This supplement contains the following items:

1.Final protocol, summary of changes from the published original protocol.

2. Final statistical analysis plan, summary of changes from the published original protocol.

The efficacy and safety of electroacupuncture for women with stress urinary incontinence: study protocol for a multicenter randomized controlled trial

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2. Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine
3. West China Hospital of Sichuan University
4. Xiyuan Hospital, China Academy of Chinese Medical Sciences
5. Hengyang Hospital affiliated to Hunan University of Chinese Medicine
6. The First Hospital of Hunan University of Chinese Medicine
7. Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated to Shanghai University of Traditional Chinese Medicine
8. The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine
9. Shanxi Province Hospital of Traditional Chinese Medicine
10. Jiangsu Province Hospital of Traditional Chinese Medicine
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Data:

Original protocol date: November 5, 2012

Amendment date: October 6, 2013

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2. Study Design

2.1 Study Overview

The objective of this study was to assess the efficacy of EA for women with stress urinary incontinence (SUI).

2.2 Background

Stress urinary incontinence (SUI), the most common type of urinary incontinence (UI), is defined as an involuntary loss of urine on physical exertion, sneezing, or coughing by the International Consultation on Incontinence[1]. SUI is a common health problem and affects many women globally. About 50% of women with UI report symptoms of stress incontinence. The prevalence of female SUI was reported to be 24.8% (95% CI: 23.4-26.3) according to a survey data (from 2001-2008) from the U.S. National Health and Nutrition Examination Survey[2] and 18.9% in a large sample cross-sectional survey in China[3]. Many studies show that SUI has a negative impact on patient's physical health, social and psychological well-being[4,5]. Incontinent women are more likely to become anxious, depressed and self-abased than continent women for uncontrollable leakage of urine, which makes them avoid social activities, such as visiting friends, sports, shopping or going to work[5]. These negative effects on quality of life are greater than major chronic conditions (diabetes, hyperlipidemia, and chronic kidney disease)[6].

Pelvic floor muscle training (PFMT) is the first line conservative therapy recommended for women with SUI by all major guidelines on urinary incontinence, including guidelines of ICUD[7], EAU[8], NICE[9], etc. A short-term success rates of PFMT was quoted as 50-75%[10], while the long-term success rate of PFMT varied between 41-85%[11]. However, a length of at least three months was recommended for the practice of PFMT to see a major change[7,8,12]. It was reported that strength and/or timing of the contraction could be improved within 4–8 weeks[13], but clinical

improvement might take as long as 5 months[14]. Besides, a low adherence rate was observed. It was reported that the long-term adherence to PFMT varied between 10-70%[11].

Midurethral slings (MUS) are the primary gold standard procedure for treating moderate to severe SUI with long-term cure rates of 77–90%[15]. The use of surgical mesh increases incidence of adverse events, like pain, infection, dysuria, neuromuscular problems and so on. An FDA safety communication on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse has been issued to inform the medical community and patients on July 13, 2011[16]. It was reported that acupuncture was useful for SUI with an effective rate up to 80%[17]. However, randomized controlled trials of acupuncture were few and often with methodological flaws (small sample size, improper control, neglect of blinding, etc). Our systematic review showed that acupuncture might be effective for SUI[18] with limited evidences. Our pilot study has shown that electro-acupuncture (EA) might be effective for female SUI in decreasing urine loss and improving quality of life, and might have a long-lasting effect[19]. Therefore, electro-acupuncture might be a good alternative therapy for female SUI. To our best knowledge, there has been no trials using sham or placebo control to assess the efficacy of acupuncture for female SUI.

2.3 Study Objectives and Hypothesis

The objective of this study is to assess the efficacy of EA for women with SUI. We hypothesize that EA is better than SA in decreasing urine leakage for women with SUI.

2.4 Methodology

2.4.1 Trial design

This is a multicenter, patient-blinded, parallel-group, randomized controlled study at 12 centers in China. Women with SUI will be randomized into electro-acupuncture

(EA) group or sham electro-acupuncture (SA) group in a 1:1 ratio.

2.4.1.1 Randomization

In this study, we will use blocks randomization, stratified according to center. A central randomization system will be applied in our trial. The randomizing scheme will be produced by staff of the clinical evaluation center of CACMS using statistical analysis software SAS9.3 with “proc plan” program. After production, it will be signed and sealed by the staff who produce it and keep 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. Acupuncturists in each center will be responsible for getting random numbers. Via inputting the participants’ sex and birthday in the central randomization system through the phone or the web, they will get the random number.

2.4.1.2 Blinding

In this study, participants, outcome assessors and statisticians will be blinded to treatment allocation.

Patient blinding will be achieved via a pragmatic placebo needle and sham EA electrode lines. The pragmatic placebo needle will be mainly consisted by an adhesive pad and a blunt-tipped placebo needle. Details of the constitution, usage and validity of the pragmatic placebo needle will be published elsewhere. The sham electrode lines will be identical with the real ones but the inner metal wire will be cut off. When switched on, the EA apparatus with sham electrode lines have the same working power indicator and sound as those with normal electrode lines, suggesting to participants that the EA apparatus is functional even though it actually had no current output.

For blinding assessment, two centers will be randomly chosen from the 12 centers. All participants in the two selected centers will be requested to guess whether they received EA or SA within five minutes after their treatments at weeks 3 and 6.

2.4.1.3 Sample Size

Based on findings from our previous study, we calculated a sample size of 144 participants per group to provide 90% power to detect a difference of 1 g between

groups in the 1-hour AUL, assuming a standard deviation (SD) of 2.61 and a two-sided significance level of 5%. To compensate for a 20% loss to follow-up and pre-specified subgroup analysis, the sample size will be increased to 250 participants in each group (500 participants in total).

2.4.2 Subjects

2.4.2.1 Eligibility criteria

Women with SUI will be recruited through newspaper and online advertisements, posters and specialist's recommendations from 12 centers in China.

Inclusion criteria:

Women will be included in the study if they met the following criteria. (1) aged 40-75 years; (2) involuntary urine leakage on effort, exertion, sneezing or coughing, which stopped when the stress ends; (3) visible involuntary leakage from the urethra synchronous with increased abdominal pressure, or a pad weight gain >1 g in 1-hour pad test; (4) without symptoms of urinary frequency and urgency; (5) volunteer to join this research and sign the informed consent. These criteria are consistent with clinical diagnosis recommendations for female SUI by the International Consultation on Urological Diseases (ICUD)[7].

2.4.2.2 Exclusion criteria

Women will be excluded from the study if they met the following criteria. (1) urge urinary incontinence, mixed urinary incontinence, overflow urinary incontinence, etc; (2) having ever received operation for urinary incontinence or pelvic floor operation; (3) pelvic organ prolapse greater than degree 2; (4) symptomatic urinary tract infection; (5) residual urinary volume (RUV) >30 ml; (6) maximum flow rate (Qmax) ≤ 20 ml/s; (7) limited in walking, stairs climbing and running; (9) receiving specific treatment for SUI, or taking medicine which may affect bladder function; (10) serious cardiovascular, cerebral, liver, kidney, or psychiatric disease, diabetes, multiple system atrophy, injury of cauda equina, or myeleterosis; (11) in pregnancy or lactation period; (12) with cardiac pacemaker, metal allergy or severe needle phobia.

2.4.2.3 Subject Withdrawals

There will be at least one urologist or gynecologist in each center. They would assess the severe adverse events (SAEs) and then determine whether the participant to continue or terminate the trial. Subjects may leave the study at their own discretion or the investigator may 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.

2.4.2.4 Subject Recruitment, Screening and Group Assignment

Participants with SUI will be recruited through posters, or advertisements on newspapers, or websites. Research assistants of each site will preliminarily screen the participants by recording their disease condition, history of the disease and treatment, and the demographic data. Physicians from the urology department of each site will take charge of the diagnosis and the differential diagnosis of SUI. Potential participants will receive a one-week baseline assessment, during which they have to take a 1-hour pad test and fill out a 3-day bladder diary. Eligible participants then will be randomized to EA or SA group. Acupuncturists will be in charge of participant assignment, and the EA or SA procedures. They will also be responsible for the assessment of safety during treatment. During the trial, independent evaluators of each site will instruct the participants how to fill in their bladder diaries and patients' self-assessment related to the trial. The evaluators will record the data on the case report form (CRF) through the whole trial period. The subject flow was shown in Figure 1.

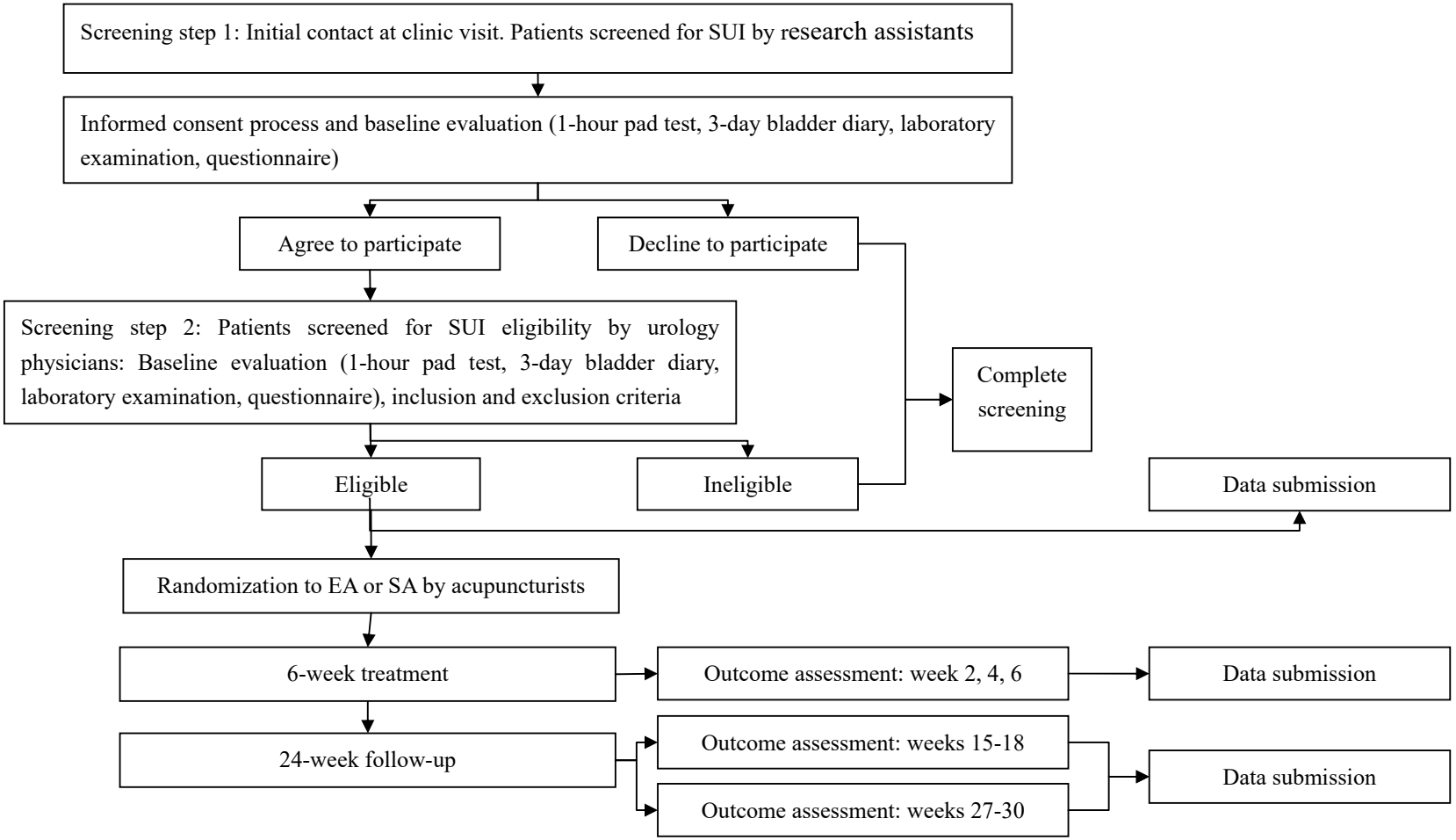

Figure 1. Subject flow

2.4.3 Trial flow Chart

The trial flow chart was shown in Figure 2.

	STUDY PERIOD												
	Baseline	**Allocation**	**Treatment**			**Follow-up**							
VISIT	**1**	**0**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
TIMEPOINT (W，week)	-1 w		W2±2d	W4 ±2d	W6 ±2d	W15 ±3d	W16 ±3d	W17 ±3d	W18 ±3d	W27 ±3d	W28 ±3d	week 29 ±3d	week 30 ±3d
Enrollment													
Informed consent	×												
Eligibility criteria	×												
Demography characteristics	×												
Disease history of SUI	×												
Urine routine	×												
Urine flow rate	×												
Residual urine volume	×												
Allocation		×											
Interventions													
EA			×	×	×								
SA			×	×	×								

Assessments													
1-hour AUL	×		×		×								
72-hour IEF	×		×	×	×	×	×	×	×	×	×	×	×
Sevirity of SUI	×		×	×	×	×	×	×	×	×	×	×	×
Mean 24h water input	×		×	×	×	×	×	×	×	×	×	×	×
Consumption of urinal pads	×		×	×	×	×	×	×	×	×	×	×	×
Application of other treatments for SUI	×		×	×	×	×	×	×	×	×	×	×	×
ICIQ-SF Score	×			×	×				×				×
Patient self-evaluation of therapeutic effect					×				×				×
Assessment of blinding				×(W3)	×								
Adverse events	×	×	×	×	×	×	×	×	×	×	×	×	×

411 Abbreviations: SUI, stress urinary incontinence; 1-hour AUL, amount of urine leakage measured by the 1-hour pad test; IEF, incontinence episode frequency; ICIQ-SF,

412 International Consultation on Incontinence Questionnaire-Short Form.

413 **Figure 2.** The schedule of enrollment, interventions, and assessments

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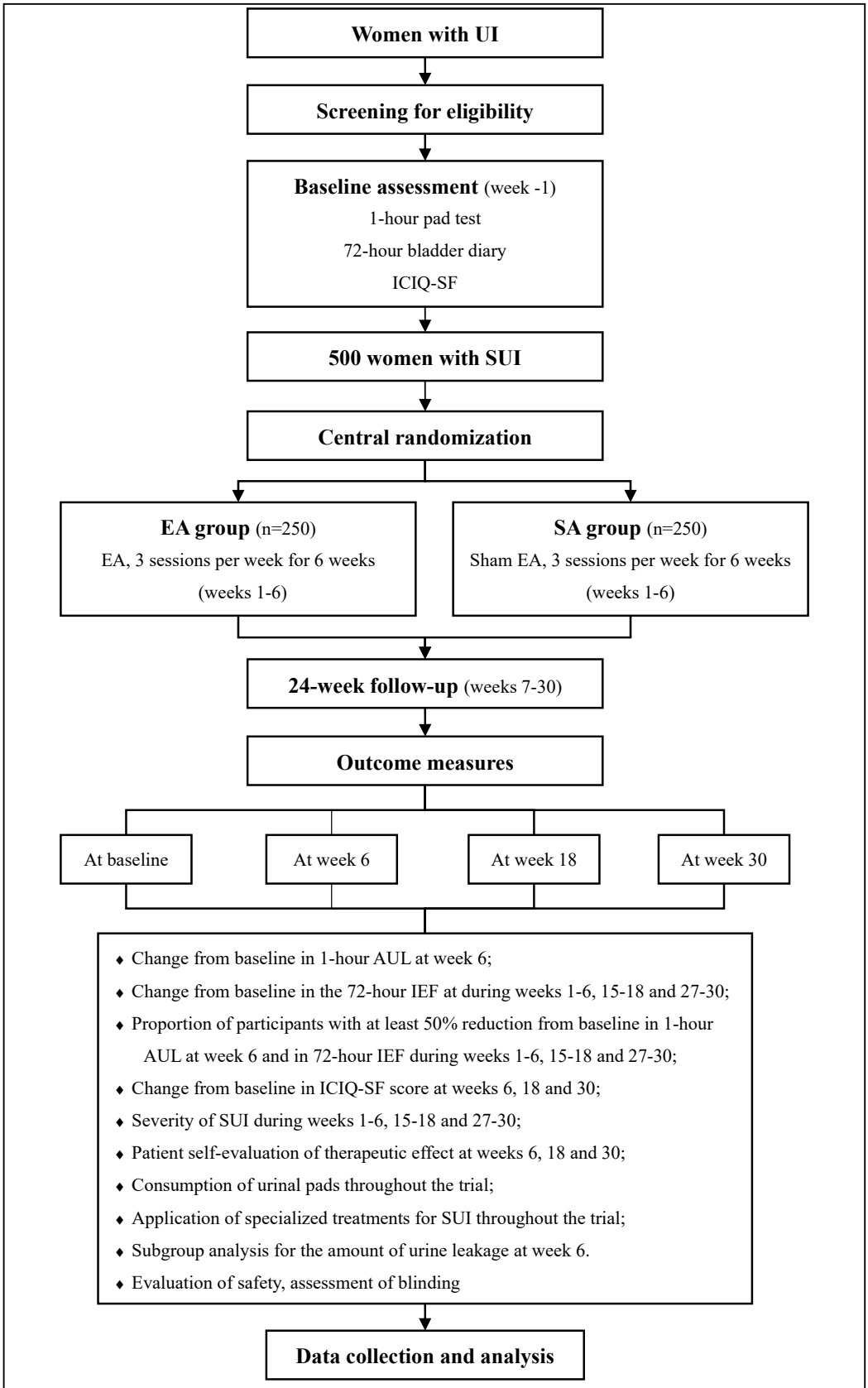

Figure 2. Trial flow chart

2.4.4 Outcomes Measurements

2.4.4.1 Primary Outcome

The primary outcome will be the change from baseline in the amount of urine leakage measured by 1-hour pad test (1-hour AUL) at week 6.

The 1-hour pad test will be performed according to the International Continence Society instructions[20]. The participants will be instructed to void 2 hours before the pad test. On arrival, they received a pre-weighed pad and will be asked to sit and drink 500 ml in 15 minutes. Next, the women will be instructed to walk for 30 minutes, including going up and down 24 stairs. On returning to the clinic, the participants will be instructed to perform several activities, including standing and sitting 10 times, coughing vigorously 10 times, running on the spot for 1 minute, picking up a coin from the floor 5 times, and putting their hands under water for 1 minute. After the activities are completed, the pad will be reweighed to measure the amount of urinary leakage.

Outcome assessments will be postponed when the participants are in their menstrual periods or suffering from severe cough, and reran until the end of periods or remission of cough. Additionally, the change at week 2 from baseline in the 1-hour AUL will also be assessed.

2.4.4.2 Secondary Outcomes

We mainly assessed the influence of EA on incontinence episode frequency (IEF), severity of SUI and quality of life. The frequency and severity of SUI will be based on data from 72-hour bladder diary recorded by participants on baseline (week -1), treatment period (weeks 2, 4 and 6) and follow-up period (weeks 15-18, and weeks 27-30). The bladder diaries recorded in detail the time and frequency of UI, activity that occurred at the time of leak, and the type and volume of liquid intake.

In each center, data of bladder diaries will be checked by two full-time research assistants first, and then entered into e-bladder diary database by two independent data entry clerks. The audited data of e-bladder diary will be finally carried forward into effectiveness data by statisticians. The ICIQ-SF questionnaire used to assess the

quality of life of participants will be filled out by participants at baseline (week -1), weeks 4 and 6 (treatment period) and weeks 18 and 30 (follow-up period) under the guidance of doctors.

① Change from baseline in the mean 72-hour IEF during weeks 1-6, 15-18 and 27-30.

Calculation methods of the mean 72-hour IEF at different timepoints:

a. Mean 72-hour IEF during weeks 1-6 equals the total of 72-hour IEF at weeks 2, 4 and 6 divided by 3;

b. Mean 72-hour IEF during weeks 15-18 equals the total of 72-hour IEF at weeks 15-18 divided by 4;

c. Mean 72-hour IEF during weeks 27-30 equals the total of 72-hour IEF at weeks 27-30 divided by 4.

② a. Proportion of patients with at least 50% decrease from baseline in the 1-hour AUL at week 6;

b. Proportion of patients with at least 50% decrease from baseline in the mean 72-hour IEF during weeks 1-6, 15-18 and 27-30.

③ Change from baseline of the total ICIQ-SF scores at weeks 6, 18 and 30.

International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF)[21,22]will be used to assess the influence of UI on quality of life during the past 4 weeks retrospectively. It contained three items on frequency, amount of leakage, and overall impact on quality of life, and a fourth, non-scored item for the assessment of type of incontinence. Scoring will be additive (0-21), with higher values indicating increased severity. The total score of week 6 will be the average of the sum of weeks 4 and 6.

④ Severity of SUI during weeks 1-6, 15-18 and 27-30.

The between-group differences of severity of SUI will be assessed at weeks 6,18 and 30 using number and percent of subjects with different SUI severity ratings.

The severity of SUI will be rated according to the amount of UI in usual conditions without extreme activities like severe cough, strenuous exercise or carrying heavy loads in the past 72 hours[23]: no; mild, several drops of leak; moderate, leak that

soaked through underwear; severe, leak that soaked through outerwear. In case that participants worn urinal pads, the severity of SUI will be graded as follows. Mild: several drops of leak; moderate: soaked urine pads in patches by several leaks; severe: soaked urine pads in patches by one leak.

The most severe degree of urine leakage in patient's 3-day bladder diaries over the assessment period, regardless of its frequency of recording, will be selected as the severity of SUI (subjective) for analyses. The severity of SUI (subjective) during weeks 1-6 will be the most severe degree of urine leakage recorded in patient's 3-day bladder diaries among weeks 2, 4 and 6. The severity of SUI during weeks 15-18 will be the most severe degree of urine leakage recorded in patient's 3-day bladder diaries during weeks 15-18. The severity of SUI during weeks 27-30 will be the most severe degree of urine leakage recorded in patient's 3-day bladder diary during weeks 27-30.

⑤ Patient self-evaluation of therapeutic effects at weeks 6, 18 and 30.

A 4-point scale will be used to measure the extent of help that the participants think they received from treatment (0, no help; 1, little help; 2, moderate help; 3, great help).

The between-group differences of patient self-evaluation of therapeutic effects will be assessed at weeks 6, 18 and 30 using number and percentage of subjects with different point scale.

⑥ Consumption of urine pads:

The weekly consumption of urine pads will be compared between groups during weeks 1- 6, 7-18 and 19-30. The weekly consumption of urine pads will be assessed.

Calculation methods of weekly consumption of urine pads at different timepoints:

a. weekly consumption of urine pads during weeks 1-6 equals the total of urine pads consumed during weeks 1-6 divided by 6;

b. weekly consumption of urine pads during weeks 7-18 equals the total of urine pads consumed during weeks 7-18 divided by 12;

c. weekly consumption of urine pads during weeks 7-18 equals the total of urine pads consumed during weeks 19-30 divided by 12.

⑦ Application of drugs and other treatments for SUI during weeks 1-6, 7-18 and 19-30.

Other treatments for SUI mainly refer to pelvic floor muscle training, electrical stimulation, biofeedback, vaginal cone and medication.

The number and percent of patients who used other treatments will be compared between groups during weeks 1-6, 7-18 and 19-30.

⑧ Subgroup analysis: The objective of subgroup analysis will be to explore the effect of EA for different degrees of SUI. Participants will be divided into 3 subgroups, mild group (with a urine leakage of 1.1-9.9 g), moderate group (with a urine leakage of 10-49.9 g), or severe group (with a urine leakage of ≥ 50 g), according to the severity of urine leakage measured by 1-hour pad test at baseline[24].

The change from baseline of urine leakage measured by 1-hour pad test between EA and sham EA will be compared in each subgroup respectively at week 6.

⑨ Blinding Assessment

Due to the limited budget, we will only assess the blinding results of EA in 84 participants from two randomly selected centers instead of all participants in 12 centers.

Participants in the two selected centers will be asked to guess whether they received EA or SA within 5 minutes after one treatment at weeks 3 and 6.

3. Safety Assessment

All the serious adverse events (SAEs) and adverse events (AEs) will be recorded and measured by both participants themselves and acupuncturists through the whole trial. In our trial, the SAEs will be defined as events requiring hospitalization, causing disability or impaired ability to work, threatening life or resulting in death. AEs will be categorized as treatment related or non-treatment related based on its potential association with acupuncture needling procedure by acupuncturists and related specialists within 24 hours. The treatment related AEs defined as follows:

broken needle, needle phobia, intense pricking, pricking lasting more than half an hour (no matter how intense it is) after acupuncture, hematoma, bleeding, infection, abscess formation at the needling site, other discomfort induced by acupuncture (such as fatigue, drowsiness, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, insomnia, etc), and aggravation of existing symptoms, etc. Pricking caused by acupuncture will be assessed using a 10-point visual analogue scale (VAS, 0 indicates no pain, and 10 indicates the severest pain). Given that acupuncture is a minimally invasive therapy inevitably causing pain, pricking with a spontaneously remission within 30 min after acupuncture will be not regarded as AE. The numbers of cases and sessions of AEs will be recorded. We will compare the proportion of participants who get treatment-related AEs. Participants who get treatment-related adverse effects at least once will be counted in for the comparison of the proportion.

4. Interventions

The intervention scheme of this trial will be based on expert consensus and result of prior study. There will be 2 full-time acupuncturists per center (20 acupuncturists in total in 12 centers) responsible for operation of EA and SA. In general, acupuncturists will be assigned to the same participants throughout the 6-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 needle (size 0.30×75 mm), pragmatic placebo needle (size 0.30×25 mm) and SDZ-V EA apparatus (all will be Hwato Brand, Suzhou Medical Appliance Factory, Suzhou, China) will be used in this trial.

It took 31 weeks in total for a patient to complete the trial, 1 week's baseline assessment, 6 weeks' treatment, and 24 weeks' follow up.

4.1 EA

Acupoints of bilateral Zhongliao BL33 and Huiyang BL35, which will be located

according to the WHO Standardized Acupuncture Points Location[25] will be used. After sterilizing the skin, sterile adhesive pads will be pasted on acupoints first, and then needles of size 0.30×75 mm will be inserted into bilateral BL33 to a depth of 50-60 mm with an angle of 30-45° inward and downward, and Bilateral BL35 to a depth of 50-60 mm outward and upward slightly. Needles will be lifted, thrusted and twirled evenly for 3 times to achieve deqi. Paired electrodes of EA apparatus will be attached transversely to bilateral BL33 and BL35 respectively with a continuous wave of 50 Hz and a current intensity of 1-5 mA (preferably with the skin around the acupoints shivering mildly without pain) for 30 min. Patients will be treated with EA 3 sessions a week on alternate days for 6 successive weeks, 18 sessions for each patient in total.

4.2 SA

Sham BL33 and BL35, which are 1 cun lateral to BL33 and BL35 respectively, will be used. After sterilizing the skin, placebo needles of size 0.30×25 mm will be needled into adhesive pads without skin penetration or needle manipulation. The sham electrode lines will be attached to needles of bilateral sham BL33 and sham BL35 respectively. The sham electrode lines will be identical with the real one but the inner metal wires will be cut off. Therefore, though the EA apparatus showed a power-on state with lighted power indicator and voice of clatter, no current will be outputted in fact. The parameters of sham EA apparatus and the treatment course will be the same as in the EA group.

Patients will be treated individually to avoid communication on the treatments they received. During the treatment period, if a participant is in her menstrual cycle, the treatment would be postponed until the cycle ended. The length of delay will be not included in the treatment period. So the treatment period still lasted for 6 weeks with 18 treatment sessions.

4.3 Permitted and prohibited concomitant treatments

Throughout the whole trial, participants will be discouraged from any specific

585 treatments of SUI, such as duloxetine, imipramine and estrogen, pelvic floor muscle
586 training, feedback therapy, electrical or magnetic stimulation via pelvic floor, vagina
587 or anus, and transcutaneous electrical nerve stimulation to pelvic floor. For any
588 treatment already used, related information should be recorded in case report form.

589 **5. Informed Consent**

590 **Informed Consent: Study Introduction**

591 Dear women participants:

592 If your doctor thinks you have stress urinary incontinence (SUI), we invite you to
593 participate in this study aiming to evaluate the effectiveness and safety of
594 acupuncture for management of SUI. This study is supported and funded by the "the
595 12th Five-Year Program'' of the National Science and Technology Pillar Program
596 (2012BAI24B01; 2012BAI24B02).

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

603 Introduction

604 I. Background and purposes

605 The prevalence of SUI is high, and it affects 24.8% (95% CI: 23.4-26.3) women in US,
606 18.9% in China and between 4.6-28% in Europe. The first line recommended
607 conservative treatment is pelvic floor muscle training (PFMT), however, it takes at
608 least three moths to take effect and the compliance is low. A systematic review
609 shows that acupuncture may be effective for treating SUI and our previous pilot
610 study indicates that electro-acupuncture (EA) may be effective for management of
611 SUI with an off-treatment effect and a good safety profile. In this study, a randomized

controlled trial design will be used and we aim to evaluate the effectiveness and safety of EA treatment for SUI. This study will be carried out simultaneously in 12 class A tertiary hospitals all over China, and we expect a total number of 500 participants for voluntary participation.

II. Exclusion criteria

(1) Younger than 40 or older than 75;

(2) The amount of urine leakage measured by 1-hour pad test is less than 1 g;

(3) Other types of UI (urge, mixed, or overflow UI, etc);

(4) Ever received anti-incontinencesurgery or pelvic surgery;

(5) A pelvic organ prolapse severer than degree 2;

(6) With a symptomatic urinary tract infection;

(7) Residual urinary volume (RUV) >30 ml; or maximum flow rate (Qmax) ≤ 20 ml/s;

(8) Limited in walking, stairs climbing and running;

(9) Receiving specific treatment (like PFMT, electrical or magnetic stimulation via pelvic floor, etc) for SUI, or taking medicine which may affect bladder function;

(10) With serious cardiovascular, cerebral, liver, kidney, or psychiatric diseases, diabetes, multiple system atrophy, injury of caudaequina, or myeleterosis;

(11) Being pregnant or lactating;

(12) With a cardiac pacemaker, metal allergy or needle phobia.

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

1. Before your enrollment in the study, you will receive the following exams to determine whether you are eligible to participate in the study:

The doctor will ask and record your medical history and perform related physical examination.

You will be required to get 1-hour pad test, urine routine, urine flow rate, residual urine volume and others for the confirmation of your diagnosis.

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 electro-acupuncture (EA) or sham electro-acupuncture (SA) groups. Participants in the EA group will receive deep needling on the BL33 and BL35 with a continuous wave of 50 Hz and a current intensity of 1-5 mA for 30 min; participants in the SA group will receive placebo needling on the sham BL33 and sham BL35 without electric current output.

(2) In the study, Huatuo 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. Needle size: 0.30×25mm, 0.30×75mm, indicating the diameter of needle is 0.30mm and the length of needle is 1 Cun, and 3 Cun, respectively. Huatuo's EA apparatus will be used.

(3) The duration of this study is 31 weeks, including 1-week baseline, a treatment period of 6 weeks, and a follow-up period of 24 weeks. Frequency and duration of EA treatment: 3 sessions per week in weeks 1-6. The patients will receive 18 sessions of treatment in total.

(4) During the study period, you need to record detailed diary faithfully. After treatment, you will need to hand in your diary to the doctor timely, and the doctor will record your signs and symptoms in detail.

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 outpatient 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 (during follow-up, the doctor may get to know your conditions by phone or visiting your home). Your follow-up is very important because the doctor will determine whether the treatment that you are receiving really works, and the doctor will be able to guide the prevention and management of your symptoms timely.

During the study, you are not allowed to use other treatments for SUI. 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 SA. The study may also help doctors and researchers to further evaluate the efficacy of EA for SUI. 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 is 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: Electroacupuncture for women with stress urinary incontinence: a multicenter, 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

762 doctor’s orders to the best I can.

763 Signature of patient: Year month day

764 Telephone:

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

768 Signature of doctor: Year month day

769 Office phone number of doctor:

770 **6. Quality Control**

771 To guarantee the quality of the study, the trial protocol will be reviewed and may be
772 revised by expert acupuncturists, urologist, and statisticians several times. A central
773 randomization system will be adopted to avoid selection bias. Strict eligible criteria
774 will be pre-set to restrict the research population. Blinded effect assessment and
775 blinded statistics will be designed to guarantee the objectivity of the data. All
776 research staffs, especially the research assistants, acupuncturists and data entry
777 clerks, will be required to attend a series of training on how to use the central
778 randomization system and data entry system, how to fill the case report form and
779 diary, how to manipulate interventions correctly, and how to assess the outcomes,
780 etc. A double-entry method will be used in this trial. The data of therapeutic
781 evaluating will be calculated by the statisticians. A three-level inspection plan will be
782 designed for quality inspecting.

783 **7. Data Management**

784 **7.1 The Raw Data Management and Archiving**

785 We will use Remote Data Capture (RDC) system to perform data entry. The research
786 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.

7.2 Data Entry and Storage

7.2.1 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 far 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 are also need to be updated.

7.2.2 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 electrically to let the data go in to effect.

7.3 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.

7.4 Medical Coding

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

7.5 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 the solution during the 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; (7) classifying plan of the statistical analysis population. Data report will be performed monthly since the first entry of the eCRF.

7.6 Data Auditing and Blinding Review

When the data checking is finished, a data auditing and blinding review meeting will be hold. On the meeting, the data administrators, statisticians, researchers, clinical inspectors, and other related members would 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 should sign the data locking consent, and the data auditing resolution.

7.7 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.

8. STATISTICAL CONSIDERATION

The following is an overview of the statistical considerations. Details of the pre-specified statistical analyses can be found in the Statistical Analysis Plan (SAP).

8.1 Statistical Analysis

The primary study hypothesis is that EA is more effective than SA in reducing urine leakage in women with stress urinary incontinence. The primary outcome is the change from baseline in the amount of urine leakage at week 6 measured by 1-hour pad test. The primary analysis will be intention-to-treat with multiple imputations. Amount of urine leakage will be summarized in each treatment group and compared using mixed-effects model. The change at week 2 from the baseline will also be

assessed. Pre-specified subgroup analysis will also be performed according to the Statistical Analysis Plan.

The following secondary outcomes will be analyzed using the t test, repeated measures analysis, Wilcoxon rank-sum test, Chi-square test or Fisher's exact test, as appropriate and the intent-to-treat principal:

1. 72-hour IEF
2. Reduction at least 50% from baseline in 72-hour IEF
3. Reduction at least 50% from baseline in 1-hour AUL
4. ICIQ-SF score
5. SUI Severity
6. Patient self-evaluation of therapeutic effect
7. Consumption of urine pads
8. Application of other treatments for SUI
9. Subgroup analysis
10. Success rate of blinding

A two-side test with $p<0.05$ will be considered significant for all analyses.

8.2 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.

9. Ethical principle

For every study site, only when the trial protocol is approved by the IRB, the enrollment of participant will begin, but all should be after October 8, 2013.

10. Funding

This study is supported and funded by the program of “the 12th Five-year’’ National Science and Technology Pillar Program (2012BAI24B01; 2012BAI24B02) by the Ministry of Science and Technology of the People’s Republic of China.

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12. Update on the Published Protocol

As compared to the published protocol (Liu Z, Xu H, Chen Y, et al. The efficacy and safety of electroacupuncture for women with stress urinary incontinence: study protocol for a multicenter randomized controlled trial. Trails 2013, 14: 315), the present finalized study protocol had made several amendments because of practicality.

(1) langue revision for precision presentation and readers' better understanding:

a, Time frame "weeks 6, 18, and 30" for mean 72-hour IEF and SUI severity was revised to "weeks 1-6, weeks 15-18 and weeks 27-30". Time frame "weeks 6, 18 and 30" for consumption of urine pads and application of other treatment was revised to "weeks 1-6, 7-18 and 19-30".

b, SUI severity, consumption of urine pads and patient self-evaluation of therapeutic effect were compared between groups, without consideration of the change from baseline.

c, The "clinically important" was dropped due to no related clinically important difference papers found. So the statements of "clinically important difference of 1g between groups" were corrected as "difference of 1g between groups".

(2) "After sterilizing the skin, placebo needles of size 0.30×25 mm were needled through adhesive pads to the skin with non-penetrating, and then were lifted, thrusted and twirled evenly for 3 times" was changed to "After sterilizing the skin, placebo needles of size 0.30×25 mm will be needled into adhesive pads without skin penetration or needle manipulation." Reasons for change is that in actual trial implementation, no manipulation was performed in the SA group.

(3) Major amendments for mistake correction or better presentation (Table 1):

Table 1. Major update of the published protocol

No.	Item	Published version	Final version
1	Sample size	To detect a clinically important difference of 1 g on the volume of urine leakage from a 1-h pad Test, using a one-tailed t-test of the	To detect a difference of 1 g between groups in the 1-hour AUL with a two-sided

		difference between means, with a significance level of 5%, and a power of 90%. The sample size was expanded to 500 cases (250 cases in each group).	significance level of 5% and a power of 90%. The sample size was increased to 250 participants in each group (500 participants in total).
2	Secondary outcome 2		Added secondary outcomes, a. Proportion of patients with at least 50% decrease from baseline in the 1-hour AUL at week 6; b. Proportion of patients with at least 50% decrease from baseline in the mean 72-hour IEF during weeks 1-6, 15-18 and 27-30.
3	Secondary outcome 8	Subgroup analysis stratified by incontinence severity: Evaluated at weeks 6, 18 and 30. Week 6: the change in amount of urine leakage at week 6 from baseline measured by 1-hour pad test; week 18: the change of average 72-hour IEF at week 18 from baseline; week 30: the change of average 72-hour IEF at week 30 from baseline.	Subgroup analysis: evaluated at week 6, the change from baseline in amount of urine leakage measured by 1-hour pad test. Delete the subgroup analysis of 72-hour IEF at weeks 18 and 30.
4	Blinding assessment	Assessment of the subject blinding success rate: The percentage of subjects from each group who believe that they received a true EA treatment (regardless of whether they received an actual true or actual sham treatment) will be recorded as P1 in week 3 and P2 in week 6. The subject blinding success rate will be defined as the average of P1 and P2. The difference in the subject blinding success rates between the two groups will be analyzed.	Blinding assessment: Participants in the two selected centers were requested to guess whether they received EA or SA after their treatments at weeks 3 and 6. The number and percent of subjects guess EA or SA in the selected two centers will be analyzed between groups with the integrated results of weeks 3 and 6.

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Electroacupuncture for Women with Stress Urinary Incontinence: A Multicenter, Randomized Controlled Trial

(Electroacupuncture for Stress Urinary Incontinence, ESUI)

Statistical Analysis Plan

Final version: October 20, 2013

Trial Registration: Clinical Trials.gov identifier NCT01784172.

Prepared for and approved by the Executive committee of the study:

Dr. Baoyan Liu (Chair), China Academy of Chinese Medical Sciences

Dr. Zhishun Liu (Member), Guang'an men Hospital Affiliated to China Academy of Chinese Medical Sciences

Dr. Huanfang Xu (Member), Guang'an men Hospital Affiliated to China Academy of Chinese Medical Sciences

Prepared by an Independent Statistician:

Dr. Yan Liu (Statistician), Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences

Table of Contents

1. Introduction

Stress urinary incontinence (SUI), the most common type of urinary incontinence (UI), is defined as an involuntary loss of urine on physical exertion, sneezing, or coughing by the International Consultation on Incontinence. SUI is a common health problem and affects many women globally. About 50% of women with UI report symptoms of stress incontinence. The prevalence of female SUI was reported to be 24.8% (95% CI: 23.4-26.3) according to a survey data (from 2001-2008) from the U.S. National Health and Nutrition Examination Survey and 18.9% in a large sample cross-sectional survey in China. SUI affects not only a patient's physical health but also her social and psychological wellbeing. Patients are more likely to become depressed and are more prone to develop self-abasement than other women because of the uncontrollable leakage of urine. This makes them nervous about taking long journeys or participating in social activities. These negative effects on quality-of-life are greater than those resulting from some major chronic conditions (diabetes, hyperlipidemia, and chronic kidney disease).The International Consultation on Urological Diseases (ICUD) recommends lifestyle regulation, behavior therapy, pelvic floor muscle training (PFMT), and functional electrical stimulation as conventional therapies for mild and moderate female SUI. A systematic review supported PFMT as a conservative grade-A recommended therapy for female SUI with a 30-60% effective rate; however, for it to be maximally effective it needs to be practiced for at least 3 months. Additionally, the positive effects of PFMT are closely related with patient compliance, which decreases over time. PFMT is seldom used in China due to a lack of skilled physiotherapists. For moderate to severe SUI, a mid-urethral sling with surgical mesh is widely used. However, the use of surgical mesh increases adverse events such as pain, infection, dysuria, and neuromuscular problems. A safety communication from the U.S. Food and Drug Administration (FDA) on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse was issued on 13 July 2011. Several randomized controlled trials

(RCTs) showed that acupuncture, by decreasing urine leakage and improving patients' quality of life, maybe an alternative therapy for SUI. However, because of the limited evidence, high-quality RCTs are needed to assess the efficacy of acupuncture for treating SUI.

2. Study Objective

The primary objective is to evaluate whether EA is more effective than sham acupuncture(SA) in reducing urine leakage in women with stress urinary incontinence.

3. Design

3.1 Overview

This multicenter, patient-blinded, randomized controlled study will be performed to demonstrate the safety and effectiveness of the EA for women with SUI.

3.2 Inclusion/Exclusion Criteria

3.2.1 Inclusion Criteria

1. Subject is 40–75 years old;
2. Subject has involuntary leakage of urine on effort, exertion, sneezing or coughing that stops when the stress ends;
3. Subject has visible involuntary leakage from the urethra synchronous with increased abdominal pressure, or a pad weight gain >1 g in a 1-h pad test;
4. Subject has no symptoms of urinary frequency and urgency;
5. Subject voluntarily joins the research and signs the informed consent.

See details in Protocol 2.4.

3.2.2 Exclusion Criteria

1. Subject has urge urinary incontinence, mixed urinary incontinence, or overflow urinary incontinence;
2. Subject has had an operation for urinary incontinence or on the pelvic floor;
3. Subject has female genital prolapse greater than degree 2;
4. Subject has symptomatic urinary tract infection;
5. Subject has residual urinary volume (RUV) >30 mL;
6. Subject has maximum flow rate (Qmax) ≤20 mL/s;
7. Subject is limited in walking, stair climbing, or running;
8. Subject is receiving other treatment for SUI, or taking medicine that may affect bladder function;
9. Subject has serious cardiovascular, cerebral, liver, kidney, or psychiatric diseases, diabetes, multiple system atrophy, injury of cauda equina, or myeleterosis;
10. Subject during pregnancy or lactation;
11. Subject has a cardiac pacemaker implanted, a metal allergy, or a severe needle phobia.

See the details in Protocol 2.4.

4. Study Schema

	STUDY PERIOD												
	Baseline	**Allocation**	**Treatment**			**Follow-up**							
VISIT	**1**	**0**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
TIMEPOINT (W，week)	-1 w		W2±2d	W4 ±2d	W6 ±2 d	W15 ±3d	W16 ±3d	W17 ±3d	W18 ±3d	W27 ±3d	W28 ±3d	week 29 ±3d	week 30 ±3d
Enrollment													
Informed consent	×												
Eligibility criteria	×												

Demography characteristics	×												
Disease history of SUI	×												
Urine routine	×												
Urine flow rate	×												
Residual urine volume	×												
Allocation		×											
Interventions													
EA			×	×	×								
SA			×	×	×								
Assessments													
1-hour AUL	×		×		×								
72-hour IEF	×		×	×	×	×	×	×	×	×	×	×	×
Sevirity of SUI	×		×	×	×	×	×	×	×	×	×	×	×
Mean 24h water input	×		×	×	×	×	×	×	×	×	×	×	×
Consumption of urine pads	×		×	×	×	×	×	×	×	×	×	×	×
Application of other treatments for SUI	×		×	×	×	×	×	×	×	×	×	×	×
ICIQ-SF Score	×			×	×				×				×
Patient self-evaluation of therapeutic effect					×				×				×
Assessment of blinding				×(W3)	×								
Adverse events	×	×	×	×	×	×	×	×	×	×	×	×	×

Abbreviations: 1-hour AUL, amount of urine leakage measured by the 1-hour pad test.

Figure 1. The schedule of enrollment, interventions, and assessments

5. Efficacy and Safety outcomes

5.1 Efficacy outcomes

5.1.1 Primary Efficacy outcome

The primary efficacy endpoint will be the change from baseline in the amount of urine leakage measured by the 1-hour pad test at week 6. The change at week 2 from the baseline will also be assessed. The 1-h pad test will be conducted based on the International Continence Society (ICS) guidelines at the baseline, week 2, and week 6.

5.1.2 Secondary Efficacy outcomes

1. Mean 72-hour IEF
2. Proportions of patients with at least 50% decrease from baseline in the 1-hour AUL
3. Proportions of patients with at least 50% decrease from baseline in the mean 72-hour IEF
4. ICIQ-SF score
5. Severity of patient-reported SUI
6. Patient self-evaluation of therapeutic effect
7. Consumption of urine pads
8. Application of other treatments for SUI
9. Subgroup analysis
10. Success rate of blinding

6. Statistical Considerations

6.1 Study hypothesis

The primary study hypothesis is that EA is more effective than sham EA in reducing urine leakage in women with stress urinary incontinence.

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.

Multicenter study

To estimate the overall variability of the center effects, we used the random center effects (RCE) accounting for center effects.[1] Therefore, mixed-effect model was used

for the primary outcome.

Missing data

Regardless of any violations, compliance or early withdrawal from the trial, if the patient is randomized, her data will be analyzed in our primary outcome analyses.

We will use multiple imputation method under the missing at random (MAR) assumption for the primary outcome with missing data. Multiple imputations use the observed data to fill in the missing values repeatedly to give rise to multiple "pseudo-complete" datasets. We will impute the missing data 100 times using the following one of methods 1) regression imputation, if data sets with monotone missing patterns, or 2) Markov chain Monte Carlo imputation, if data sets with other patterns. For this we will use the SAS procedure Proc MI process. Each method will give rise to 100 different imputed data sets. We will fit our final model described before to each of these imputed datasets and then compute an overall estimate of the intervention effect as an average of the imputation specific estimates. The standard error of the overall intervention effect estimate will be calculated using Rubin's formula. SAS procedure Proc MIANALYZE will be used to implement these tasks.

To examine sensitivity to the MAR assumptions about the missing data, we will perform a sensitivity analysis under the missing not at random (MNAR) assumption. [2]

Multiple Comparisons

Since only one 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 done 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

The amount of urine leakage (AUL) will be summarized by the mean and standard deviation (or median and interquartile range if data are skewed) in each group and compared using mixed-effect model adjusted for the baseline value, with site and interaction between site and group as random effects. In case of serious violations of the model assumptions (normality and constant variance of the residuals), a log-transformation may be applied. If not appropriate, a Wilcoxon rank-sum test will be used. The effect of the treatment will be estimated by the difference (or ratio, in case of log-transformation) between treatments and will be presented along with its associated 95% confidence interval. The same method will be used for the analyses of the 1-hour AUL at week 2.

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.[3] A straightforward sensitivity analysis for the MAR assumption in multiple imputation is based on the pattern-mixture or control-based pattern imputation model under the

MNAR assumption by using the SAS procedure Proc MI process.[4] 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 observed cases, 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. Comparisons between groups will be made with the two-sample t-test to evaluate the changes from baseline at 6-, 18-, and 30-weeks. In case of serious violations of the model assumptions (normality and constant variance of the residuals), the Wilcoxon rank-sum test will be used.

Categorical data or ordinal data will be compared between groups using a Wilcoxon rank-sum test, chi-square test or Fisher's exact test, as appropriate.

The proportion of patients with 1-hour AUL decrease of at least 50% from baseline at week 6 will be compared between groups. The proportion of patients with a mean weekly 72h-IEF decrease of at least 50% from baseline at each visit will be compared between groups.

The change in 1-hour AUL at week 2 from the baseline will be analysed using the same approach as the primary outcome.

6.3.5 Safety Analyses

- Adverse events

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 EA and sham EA groups. P-value will not be corrected for multiple tests.

- Participant's compliance

The number and percentage of subjects who received at least 15 sessions(≥80%) of the planned treatments will be analyzed with Chi-square test or Fisher's exact test.

- Blinding assessment

The number and percentage of subjects who answer Yes/No when asked if they received the EA treatment to each of these questions respectively will be summarized by treatment and Chi-square test or Fisher's exact test will be used to compare the difference of blinding situation between the two groups.

6.4 Changes to the original analysis plan

As compared to the initial statistical analysis plan (SAP) published in Trials (Liu Z, Xu H, Chen Y, et al. The efficacy and safety of electro-acupuncture for women with pure stress urinary incontinence: study protocol for a multicenter randomized controlled trial. Trials 2013;14:315), The original Analysis Plan has been amended as follows:

Table 1. Major update of the published protocol

No.	Item	Published version	Final version
1	Primary outcome analysis	ANCOVA for primary outcome using baseline and **centers as covariates**. Meanwhile, a covariance model including interactions between centers and group will be made to analyze the center effect.	Mixed-effects model for primary analysis using baseline and treatment as fixed effects, **centers and interaction centers and treatment as random effects.**
2			More details were provided for the violations of the model assumptions (normality and constant variance of the residuals) in primary analysis (see 6.3.3).
3	Secondary outcomes		Imputation of missing data was used only for primary outcome using

			multiple imputation by regression or MCMC method (see 6.3.1).

References

[1] Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. Ann Intern Med. 2001. 135(2): 112-123.

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[3] Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012. 367(14): 1355-60.

[4] Bohdana Ratitch Q, Montreal Q, Canada Michael O'Kelly Q, Dublin I. Implementation of pattern-mixture models using standard SAS/STAT procedures. 2011. http://pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf. Accessed July 25,2012.