 seconds without manipulations.

Step 6:

After another 10 minutes, acupuncturist will remove the needles.

7.4 Permitted and Prohibited Concomitant Treatments

The use of medications or other therapies specific for symptoms of CP/CPPS will be discouraged during this trial, such as α blocker. However, medication use is allowed for intolerable symptoms as long as it is recorded accordingly, including the name and the dosage of the medication use. We will compare the proportion of subjects using rescue medications between groups.

8. Subject Evaluation

8.1. Outcomes Measurements

8.1.1 Primary Outcomes

The two co-primary outcomes include the proportions of responders at week 8 and week 32. The

responder is defined as a participant with a decline of 6 points or more from baseline in the total score of the Chinese version NIH-CPSI. As a validated, self-reported questionnaire, NIH-CPSI is widely used to assess CP/CPPS symptoms[29, 30]. NIH-CPSI consists of 9 items divided into 3 discrete domains: pain (0–21 points), urinary symptoms (0–10 points) and QoL (0–12 points), with a total score of 0–43 points (a higher score indicates worse symptoms). A decline of at least 6 points in NIH-CPSI has been identified as the minimal clinically important difference (MCID)[25].

8.1.2 Secondary Outcomes

Secondary outcomes include:

(1) Proportion of responders during weeks 1-7, and at week 20.

The NIH-CPSI will be assessed once a week during treatment, and at week 20 and week 32. The responder is defined as who has a decline of 6 or more than 6-point from baseline measured by using the NIH-CPSI.

(2) The change from baseline in NIH-CPSI total score during weeks 1-8, at week 20, and at week 32.

(3) The change from baseline in NIH-CPSI subscales (pain, urinary symptoms and QoL) during weeks 1-8, at week 20, and at week 32.

(4) The change from baseline in IPSS at week 4, week 8, week 20, and week 32.

IPSS is a valid, reliable and sensitive measure for patients with lower urinary tract symptoms (LUTS); it is widely used in clinical practice and research to determine the severity of LUTS, including incomplete bladder emptying, frequency of urination, intermittency, urgency, weak urine stream, straining and nocturia[31, 32]. Each of the questions is rated from 0 (not at all) to 5 (almost always); severity of LUTS can be graded as mild (0–7), moderate (8–19) or severe (20–35). IPSS will be assessed at the end of the 4th, 8th, 20th, and 32nd week.

(5) The change from baseline in HADS at week 8, week 20, and week 32.

HADS will be assessed at the end of the week 8, week 20, and week 32. HADS is made up of 7 items for the assessment of depression and anxiety; the completion of this scale usually requires 2–5 minutes[33].

(6) The change from baseline in IIEF-5 at week 8, week 20, and week 32.

Chinese version IIEF-5 will be assessed at the end of the week 8, week 20, and week 32. The IIEF-5 consists of 15 items in 5 domains with a total score ranging from 5 to 25 (mild ED, 12–21; moderate ED, 8–11; severe ED, 5–7); it is a psychometrically valid and reliable instrument with high sensitivity and specificity for detecting treatment effects in patients with ED of a broad spectrum of aetiology[34].

(7) The change from baseline in EQ-5D-5L at week 8, week 20, and week 32.

The EQ-5D-5L will be assessed at the end of week 8, week 20, and week 32. The EQ-5D-5L is a generic instrument designed for self-completion and postal surveys; it is well-established and suitable for evaluation of QoL in participants with CP/CPPS[35].

(8) The proportions of participants in each response category of the Global Response Assessment (GRA) at week 4, week 8, week 20, and week 32.

The proportions of participants in each response category of the GRA in the two groups after treatment will be measured at the end of the week 4, week 8, week 20, and week 32. GRA consists of 7 response categories: markedly worsened, moderately worsened, slightly worsened, no change, slightly improved, moderately improved, and markedly improved. We will identify a participant who reports "moderate" or "marked improvement" as a responder[40].

(9) The change for peak and average urinary flow rate from baseline at weeks 8 and 32.

Peak and average urinary flow rates will be measured at weeks 8 and 32.

(10) Expectation assessment at baseline

Expectation assessment will be assessed at baseline, which includes two brief questions to investigate whether patients are confident that acupuncture treatment will help their CP/CPPS: “In general, is acupuncture effective for controlling the illness?”, “Do you think acupuncture will be helpful to improve your CP/CPPS symptoms?” For each question, participants could choose “Yes”, “No” or “Unclear” as the answer.

8.2 Evaluation Procedures

8.2.1 Schedule of Evaluation

	STUDY PERIOD											
	Enrolment	**Allocation**	**Treatment**								**Follow-up**	
TIMEPOINT (W, week)	**-2 and -1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**20**	**32**
Enrolment												
Informed consent	×											
Eligibility criteria	×											
Demography characteristics	×											
Allocation		×										
Interventions												
Acupuncture			×	×	×	×	×	×	×	×		
Sham acupuncture			×	×	×	×	×	×	×	×		
Assessments												
Proportion of responders										×		×
NIH-CPSI	×		×	×	×	×	×	×	×	×	×	×
IPSS	×					×				×	×	×
IIEF-5	×									×	×	×
HADS	×									×	×	×
EQ-5D-5L	×									×	×	×
GRA						×				×	×	×
Expectation assessment	×											
Urinary flow rate	×									×		×

Table 2. Enrolment, Intervention and Evaluation Schedules

Abbreviations: NIH-CPSI National Institutes of Health Chronic Prostatitis Symptom Index, IIEF-5 International Index of Erectile Function 5, HADS Hospital Anxiety and Depression Scale, GRA Global Response Assessment, EQ-5D-5L Five-level EuroQol five-dimensional questionnaire, VAS visual analogue scale

8.2.2 Baseline assessment

The baseline demographic information and outcome assessment will be collected in Visit 1 and Visit 2, which has been described in 5.2 Screening and Baseline Assessment.

8.2.3 Eight-week Treatment Phase

During the 8-week treatment (weeks 1-8), Visits 3-10 are scheduled weekly.

Participants will complete the NIH-CPSI every week; IPSS and GRA at weeks 4 and 8; and IIEF-5, HADS and EQ-5D-5L at week 8. We will provide a self-assessment questionnaires/scales notebook for each participant. They will be asked to complete the notebook at home weekly, and bring the manual to hospital the following week. Data from the notebook will be checked by outcome assessors, and then entered into the electronic database by CRC. Both the outcome assessors and CRC are unaware of the group allocation. The data from the notebook will be the raw data for analysis.

The urinary flow rate will be collected at week 8 after the treatment at hospital.

Within 5 minutes after treatment (sessions 19 or 20) at the week 8, the success of blinding will be assessed by outcome assessors at hospital.

8.2.4 Twenty-four-week Follow-up Phase

During the 24-week follow-up (weeks 9-32), Visit 11 will be scheduled at week 20, and Visit 32 will be scheduled at week 32.

Participants will complete the NIH-CPSI, IPSS, GRA, IIEF-5, HADS and EQ-5D-5L at weeks 20 and 32. Urinary flow rate will be completed at week 32.

For the results of Visit 11 (week 20), the notebook could be mailed to hospitals or submit to hospitals by participants in person. At weeks 32, participants need to visit the hospital in person for the examination of urinary flow rate, therefore they will bring the notebook to hospital by themselves.

9. Safety Assessment and Subject Withdrawal

9.1 Adverse Events

We will handle and document the adverse events using the standard operating procedures for monitoring and reporting all adverse events.

According to their potential association with the treatment, AEs will be categorized as treatment-related or non-treatment-related within 24 hours after their occurrence. Treatment-related adverse events include pain, haematoma, localized infection, broken needle, fainting, nausea, headache, dizziness, insomnia, vomiting, or palpitations during or after treatment.

Serious adverse events will be defined as events requiring hospitalization, causing disability or impaired ability to work, threatening life or resulting in death. Any serious adverse events will be immediately reported to the principal investigator (ZL) and Medical Ethics Committee at individual clinical site and Guang'anmen Hospital within 24 hours. A research assistant will be required to record serious adverse events, including information on the time of occurrence, severity, duration, measurement, management, and its outcome.

All the serious adverse events and adverse events will be recorded and measured by participants themselves, acupuncturists and urologists through the whole trial. Guang'anmen Hospital has insurance covering for harm associated with the interventions during this trial.

9.2 Subject Withdrawals

Participants may withdraw from the trial at any time at their own discretion; the investigator may also determine whether it is in the best interest of subjects to withdraw from the trial due to worsening of symptoms, or the occurrence of a serious adverse event.

10. Administrative Responsibilities

10.1 Institutional Review Board

For every study site, only when the trial protocol is approved by the institutional review board, the enrollment of participant will begin, but all should be after July 25, 2017.

10.2 Funding

This study was supported and funded by the “the first batch of key research program in the 13th Five-year” (ZZ10-012) by the China Academy of Chinese Medical Sciences. The funder will not interfere the data collection, analysis, and interpretation; nor in the finishing of the manuscript, and decision to submit the manuscript for publication.

10.3 Compliance Improvement

(1) Participants should participate in the trial voluntarily, and sign the informed consent;

(2) Researchers assistants should record the participants’ contact information in detail for the convenience of follow-up;

(3) Before randomization, researchers should inform the participants that all the cost related to the examination and treatment would be exempted;

(4) Each participant’s participation in the trial should be taken charge of by the same research assistant and outcome assessor throughout the trial. They will explain the contents of notebook to participants if necessary, remind the participants of their schedule by phone or we-chat, and instruct participants to complete the notebook.

(5) For participants who have less compliance, we will still follow them up to record outcome measurements through phone or message;

10.4 Data Management

10.4.1 The Raw Data Management and Archiving

We will use Remote Data Capture (RDC) system to perform data entry. The research assistants will fill out all the electrical CRF through RDC system. Researchers will inspect the eCRF, and signed electrically for the eCRF going into effect. The eCRF and the trace of eCRF revising will be left in the Oracle database.

10.4.2 Data Entry and Storage

10.4.2.1 Database Building and Testing, Data Entry Interface

The eCRF will be noted through CDISC SDTM standard, and the data entry interface will be generated through the Oracle Clinical software. The data entry interface should be in accordance with the paper version CRF as close as possible. The inputted data will be stored in the Oracle database. After preliminarily setting up the database, the entry clerks will input some analog data according to the CRF to test the database. The testing contains: (1) the agreement of the data entry interface and the paper version CRF; (2) the agreement of the exported data from the database and the analog data; (3) the agreement of the structure of the exported database and the paper-version CRF. After the testing, data administrators should revise the database and make a testing report. Then they electrically signed on the approval page of the database to indicate that the testing is completed. The electrical files of the analog CRF, Noted CRF, screenshot of the data entry interface, database testing report, and the approval page of the database should be saved. If the database updates during the trial, the electrical files mentioned above will also need to be updated.

10.4.2.2 Data Entry and Inspection

The research assistants take charge of the data entry for our trial. Before the entry, all the research assistants will accept the related training according to the data entry handbook. Researchers will inspect

the database, and then sign electronically to let the data go in to effect.

10.4.3 Data Verification and Problems Solving

Researchers will verify the data through Data Verification Plan (DVP) approved by the data administrator and the statisticians. Data queries will be inputted to a data query database, and form the DCF. After being inspected, the DCF will then be handed back to the original site, and the researchers of the site should answer the queries. Any revision of the database will be recorded through the RDC software.

10.4.4 Medical Coding

A data administrator who has the medical background will take charge of the medical coding. The contents of the coding are the clinical history, adverse events, and combined medication use if any. The clinical history and adverse events will be coded through MedDRA dictionary (Version 13.0), and the combined medication use will be coded via WHO DD dictionary (Version 2007.03). The lead researchers will verify the coded e-files.

10.4.5 Data Report

Data report contains the aspects as followed: (1) members of the project; (2) disagreement from the primary data management plan; (3) actual finish time of every project; (4) problems and solutions during data management (if have any); (5) reconstruction of the database (if have any); (6) distribution of the participants; (7) participants who disobey the trial protocol; (8) classifying plan of the statistical analysis population. Data report will be performed monthly since the first entry of the eCRF.

10.4.6 Data Auditing and Blinding Review

When the data checking is finished, a data auditing and blinding review meeting will be hold. In the meeting, the data administrators, statisticians, researchers, clinical inspectors, and other related members will have a discussion on the following items according to the data management report and the data lists:

•Distribution of the participants;
•Protocol disobeying or not;
•Possible outlier;
•Baseline data;
•Outcomes;
•Statistical analysis plan.

Participants will be classified to their suitable statistical analysis sets according to the definition in the protocol. No patient can be excluded from the analysis, unless getting the permission of the meeting participants. All the meeting participants will sign the data locking consent, and the data auditing resolution.

10.4.7 Database Locking

The database will be locked if it fulfills all the aspects as followed: All the queries have been solved, and the database has been updated; No query has been found through the data inspection; The medical coding has been completed; The plan of the participants' classification has been approved; The final draft of the SAP has been made, and approved by the project leader.

The statisticians and the data administrators will sign the data locking form, and then the database will be locked. The locked database will be sent to the statisticians for further statistical analysis through the data format of SAS.

10.5 Quality Control

(1) To guarantee the quality of the study, the trial protocol will be reviewed and may be revised by

expert acupuncturists, urologist, and statisticians several times.
(2) A central randomization system will be adopted to avoid selection bias.
(3) Strict eligible criteria will be pre-set to restrict the research population. The diagnosis, inclusion and exclusion criteria are designed in accordance with the guidance of NIH Chronic Prostatitis Clinical Research Network;
(4) Trial-specific (standardized operation procedure) extensive training will be given to all the research staff participating the trial at the project launching session. Acupuncturists will be trained on how to use the central randomization system, the standardized manipulation method and needling rituals. Outcome assessors will be trained how to fill the case report form. Clinical Research Assistants (CRC) will be trained to use data entry system.
(5) We will provide a self-assessment questionnaires/scales notebook for each participant. Participants will be asked to complete the notebook at home. During 8-week treatment period and the last assessment (Visit 12), participants will bring the notebook to hospital themselves. For the outcome assessment at week 20, they can mail the notebook to hospital or bring the manual to hospital themselves. The data from the notebook will be the raw data for analysis, and will be checked and recorded in CRF by outcome assessors. The data in CRF will be entered into the electronic database by CRC in a double-entry method. The statistical analysis of the data will be calculated by independent statisticians. The participants, outcome assessors, CRC and statisticians will all be unaware of the group allocation.
(6) Participation processes in the trial of the same participants should be taken charge of by the same acupuncturist, research assistant and outcome assessor throughout the trial.
(7) A 3-level monitoring system will be established to periodically assess the performance of the trial: Level 1, Inspection; Level 2, Supervision; Level 3, Audit. Inspection: The investigator of each center will designate at least one researcher who take no part in the intervention to conduct a quality review of the center; Supervision: for each center, the study organizer (Guang'anmen Hospital, China Academy of Chinese Medical Sciences) will designate at least three researchers who take no part in the intervention to monitor the quality of the studies of that center; Audit: the China Academy of Chinese Medical Sciences will designate at least five quality control personnel to conduct a quality audit of the research.

11. Statistical consideration

11.1 Sample Size Calculations

Sample-size calculations were based on 90% power to detect a difference of 17% between response rates in the two groups (63.7% in the acupuncture group compared with 46.7% in the control group) for the primary outcome, defined as a decline of 6 or more points in the NIH-CPSI total score[21]. These values are equivalent to an odds ratio of 2.0. On the basis of a two-sided alpha level of 0.05, we calculated that a sample of 440 participants will be required (220 in each group). This proposed sample size includes a 15% increase to account for dropouts. To control for type I error, the two time points in the primary outcomes will have to be positive in order for the trial to prove the efficacy of acupuncture.

11.2 Statistical Analysis

Details of the pre-specified statistical analyses can be found in the Statistical Analysis Plan (SAP). Prior to database lock and before code breaking, a final version of the SAP shall be issued and approved by the study statistician, and the principal investigator. The SAP will define all "pre-specified, planned analyses" and provide the general specifications for the analysis of the data to be collected and presented in the Clinical Study Report.

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Appendix 1 Patient Informed Consent

Dear male participants:

If your doctor thinks you have chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), we invite you to participate in this study aiming to evaluate the effectiveness and safety of acupuncture for management of CP/CPPS. This study is supported and funded by China Academy of Chinese Medical Sciences (ZZ10-012).

Before you decide to participate in the study, please read the following information carefully. It is helpful for you to know this study, understand why the study is performed, the study procedures, the duration and benefits of the study, risks and potential discomforts during and after study participation. If you like, you can also discuss this study with your relatives and friends, or consult doctors for explanation and help to make the decision.

Introduction

I. The prevalence of CP/CPPS is high, and it affects approximately 10–16% of men worldwide. The diagnosis of CP/CPPS is mainly based on symptoms. Definitive treatments for CP/CPPS are still lacking, and pharmacological interventions are accompanied with adverse effects. Previous studies suggest that acupuncture may be a potential treatment for CP/CPPS.

In this study, a randomized controlled trial design will be used and we aim to evaluate the effectiveness and safety of acupuncture for relieving symptoms of CP/CPPS. This study will be carried out simultaneously in 10 hospitals all over China, and we expect a total number of 440 participants for voluntary participation.

II. Exclusion criteria

(1) Prostate, bladder, or urethral cancer, seizure disorder in any medical history;

(2) Inflammatory bowel disease, active urethral stricture, neurologic disease or disorder affecting the bladder, liver disease, neurologic impairment or psychiatric disorder preventing understanding of consent and self-report scale;

(3) Urinary tract infection with a urine culture value >100,000 colony forming units (CFU)/mL, clinical evidence of urethritis, including urethral discharge or positive culture, diagnostic of sexually transmitted diseases (including gonorrhoea, chlamydia, mycoplasma or trichomonas, but not including HIV/AIDS), symptoms of acute or chronic epididymitis;

(4) Residual urine volume≥100 mL;

(5) Qmax≤15mL/s;

(6) During previous 4 weeks used androgen hormone inhibitors (finasteride), alpha-blockers (terazosin, doxazosin mesylate. tamsulosin hydrochloride), antibiotics (ciprofloxacin hydrochloride), or any other prostatitis-specific medication (including herbal and Chinese medicine).

III. What do you do next, if you decide to participate?

Before your enrollment in the study, your medical history will be collected and you will receive a series of examinations to determine whether you are eligible to participate in the study, including physical examination, urinalysis and a urine culture, collection of expressed prostatic secretion, abdominal ultrasound, prostate ultrasound, serum PAS testing and urinary flow rate (certain patients may also need to receive cystoscopy). You will also need to complete a series of questionnaires to assess the severity of the disease and the influence on quality of life.

2. If the results of the above screening examinations meet the inclusion criteria and you are willing to participate in this study, you will be invited to continue study participation in the following steps:

(1) Based on the random number generated from the computer, the doctor will assign you to either

the traditional acupuncture or sham acupuncture group. Participants in the traditional acupuncture group will receive deep needling on the Zhongliao (BL33), Huiyang (BL35), Shenshu (BL23), and Sanyinjiao (SP6) for 30 min; participants in the sham acupuncture group will receive minimally invasive, superficial needle insertion of 2-3mm on the sham Zhongliao (BL33), Huiyang (BL35), Shenshu (BL23), and Sanyinjiao (SP6).

(2) In the study, Hwato brand disposable needles (Suzhou Medical Appliance, Jiangsu, China, Jiangsu Food, Drug, and Medical Appliance Administration production approval No.: 2001–0020, Registration No:2270202 in Year 2004) will be used.

(3) The duration of this study is 34 weeks in total for a patient including 2-week baseline assessment, 8-week treatment, and 24-week follow up. Frequency and duration of acupuncture: 3 sessions per week in weeks 1-4, and 2 sessions per week in weeks 5-8. The participants will receive 20 sessions of treatment in total.

(4) During the study period, you need to complete the questionnaires faithfully.

3. Other requirements for your cooperation

As a participant of this study, you will have some relevant responsibilities, such as adherence to the schedule for examination, treatment, and clinical follow-up. Additionally, you are also responsible for reporting any changes in your physical and mental status to your doctor during the study process regardless of whether you think these changes are related to the study or not. You should follow the scheduled appointments with the doctor to come to the hospital for treatment. Your follow-up is very important because the doctor will determine whether the treatment that you are receiving really works and their safety profile.

During the study, you are not allowed to use other treatments for CP/CPPS. However, if you use, please inform the doctor the treatment you received in detail. Every use of specialized treatment should be recorded as required.

IV. Potential benefits of study participation

You may benefit from this study. The benefits may include improvement of symptoms, even by sham acupuncture. The study may also help doctors and researchers to further evaluate the efficacy of acupuncture for CP/CPPS. The information will be beneficial in the management of other patients with a similar condition in the future. If you decide to participate in the study, you will get relevant physical and biochemical examination as well the study intervention for free during the study period.

V. Potential side effects, risks, discomforts, and inconveniences

The doctors will make every effort to prevent and treat any side effects brought on by this study. During treatment, you may feel soreness, numbness, heavy, distension sensation, etc., which are normal reactions to acupuncture. Acupuncture treatment may have some adverse effects, but it is rare and mild. You may feel fainting due to your individual physique or emotional stress when receive acupuncture needling. Your symptoms should be relieved after the cessation of acupuncture treatment and rest. Bleeding, hematoma, and other phenomena may occur after acupuncture treatment, and these phenomena should disappear after applying local pressure. If infection occurs in the needle site, your doctor will handle it timely. With the treatment following the study protocol in the study, if you experience adverse reactions and events related to acupuncture treatment, please feel free to call your doctor for help. The doctor will provide you timely treatment. If injuries have been confirmed and are caused by adverse reactions and events of the study, the study group will deal with them appropriately in accordance with relevant provisions. If you experience any discomfort or new change of your symptoms, or any other unforeseen circumstances during study period, regardless of whether these

events are relevant with treatment of the study or not, you shall promptly notify your doctor, and he / she will evaluate the condition and give you appropriate medical treatment.

VI. Payments/compensation for participation

If you participate in the study, during the study, you will get relevant physical and biochemical examination and acupuncture treatment for free. If adverse events occur during the study, they will be managed accordingly by medical experts who will also identify whether they are related to the study or not. The treatment and examination required for your concomitant diseases nonrelated to the study will not be free of charge.

VII. Confidentiality of personal information

All the information related to your participation in this study will be kept confidential by the institute where your participation takes place. Only the institutes responsible for the study, clinical research institutes, and ethics committees may have access to your medical records. Your name will not appear in any publication or report related to this study. We will make every effort to protect the privacy of your personal medical information as per legal requirements and laws.

VIII. How to acquire extra information?

You can ask any questions about the study at any time and will get answers timely. If we notice any new information that may affect your willingness and decision to continue participating in the study, the doctor will keep you informed

IX. Can you voluntarily choose to participate in or withdraw from the study?

Whether to participate in this study or not entirely depends on your desire. You can refuse to participate in the study, or withdraw from the study at any time during the study, which will not affect the relationship between you and your doctor and will not affect your medical interests or interests in other areas. For the consideration of your best interests, doctors or researchers may terminate your participation in this study at any time. If you withdraw from the study for any reason, you may be asked for information related of acupuncture treatment or the use of other medications during your participation of the study. If the doctor considers it necessary, you may also be asked to have some laboratory tests and physical examinations performed.

X. What you need to do now?

Decide whether to participate in this study or not. Before you make the decision to participate in the study, please ask your doctor if you have any concerns.

Thank you for reading the above information. If you decide to participate in this study, please tell your doctor, he / she will help you make arrangement for the study.

Please keep this document for your own record.

Informed Consent: Signature Page

Study title: Acupuncture for chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial

Organizer of this study: Guang'anmen Hospital, China Academy of Chinese Medical Sciences

Collaborative institute:

Statement of agreement:

I have read the above information about this study and have the opportunity to discuss this study with my doctor and ask questions. All my questions were answered satisfactorily. I understand the potential risks and benefits from participation in this study. I understand the participation of the study is voluntary and I confirm that I was given sufficient time for consideration of study participation. I confirm that I understand that:

I can always ask the doctor for additional/more information.

I can withdraw from the study at any time without discrimination or retaliation and my medical treatment and interests will not be affected.

I understand that if I withdraw from the study, I will tell the doctor the changes of my disease condition and complete the relevant physical and biochemical examinations if needed, which will be very helpful for the whole study.

If I need to take any other medications due to the changes of my medical condition, I will seek medical advice from the doctor beforehand or afterwards tell the doctor truthfully.

I agree to allow the research institute, collaborative institutes, and ethics committees to inspect the data relevant to my study participation.

I will receive a signed and dated copy of the informed consent form.

Finally, I decide and agree to participate in this study and ensure the adherence to doctor's orders to the best I can.

Signature of patient: Year month day

Telephone:

I confirm that I have explained this study in detail to the patient, including patient's rights as well as the potential benefits and risks, and have given the patient a signed copy of the informed consent form.

Signature of doctor: Year month day

Office phone number of doctor:

Appendix 2 Outcome Assessment Tools

List of the outcome assessment tools:

National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)

International Prostate Symptom Score (IPSS)

Hospital Anxiety and Depression Scale (HADS)

International Index of Erectile Function 5 (IIEF-5)

European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)

Expectation Assessment

National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?	Yes	No
a. Area between rectum and testicles (perineum)	☐1	☐0
b. Testicles	☐1	☐0
c. Tip of the penis (not related to urination)	☐1	☐0
d. Below your waist, in your pubic or bladder area	☐1	☐0

2. In the last week, have you experienced:	Yes	No
a. Pain or burning during urination?	☐1	☐0
b. Pain or discomfort during or after sexual climax (ejaculation)?	☐1	☐0

3. How often have you had pain or discomfort in any of these areas over the last week?

☐0 Never
☐1 Rarely
☐2 Sometimes
☐3 Often
☐4 Usually
☐5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGING

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

☐0 Not at all
☐1 Less than 1 time in 5
☐2 Less than half the time
☐3 About half the time
☐4 More than half the time
☐5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

☐0 Not at all
☐1 Less than 1 time in 5
☐2 Less than half the time
☐3 About half the time
☐4 More than half the time
☐5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

☐0 None
☐1 Only a little
☐2 Some
☐3 A lot

8. How much did you think about your symptoms, over the last week?

☐0 None
☐1 Only a little
☐2 Some
☐3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

☐0 Delighted
☐1 Pleased
☐2 Mostly satisfied
☐3 Mixed (about equally satisfied and dissatisfied)
☐4 Mostly dissatisfied
☐5 Unhappy
☐6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 =_____

Urinary Symptoms: Total of items 5 and 6 =_____

Quality of Life Impact: Total of items 7, 8 and 9 =_____

International Prostate Symptom Score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times	
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

1. I feel tense or 'wound up':	**8. I feel as if I am slowed down:**
3 Most of the time	3 Nearly all the time
2 A lot of the time	2 Very often
1 From time to time, occasionally	1 Sometimes
0 Not at all	0 Not at all
2. I still enjoy the things I used to enjoy:	**9. I get a sort of frightened feeling like 'butterflies' in the stomach:**
☐0 Definitely as much	☐0 Not at all
☐1 Not quite so much	☐1 Occasionally
☐2 Only a little	☐2 Quite Often
☐3 Hardly at all	☐3 Very Often
3. I get a sort of frightened feeling as if something awful is about to happen:	**10. I have lost interest in my appearance:**
☐3 Very definitely and quite badly	☐3 Definitely
☐2 Yes, but not too badly	☐2 I don't take as much care as I should
☐1 A little, but it doesn't worry me	☐1 I may not take quite as much care
☐0 Not at all	☐0 I take just as much care as ever
4. I can laugh and see the funny side of things:	**11. I feel restless as I have to be on the move:**
☐0 As much as I always could	☐3 Very much indeed
☐1 Not quite so much now	☐2 Quite a lot
☐2 Definitely not so much now	☐1 Not very much
☐3 Not at all	☐0 Not at all
5. Worrying thoughts go through my mind:	**12. I look forward with enjoyment to things:**
☐3 A great deal of the time	☐0 As much as I ever did
☐2 A lot of the time	☐1 Rather less than I used to
☐1 From time to time, but not too often	☐2 Definitely less than I used to
☐0 Only occasionally	☐3 Hardly at all
6. I feel cheerful:	**13. I get sudden feelings of panic:**
☐3 Not at all	☐3 Very often indeed
☐2 Not often	☐2 Quite often
☐1 Sometimes	☐1 Not very often
☐0 Most of the time	☐0 Not at all
7. I can sit at ease and feel relaxed:	**14. I can enjoy a good book or radio or TV program:**
☐0 Definitely	☐0 Often
☐1 Usually	☐1 Sometimes
☐2 Not Often	☐2 Not often
☐3 Not at all	☐3 Very seldom

International Index of Erectile Function 5 (IIEF-5)

1. How do you rate your confidence that you could get and keep an erection?	☐0 No confidence ☐1 Very low ☐2 Low ☐3 Moderate ☐4 High ☐5 Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	☐0 No sexual activity ☐1 Almost never/never ☐2 A few times (much less than half the time) ☐3 Sometimes (about half the time) ☐4 Most times (much more than half the time) ☐5 Almost always/always
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	☐0 No sexual intercourse ☐1 Almost never/never ☐2 A few times (much less than half the time) ☐3 Sometimes (about half the time) ☐4 Most times (much more than half the time) ☐5 Almost always/always
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	☐0 No sexual intercourse ☐1 Extremely difficult ☐2 Very difficult ☐3 Difficult ☐4 Slightly difficult ☐5 Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	☐0 No sexual intercourse ☐1 Very low ☐2 Low ☐3 Moderate ☐4 High ☐5 Very high

European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)

MOBILITY	
I have no problems in walking about	□
I have slight problems in walking about	□
I have moderate problems in walking about	□
I have severe problems in walking about	□
I am unable to walk about	□
SELF-CARE	
I have no problems washing or dressing myself	□
I have slight problems washing or dressing myself	□
I have moderate problems washing or dressing myself	□
I have severe problems washing or dressing myself	□
I am unable to wash or dress myself	□
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	□
I have slight problems doing my usual activities	□
I have moderate problems doing my usual activities	□
I have severe problems doing my usual activities	□
I am unable to do my usual activities	□
PAIN/DISCOMFORT	
I have no pain or discomfort	□
I have slight pain or discomfort	□
I have moderate pain or discomfort	□
I have severe pain or discomfort	□
I am extreme pain or discomfort	□
ANXIETY/DEPRESSION	
I am not anxious or depressed	□
I am slightly anxious or depressed	□
I am moderately anxious or depressed	□
I am severely anxious or depressed	□
I am extreme anxious or depressed	□

Expectation Assessment

In general, is acupuncture effective for controlling the illness?
☐ Yes
☐ No
☐ Unclear
Do you think acupuncture will be helpful to improve your CP/CPPS symptoms
☐ Yes
☐ No
☐ Unclear

Acupuncture for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Statistical Analysis Plan (SAP)

NCT number: NCT03213938

September 4, 2017

Prepared by an Independent Statistician:
Yan Liu (Statistician), Data Centre of Traditional Chinese Medicine, China Academy of Chinese Medical Sciences

Content

1. Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) refers to the presence of bothersome pelvic pain symptoms without an identifiable cause[1]. Table 1 illustrates the 4 categories of prostatitis per the National Institutes of Health (NIH) classification of prostatitis syndromes. CP/CPPS affects approximately 10–16% of men worldwide[1-4]. Men of all ages can be impacted, among whom those aged 36–50 years are the most commonly affected[5]. There is no apparent racial predisposition to this disease.

Common symptoms of CP/CPPS include discomfort in the perineum, suprapubic region, and lower urinary tract symptoms[6]. Patients with CP/CPPS also frequently experience a wide array of sexual dysfunctions, including erectile dysfunction (ED), painful ejaculation and premature ejaculation (PE)[7-11], on top of symptoms suggestive of negative cognition or emotional consequences[12]. The aforementioned symptoms negatively impact upon the patient's quality of life (QoL) to a similar degree or worse than those of congestive heart failure, Crohn's disease, diabetes mellitus or angina[13, 14]. Because of its high prevalence and lack of effective therapies, direct and indirect costs associated with CP/CPPS are substantial[15]. Approximately 25% of men experience loss of work and approximately 50% have reduced leisure time at some point due to CP/CPPS[16]. The direct and indirect cost of care in China approaches 8059 CNY per person in 2009[17], and data indicate that in the USA, the total annual cost for patients with prostatitis was US$4387 in 2006[15].

Unlike acute/chronic bacterial prostatitis, the cause of CP/CPPS is unknown and no well-conducted epidemiologic studies are available to support any particular risk factors[18]. The diagnosis of CP/CPPS is mainly based on symptoms. Treatments for CP/CPPS usually include alpha-blockers, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and phytotherapy. Alpha-blockers and antibiotics have moderate effects on pain, voiding and QoL[19]. Both alpha-blockers and antibiotics are recommended for patients with CP/CPPS for less than 1 year, but only antibiotics are recommended in treatment-naïve patients. NSAIDs and phytotherapy are less commonly used, because of lack of research evidence[19]. Although advances have been made in research and developing novel treatment options, definitive treatments for CP/CPPS are still lacking[19]. Besides, pharmacological interventions are accompanied with adverse effects such as dizziness, nausea, and postural hypotension, which also reduce patients' compliance to treatments[20]. Previous studies suggest that acupuncture may be a potential treatment for CP/CPPS [21-25]. However, owing to small sample sizes and other methodological limitations of clinical trials, the efficacy of acupuncture in CP/CPPS remains inconclusive [19, 26]. In addition, the durable efficacy of the acupuncture is still unclear.[27]

NIH consensus classification of prostatitis	Definition
(I) Acute bacterial prostatitis	Acute infection of the prostate
(II) Chronic bacterial prostatitis	Chronic or recurrent infection of the prostate
(III) Chronic prostatitis/chronic pelvic pain syndrome	No demonstrated infection
A. Inflammatory	Leukocytes in expressed prostatic secretions, post prostate massage urine, or semen
B. Noninflammatory	No evidence of inflammation
(IV) Asymptomatic inflammatory prostatitis	No subjective symptoms detected, inflammation shown either by prostate biopsy or the presence of leukocytes in EPS/semen during evaluation for infertility or other disorders

Table 1. NIH consensus classification and definition of 4 categories of prostatitis[1]

2. Study Objective

The objective of this multi-center, randomized, sham acupuncture-controlled trial is to assess the effectiveness, especially the long-term efficacy of acupuncture for relieving symptoms of CP/CPPS.

3. Design

3.1 Overview

This is a multicenter, participants-blinded, parallel-group, randomized controlled study conducted in China.

The participants will be recruited in 10 clinical sites, which are Dongfang Hospital Beijing University of Chinese Medicine; Beijing Fengtai Hospital of Integrated Traditional and Western Medicine; West China Hospital of Sichuan University; The Third Affiliated Hospital of Zhejiang Chinese Medical University; The First Affiliated Hospital of Anhui University of Chinese Medicine; Hengyang Hospital Affiliated to Hunan University of Chinese Medicine; The First Hospital of Hunan University of Chinese Medicine; Guangdong Provincial Hospital of Traditional Chinese Medicine; Yantai Hospital of Traditional Chinese Medicine; and Shaanxi Provincial Hospital of Traditional Chinese Medicine. Guang'anmen Hospital, China Academy of Chinese Medical Sciences will be responsible for study design and organization. A data coordination center will be established at China Academy of Chinese Medical Sciences (CACMS) to monitor data management.

3.2 Eligibility criteria

3.2.1 Inclusion Criteria

(1) History of pain perceived in the prostate region and absence of other lower urinary tract pathology for a minimum of three of the past 6 months. In addition, any associated lower urinary tract symptoms, sexual function, and psychological factors should be addressed. Physical examinations, urinary analyses, and urine cultures will be performed for all subjects;
(2) Age 18 to 50 years;
(3) NIH-CPSI total score≥15.

3.2.2 Exclusion criteria

(1) Other types of prostatitis, such as acute bacterial prostatitis, chronic bacterial prostatitis, or asymptomatic inflammatory prostatitis;
(2) Urinary tract infection with a urine culture value >100,000 colony forming units (CFU)/mL, clinical evidence of urethritis, including urethral discharge or positive culture, diagnostic of sexually transmitted diseases (including gonorrhoea, chlamydia, mycoplasma or trichomonas, but not including HIV/AIDS), symptoms of acute or chronic epididymitis;
(3) Prostate, penile, testicular, bladder, or urethral cancer, seizure disorder in any medical history;
(4) Inflammatory bowel disease, active urethral stricture, bladder outlet obstruction, neurologic disease or disorder affecting the bladder, neurologic impairment or psychiatric disorder preventing understanding of consent and self-report scale;
(5) Overactive bladder, neurogenic bladder, interstitial cystitis, glandular cystitis;
(6) Organic disease of the urinary system;
(7) Severe cardiac, lung, cerebrum, liver or renal system disease, or hematopoietic system disease;
(8) Residual urine volume≥100 mL;
(9) Qmax≤15mL/s;
(10) During previous 4 weeks prior to study participation, used androgen hormone inhibitors (finasteride), alpha-blockers (terazosin, doxazosin mesylate. tamsulosin hydrochloride), antibiotics

(ciprofloxacin hydrochloride), or any other prostatitis-specific medication (including herbal and Chinese medicine)

4. Schedule of Evaluation

	STUDY PERIOD											
	Enrolment	**Allocation**	**Treatment**								**Follow-up**	
TIMEPOINT (W, week)	**-2 and -1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**20**	**32**
Enrolment												
Informed consent	×											
Eligibility criteria	×											
Demography characteristics	×											
Allocation		×										
Interventions												
Acupuncture			×	×	×	×	×	×	×	×		
Sham acupuncture			×	×	×	×	×	×	×	×		
Assessments												
Proportion of responders										×		×
NIH-CPSI	×		×	×	×	×	×	×	×	×	×	×
IPSS	×					×				×	×	×
IIEF-5	×									×	×	×
HADS	×									×	×	×
EQ-5D-5L	×									×	×	×
GRA						×				×	×	×
Expectation assessment	×											
Urinary flow rate	×									×		×

Table 2. Enrolment, Intervention and Evaluation Schedules

Abbreviations: NIH-CPSI National Institutes of Health Chronic Prostatitis Symptom Index, IIEF-5 International Index of Erectile Function 5, HADS Hospital Anxiety and Depression Scale, GRA Global Response Assessment, EQ-5D-5L Five-level EuroQol five-dimensional questionnaire, VAS visual analogue scale

5. Efficacy and Safety outcomes

5.1 Efficacy outcomes

5.1.1 Primary Outcomes

The two co-primary outcomes include the proportions of responders at week 8 and week 32. The responder is defined as a participant with a decline of 6 points or more from baseline in the total score of the Chinese version NIH-CPSI. As a validated, self-reported questionnaire, NIH-CPSI is widely used to assess CP/CPPS symptoms[28, 29]. NIH-CPSI consists of 9 items divided into 3 discrete domains: pain (0–21 points), urinary symptoms (0–10 points) and QoL (0–12 points), with a total score of 0–43 points (a higher score indicates worse symptoms). A decline of at least 6 points in NIH-CPSI has been identified as the minimal clinically important difference (MCID)[25].

5.1.2 Secondary Outcomes

(1) Proportion of responders during weeks 1-7, and at week 20.

The NIH-CPSI will be assessed once a week during treatment, and at week 20 and week 32. The responder is defined as who has a decline of 6 or more than 6-point from baseline measured by using the NIH-CPSI.

(2) The change from baseline in NIH-CPSI total score during weeks 1-8, at week 20, and at week 32.

(3) The change from baseline in NIH-CPSI subscales (pain, urinary symptoms and QoL) during weeks 1-8, at week 20, and at week 32.

(4) The change from baseline in IPSS at week 4, week 8, week 20, and week 32.

IPSS is a valid, reliable and sensitive measure for patients with lower urinary tract symptoms (LUTS); it is widely used in clinical practice and research to determine the severity of LUTS, including incomplete bladder emptying, frequency of urination, intermittency, urgency, weak urine stream, straining and nocturia[30, 31]. Each of the questions is rated from 0 (not at all) to 5 (almost always); severity of LUTS can be graded as mild (0–7), moderate (8–19) or severe (20–35). IPSS will be assessed at the end of the 4th, 8th, 20th, and 32nd week.

(5) The change from baseline in HADS at week 8, week 20, and week 32.

HADS will be assessed at the end of the week 8, week 20, and week 32. HADS is made up of 7 items for the assessment of depression and anxiety; the completion of this scale usually requires 2–5 minutes[32].

(6) The change from baseline in IIEF-5 at week 8, week 20, and week 32.

Chinese version IIEF-5 will be assessed at the end of the week 8, week 20, and week 32. The IIEF-5 consists of 15 items in 5 domains with a total score ranging from 5 to 25 (mild ED, 12-21; moderate ED, 8-11; severe ED, 5-7); it is a psychometrically valid and reliable instrument with high sensitivity and specificity for detecting treatment effects in patients with ED of a broad spectrum of aetiology[33].

(7) The change from baseline in EQ-5D-5L at week 8, week 20, and week 32.

The EQ-5D-5L will be assessed at the end of week 8, week 20, and week 32. The EQ-5D-5L is a generic instrument designed for self-completion and postal surveys; it is well-established and suitable for evaluation of QoL in participants with CP/CPPS[34].

(8) The proportions of participants in each response category of the Global Response Assessment (GRA) at week 4, week 8, week 20, and week 32.

The proportions of participants in each response category of the GRA in the two groups after treatment will be measured at the end of the week 4, week 8, week 20, and week 32. GRA consists of 7 response categories: markedly worsened, moderately worsened, slightly worsened, no change, slightly improved,

moderately improved, and markedly improved. We will identify a participant who reports "moderate" or "marked improvement" as a responder[35].

(9) The change for peak and average urinary flow rates from baseline at weeks 8 and 32.

Peak and average urinary flow rates will be measured at weeks 8 and 32.

(10) Expectation assessment at baseline

Expectation assessment will be assessed at baseline, which includes two brief questions to investigate whether patients are confident that acupuncture treatment will help their CP/CPPS: "In general, is acupuncture effective for controlling the illness?", "Do you think acupuncture will be helpful to improve your CP/CPPS symptoms?" For each question, participants could choose "Yes", "No" or "Unclear" as the answer.

5.2 Safety outcomes

According to their potential association with the treatment, AEs will be categorized as treatment-related or non-treatment-related within 24 hours after their occurrence. Treatment-related adverse events include pain, haematoma, localized infection, broken needle, fainting, nausea, headache, dizziness, insomnia, vomiting, or palpitations during or after treatment.

Serious adverse events will be defined as events requiring hospitalization, causing disability or impaired ability to work, threatening life or resulting in death.

All the adverse events and serious adverse events, whether related to acupuncture or not, will be reported and documented.

6. Statistical Considerations

6.1 Study hypothesis

The primary study hypothesis is that acupuncture is more effective than sham acupuncture in relieving symptoms of CP/CPPS.

6.2 Study Populations

All patients with randomization will be included in the analysis set regardless of whether they receive any treatment. According to the intention-to-treat principle, all analysis will be based on the randomization set.

6.3 Statistical Analyses

6.3.1 The general principle

Summary Statistics

Summary tables (descriptive statistics and/or frequency tables) will be provided for all variables at different endpoints. For continuous variables, means and standard deviations will be presented, unless the variable has a skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the number of missing values will be reported.

Statistical Comparisons Between Groups

Continuous variables will be compared using a two-sample t-test or Wilcoxon rank-sum test if data show serious deviations from a normal distribution. Categorical data or ordinal data will be compared using a Wilcoxon rank-sum test, chi-square test or Fisher's exact test, as appropriate. All tests will be two-sided.

For the analysis of the primary and secondary outcomes, estimated treatment differences and associated 95% two-sided confidence intervals will be presented.

Multiple Comparisons

Since only one co-primary outcome is defined, no adjustments to the significance level will be required to account for multiple testing.

For the analysis of the secondary and safety outcomes, no adjustment for multiple comparisons will be made.

Analysis Software

For all statistical analyses, SAS 9.4 software will be used. All hypothesis testing will be carried out at the 5% (2-sided) significance level.

6.3.2 Demographics and Baseline Characteristics

All data recorded at baseline will be summarized by group. Comparisons between groups will be performed using the methodology described in section 6.3.1. Summaries will be presented for the ITT Set in both groups.

6.3.3 Analyses for Primary Outcome

Primary outcome analysis will be conducted with a logistic generalized linear mixed model (GLMM) for repeated measures. Responder or non-responder at each scheduled post-baseline visit (end of treatment, and 20 and 24 weeks after treatment) is the dependent variable. Subjects who discontinue without providing the NIH-CPSI score will be considered as non-responders. The logistic GLMM is fitted using the logit link and the binomial distribution. The model will include the baseline NIH-CPSI total score as a fixed-effect covariate, with treatment group (acupuncture and sham acupuncture), visit and treatment × visit interaction as fixed-effect categorical factors. The interaction will remain in the model regardless of significance. Treatment group comparisons at each visit will be estimated by differences between least squares means from the treatment × visit interaction, and will be presented as odds ratios with accompanying *p* values and 95% CIs. The predicted probability of response at each visit will also be presented. Such models provide fairly robust results for treatment comparisons when longitudinal binary responses are missing, with an assumption that data are missing at random(MAR), according to reported values[36].

Sensitivity Analyses for the Primary Outcome

Because the MAR assumption cannot be verified using the data, the sensitivity of inferences to departures from the MAR assumption should be tested[37]. A straightforward sensitivity analysis for the MAR assumption in multiple imputation is based on the control-based pattern imputation model under the MNAR assumption by using the SAS procedure Proc MI process. Therefore, mixed-effect model under MNAR assumption will be used. 6.3.4 Analyses for Secondary Outcome

Efficacy analyses for all secondary outcomes will be performed in the ITT population, without imputation of missing data.

Continuous data will be described with the average, standard deviation, median, minimum value, and maximum value, whereas categorical data will be represented by percentages as appropriate. Changes from baseline in the NIH-CPSI total score will be analyzed using linear mixed-effects model. The model will include the observed change from baseline score at each assessment point as the dependent variable; the baseline value, treatment group (acupuncture and sham acupuncture), visit and treatment × visit interaction as fixed effects. Treatment group comparisons at each visit will be estimated by differences between least squares means from the treatment × visit interaction, with accompanying p values and 95% CIs. Log-transformation may be applied in the case of serious violations of the model assumptions (normality and constant variance of the residuals). If not appropriate, the Wilcoxon rank-sum test will be used. The effect of the treatment will be estimated by the difference (or ratio, in the case of log-transformation) between treatments and will be presented along with its associated 95% CI. The same

approach will be used in other longitudinal continuous outcomes such as NIH-CPSI subscale scores (pain, urinary symptoms, and QoL).

Other categorical data or ordinal data will be compared between groups using the Wilcoxon rank-sum test, chi-square test or Fisher's exact test, as appropriate. The James and Bang blinding indices will be used to assess the success of blinding. The James blinding index is a variation on the statistic in which 1 represents perfect blinding. The Bang blinding index for each group represents the proportion of participants making a correct treatment guess beyond chance; 0 represents perfect blinding, a positive index indicates a correct guess, and a negative index indicates a guess in the opposite direction.

6.3.5 Safety Analyses

All adverse events and serious adverse events will be listed. Adverse events include the acupuncture-related adverse events and other adverse events. Chi-square test or Fisher's exact test will be used to compare the incidence of adverse events between the acupuncture and sham acupuncture groups. P-value will not be adjusted for multiple tests.

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