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Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

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10 4 **Electroacupuncture for stress-predominant mixed urinary**
11 **incontinence: a protocol for a three-armed randomized controlled**
12 **trial**
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14 6

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16 7 Yuanjie Sun, MD^{1*}; Yan Liu, MD^{2*}; Huan Chen, MD, MSc¹; Yan Yan, BS¹; Zhishun
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24 **Abstract**

25 **Introduction:** There is a lack of evidence targeted at stress-predominant mixed
26 urinary incontinence (MUI) at present. Acupuncture might help to relieve the
27 incontinence symptoms. We plan to conduct a multi-center, three-armed, randomized
28 controlled to investigate the efficacy of electroacupuncture (EA) on women with
29 stress-predominant MUI.

30 **Methods and analysis:** The trials will be conducted in 5 recruitment centers in China.
31 232 eligible participants will be randomly assigned to EA, sham electroacupuncture
32 (SE) or Waiting List (WL) group, at 2:1:1 ratio, to receive 8-week EA/SA with 24-
33 week follow-up, or 20-week watchful waiting. The primary outcome is defined as the
34 proportion of participants with at least 50% reduction in incontinence episode
35 frequency (IEF) from baseline at week 8. Secondary outcomes will mainly be
36 measured at weeks 4, 8, 12, 20 and 32 by 3-day voiding diary, International
37 Consultation on Incontinence Questionnaire-short form (ICIQ-SF) and 1-hour pad
38 test. All outcomes will be analyzed in intention to treat population (defined as
39 participants randomized) with a two-sided *P* value of less than .05 considered
40 significant.

41 **Ethics and dissemination:** The protocol was approved for by Guang'anmen Hospital
42 Institution of Review Board (2019-241-KY). Detailed information of the trial will be
43 informed to the participants and written informed content will be obtained from every
44 participant before randomization. Results of the trial will be expected to be published
45 on a peer-reviewed journal.

46 **Key words:** Acupuncture; Mixed urinary incontinence; Female;

47 **Trial registration:** Clinicaltrials.gov identifier: NCT04299932

48 **Strengths and limitations of this study**

- 49 ➤ The first randomized controlled trial to investigate the efficacy of acupuncture on
50 stress-predominant mixed urinary incontinence.
- 51 ➤ Sham control and no intervention control are designed to eliminate the influence

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4 52 of placebo effects and disease's nature course on efficacy of acupuncture;
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6 53 ➤ Minimal electroacupuncture serve as a sham intervention to blind participants in
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8 54 electroacupuncture and sham electroacupuncture groups.
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10 55 ➤ One limitation is that participants in waiting list group and acupuncturists cannot
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12 56 be blinded.
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57 INTRODUCTION

58 Mixed urinary incontinence (MUI) is a condition where incontinence occurs with
59 both physical exertion and urgency.¹ Compared with pure urinary incontinence (UI),
60 MUI tends to present with more severe symptoms and put greater burden on the
61 health of individual and economy of society.² An estimate of 21%-33% females in the
62 world³ and 9.4% females in China⁴ are troubled with MUI, while the report and
63 treatment rates are under one second⁵.

64 Stress-predominant MUI mainly constitutes of stress component, featuring leakage
65 on increased abdominal pressure, such as exertion, sneeze or cough. Though leakage
66 with urgency also exists, stress incontinence episode frequency (IEF) outnumbered
67 50% of total IEF.⁶

68 Current European Association of Urology (EAU) guideline on incontinence
69 recommends to initiate treatment targeted at predominant component of MUI.^{7 8}
70 However, as to whether the interventions for stress urinary incontinence (SUI) can be
71 effectively generalized to stress-predominant MUI, there is still no powerful evidence
72 to support it.⁶ Systematic reviews indicated that pelvic floor muscle training (PFMT)
73 can alleviate the symptoms of SUI patients, but the effects of it may decrease to some
74 degree in the treatment of MUI.⁹ For moderate to severe SUI, surgery might be more
75 useful than PFMT¹⁰, and long-term follow-up revealed that about half patients
76 conducting PFMT will turn to surgery for help at last¹¹. When it refers to surgery for
77 MUI, other therapies might need to be combined with to conquer the urgency
78 component.¹² In addition, the existence of urgency symptoms might aggravate after
79 surgery¹³, and even reduce the success rate of operation¹⁴. Considering all those
80 reasons, it is necessary to seek for interventions specific to stress-predominant MUI.

81 Results of previous studies indicated that acupuncture might help to relieve the
82 incontinence symptoms.^{15 16} It is proven effective in reducing leakage amount of pure
83 SUI patients¹⁵ and reducing IEF of MUI patients.¹⁶ Future analysis into the results of
84 the two trials showed that EA can relieve the symptoms of stress-related urinary

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4 85 incontinence.¹⁷ Considering the fact that the two trials weren't focused on stress-
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6 86 predominant MUI patients specifically, we plan to conduct this multi-center, three-
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8 87 armed, randomized controlled to evaluate the efficacy of EA, compared with sham
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10 88 electroacupuncture (SA) and waiting list (WL) on participants with stress-
11
12 89 predominant MUI.

13 14 90 **METHODS AND ANALYSIS**

15 16 91 **Hypotheses**

17
18 92 Our primary hypothesis is that, the effects of EA is superior to SA in improving
19
20 93 proportion of stress-predominant MUI participants with at least 50% reduction of
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22 94 stress IEF from baseline at week 8. Our secondary hypothesis is that the effects of EA
23
24 95 is superior to WL in improving the proportion mentioned above at week 8.

25 26 96 **Study design**

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28 97 This is a three-armed, randomized, SA and WL-controlled trial conducted in five
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30 98 recruitment centers, that is Guang'anmen Hospital, China Academy of Chinese
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32 99 Medical Sciences; Hengyang Hospital Affiliated to Hunan University of Chinese
33
34 100 Medicine; Yantai Hospital of Traditional Chinese Medicine; The third affiliated
35
36 101 hospital of Beijing university of Chinese Medicine and Jiangxi Provincial Hospital of
37
38 102 traditional Chinese Medicine. Participants will be enrolled from both hospitals and
39
40 103 communities.

41
42 104 The study durations are 33 weeks for participants in EA and SA group with one-
43
44 105 week baseline assessment, 8-week treatment and 24-week follow-up, while 21 weeks
45
46 106 for participants in WL group, with one-week baseline assessment and 20-week
47
48 107 follow-up (Figure 1. Flow Chart). Participations in EA and SA groups, outcome
49
50 108 assessors, data managers and statisticians will be blinded to the group allocations,
51
52 109 while acupuncturists and participants in WL group will not be blinded for obvious
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54 110 reasons.

55 56 111 **Inclusion criteria**

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58 112 1) Diagnosis of MUI by the coexistence of SUI and UII symptoms in accordance
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4 113 with EAU guideline⁸;
- 5
6 114 2) Female participants aged between 18 and 80;
- 7
8 115 3) Stress index > urge index in accordance with Medical, epidemiologic, and social
9
10 116 aspects of Aging(MESA) questionnaire¹⁸;
- 11
12 117 4) SUI episodes outnumber 50% total IEF documented in 3-day voiding diary;
- 13
14 118 5) Less than 12 micturition episodes in average 24 hours documented in 3-day
15
16 119 voiding diary;
- 17
18 120 6) Positive cough stress test;
- 19
20 121 7) Urine leakage > 1 g in 1-hour pad test¹⁹;
- 21
22 122 8) Voluntary participation in the trial and signed written informed content.
- 23
24 123 Participants meeting all these eight criteria might be able to be recruited in the trial.

25
26 124 **Exclusion criteria**

- 27
28 125 1) Urgency-predominant MUI, pure SUI, pure UUI, overflow UI and neurogenic
29
30 126 bladder;
- 31
32 127 2) Uncontrolled symptomatic urinary tract infection;
- 33
34 128 3) Tumor in urinary system and pelvic organ;
- 35
36 129 4) Pelvic organ prolapse \geq degree II ;
- 37
38 130 5) Residual urine volume \geq 100ml;
- 39
40 131 6) History of treatments targeted at UI, such as acupuncture and PFMT;
- 41
42 132 7) History of surgery targeted at UI or in pelvic floor, including hysterectomy;
- 43
44 133 8) Uncontrolled diabetes or severe high blood pressure;
- 45
46 134 9) Nervous system diseases that may hamper the function of urinary system, such as
47
48 135 Multiple sclerosis, Alzheimer's disease, Parkinson's disease, spinal cord injury,
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50 136 cauda equina nerve injury, or multiple system atrophy;
- 51
52 137 10) Severe heart, lung, brain, liver, kidney, mental illness, coagulation dysfunction or
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54 138 with obvious cognitive dysfunction
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56 139 11) Installed cardiac pacemaker;
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58 140 12) Inconvenient or unable to walk, run, go up and down stairs;
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4 141 13) Allergy to metal, severely fear of acupuncture needles or unbearable to EA;
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6 142 14) Pregnant at present, plan to conceive in future one year, at lactation period or
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8 143 within 12 months after childbirth.

9
10 144 Participants with either situation mentioned above will not be enrolled in the trial.

11 145 **Randomization and allocation concealment**

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13
14 146 The randomization allocation sequence will be produced by a third independent
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16 147 party (Linkermed Technology Co., Ltd. [Beijing, China]). Eligible participants will be
17
18 148 randomly assigned into EA group, SA group or WL group at 2:1:1 ratio, with varied
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20 149 blocks and using recruitment sites as stratification factor. The randomization number
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22 150 and group allocation will be acquired by acupuncturists in each recruitment site by
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24 151 logging in the Central Randomization System and typing in basic information of
25
26 152 eligible participants.

27 153 **Interventions**

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29
30 154 Participants in EA group will receive stimulation at bilateral BL33 (Zhongliao),
31
32 155 BL35 (Huiyang) and SP6 (Sanyinjiao). BL 33 is located in the third posterior sacral
33
34 156 foramen; BL 35, 0.5 cun ($\approx 10\text{mm}$) lateral to the extremity of the coccyx; and SP6
35
36 157 posterior to the medial border of the tibia, 3 cun superior to the prominence of the
37
38 158 medial malleolus.²⁰ Bilateral BL33 will be inserted by acupuncture needles (Huatuo,
39
40 159 Suzhou Medical Appliance) of 0.30×75mm size at the angle of 45° , inward and
41
42 160 downward, till the depth of 60-70mm. Bilateral BL35 will be inserted by needles of
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44 161 0.30×75mm size, slightly outward and upward, till the depth of 60-70mm. Bilateral
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46 162 SP6 will be inserted by needles of 0.30×40mm till the depth of 25-30mm. All the
47
48 163 needles will be lifted, thrust and twisted evenly for three times, right after insetion,
49
50 164 to induce the sensation of *deqi*. Electronic acupuncture apparatus (Yingdi KWD 808 I
51
52 165 electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi Electronic
53
54 166 Medical Device Co., Ltd) will be connected to the three pairs of needles transversally,
55
56 167 with continuous wave of 20Hz, electric current of 2mA-6.5mA for BL33 and BL35,
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58 168 and 1mA-3.5mA for SP6. The EA stimulation will last 30mins for each session, 3
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4 169 sessions a week (ideally every other day) for a succession of 8 weeks.
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6 170 Participants in SA group will receive minimal stimulation at bilateral sham BL33
7
8 171 (Zhongliao), BL35 (Huiyang) and SP6 (Sanyinjiao). Sham BL33 is in the area of 1
9
10 172 cun (≈ 20 mm) horizontally outside BL33; sham BL35, 1 cun (≈ 20 mm) horizontally
11
12 173 outside BL35; Sham SP6, in the middle of SP6 and tendons. The three pairs of
13
14 174 acupoints will be inserted by acupuncture needles of 0.30×40mm size to a depth of 2-
15
16 175 3mm till the needles can stand still. No manipulations will be conducted, and the
17
18 176 sensation of *deqi* will not be induced. Electronic acupuncture apparatus will be
19
20 177 connected to the three pairs of needles transversally, with continuous wave of 20Hz
21
22 178 and minimal electric current (ideally at a degree which participant can just percept). In
23
24 179 about 30 seconds, the electric current will be turned off, leaving the indicator light and
25
26 180 ticking sound on. The treatment sessions are similar to those in EA group.

27
28 181 Participants will be told ahead of time that they may receive either traditional EA
29
30 182 treatment, or modern EA treatment; they might not feel the electrical stimulation
31
32 183 during the process out of body adaption. To evaluate the success of blindness, within
33
34 184 5 minutes after the last treatment at week 8, participants in both EA and SA groups
35
36 185 will be asked to answer the question do you think you have received traditional EA,
37
38 186 and choose the answer between the options of Yes or No.

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40 187 Participants in WL group will not receive active treatments. After the trial, they
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42 188 will receive 24-session EA treatment as mentioned above as compensation.

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44 189 Participants in the three groups will receive handbook of healthcare education and
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46 190 advice on lifestyle modification, such as the conditions of exercise, fluid intake,
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48 191 weight, smoking, constipation, urinary tract infection, lifting, and respiratory
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50 192 symptoms, etc. The lifestyles changed accordingly will be documented in case report
51
52 193 form. During the process, participants are not allowed to take other specialized
53
54 194 medication and treatments for UI. Any medications that might influence the function
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56 195 of lower urinary tract function should be documented in case report form.

57 196 **Outcomes**

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4 197 **Primary outcome**

5 198 In this trial, the primary outcome is defined as the proportion of participants with at
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7 199 least 50% reduction in IEF from baseline, measured by 3-day voiding diary at weeks
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9 200 8. Three-diary voiding diary is a reliable and validated tool for urinary incontinence in
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11 201 both clinic and research, without placing great burden on participants.²¹ In 3-day
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13 202 voiding diary, IEF of different types, micturition and nocturia episodes, fluid intake,
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15 203 and pad consumptions will all be documented. Participants are required to fill in the
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17 204 diary in baseline assessment period (week 0), weeks 4, weeks 8, weeks 20 and weeks
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19 205 32 (participants in EA and SA group only).

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22 206 **Secondary outcomes**

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24 207 Secondary outcomes will be measured by 3-day voiding diary, International
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26 208 Consultation on Incontinence Questionnaire-short form (ICIQ-SF), 1-hour pad test
27
28 209 and patient global impression of improvement (PGI-I). (Figure 2. Study schedule)

29
30 210 ICIQ-SF questionnaire is a validated questionnaire to assess the severity of
31
32 211 incontinence symptoms and influence on QoL in the past four weeks. The
33
34 212 questionnaire includes items of IEF, urinary leakage amount and general influence on
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36 213 life to be scored. Total number of the score ranges from 1 to 21, with higher scores
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38 214 representing greater severity and 2.52 as minimal clinically important
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40 215 differences²². Participants will complete the Chinese-version questionnaire²³ at
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42 216 baseline assessment period (week 0), weeks 4, weeks 8, weeks 20 and weeks 32
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44 217 (participants in EA and SA group only).

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46 218 One-hour pad test is the only tool standardized with a set protocol to measure the
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48 219 urinary leakage¹⁹. Participants will be instructed to drink 500 ml solid-free water,
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50 220 and perform a series of activities including standing and sitting, coughing, running,
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52 221 picking up a coin and putting hands under water. The leakage amount in one hour will
53
54 222 be measured via pad.²⁴ Participants will conduct 1-hour pad test in baseline
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56 223 assessment period (week 0) and weeks 8.

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58 224 PGI-I is a global index, with only one item, used to rate the participants' subject
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4 225 perception on symptom improvement. In weeks 8 and 20, participants in the three
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6 226 groups will describe their impression from very much better to very much worse.²⁵
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8 227 Improvement was considered to be clinically significant if the participant's response
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10 228 is "much better" or "very much better".

11 229 To better evaluate the efficacy and safety of acupuncture, participants expectations
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13 230 towards outcome and beliefs on acupuncture will also be assessed. Adverse events
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15 231 and severe adverse events will be documented in case report form throughout the trial.
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17 232 Acupuncturists in each site will decide whether the events are related to the treatments
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19 233 or not.

22 234 **Quality control and data management**

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24 235 To ensure the quality of the study, personnel in recruitment sites will be trained by
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26 236 the principal investigator (ZS Liu) on the details of the protocol and manipulating
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28 237 methods. Acupuncture in both EA and SA groups are required to be conducted by
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30 238 licensed acupuncturists with at least two-year clinical experience. In each site, at least
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32 239 two acupuncturists are needed for rotation, while the treatment of each participant
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34 240 should be restricted to one specific doctor.

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36 241 Measures will be taken to improve the compliance. The same participants should be
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38 242 taken charged by the same outcome assessor/acupuncturist throughout the trial,
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40 243 including instruction on the documentation of voiding diary, explanation on the
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42 244 contents of handbook if necessary, and informing the assessment time by phone or
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44 245 we-chat.

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46 246 The data will be recorded in paper CRF first, and typed into EDC system within
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48 247 one week, so that the information can be traced back, monitored by CRA and system
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50 248 in time, and supplemented without delay, if missing or inaccuracy. In follow-up
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52 249 period, missing data in voiding diary can be asked by phone rather than in person. The
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54 250 database will be protected by a password and only the principal investigator will have
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56 251 access to the final dataset. Data are available upon reasonable request to the principal
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58 252 investigator, excluding the private information of patients.

253 **Sample size**

254 A sample size of 232 participants will provide the trial with 80% power to detect a
255 between-group difference of about 23% of participants with at least 50% reduction
256 from baseline in the stress IEF measured by 3-day voiding diary with a two-sided
257 significance level of 0.05 and 10% dropouts, assuming that a reduction rate of 25%
258 for the IEF in the SA group on the basis of previous study^{15 16}.

259 **Statistical analysis**

260 For primary hypothesis, we will compare the proportion of participants with at least
261 50% reduction in mean 24-hour stress IEF at week 8 among the three groups. The
262 primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test to
263 compare the rate of participants with at least 50% reduction in stress IEF at week 8
264 between the EA group and the WL group. If this analysis is significant, the
265 hierarchical testing will be used the EA group versus the SA group.

266 For other categorical variables, comparisons between treatment groups will be
267 assessed using the Fisher exact test or Chi-squared test as appropriate. We will use the
268 *t* test or Wilcoxon rank-sum test to analyze change of urinary leakage amount from
269 baseline, change of mean 24-hour IEF from baseline, change of total and sub-score of
270 ICIQ-SF from baseline, change of 24-h urgency episodes from baseline, and other
271 continuous variables. Chi-square or Fisher's exact tests will be used to compare the
272 frequency of AEs between groups.

273 All outcomes will be analyzed in intention to treat (ITT) population (defined as
274 participants randomized). Analysis will be performed using SAS version 9.4 (SAS
275 Institute Inc) with a two-sided P value of less than .05 considered significant.

276 **Patient and public involvement**

277 Patients or the public are not involved in the design, or conduct, or reporting, or
278 dissemination plans of our research.

279 **Ethics and dissemination**

280 The protocol was approved for by Guang'anmen Hospital Institution of Review

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4 281 Board (2019-241-KY), and registered on Clinicaltrials.gov (NCT04299932). The
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6 282 revisions of the protocol will be reported on the website. The trial will be conducted
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8 283 according to the Declaration of Helsinki and the International Conference on
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10 284 Harmonization Good Clinical Practice E6 Guidance for Good Clinical Practice.
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12 285 Detailed information of the trial will be informed to the participants and written
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14 286 informed content will be obtained from every participant before randomization.
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16 287 Participants in WL group will receive 24-session EA treatment for compensation.
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18 288 Results of the trial will be expected to be published on a peer-reviewed journal.

19 289 **DISCUSSION**

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22 290 MUI is a condition frustrating almost a third women globally, while about half of
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24 291 them feel embarrassed to speak it out^{3 5}. In clinic, a reduction of at least 50% IEF is
25
26 292 regarded as successful treatment.²⁶ Since the specific and non-specific effects of
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28 293 acupuncture towards stress-predominant MUI are still unclear, we make effort to
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30 294 explore the efficacy of EA under clinical meaningful outcome with SA and WL as
31
32 295 controls. The acupoint regimen and administration protocol in this trial are based on
33
34 296 the results of previous studies^{15 16} and specialist consensus.

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36 297 Apart from specific physiological effect, participants' expectation of a positive
37
38 298 outcome and belief in acupuncture may have a physiological effect on the brain,
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40 299 adding non-specific clinical response to acupuncture.²⁷ For this reason, we design
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42 300 participants' expectations towards outcome and beliefs on acupuncture to assess the
43
44 301 efficacy.

45
46 302 Given the fact that a large proportion of participants in China have received
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48 303 acupuncture treatment in their experience, to better blind the participants in SA group,
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50 304 acupuncture needles will be inserted minimally into skin at none-acupoint areas. The
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52 305 minimal insertion also makes participants to be more sensitive to the electrical current
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54 306 and percept the stimulation as soon as possible. The electrical current may further
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56 307 improve the blindness even if it is connected to needles for only about 30 seconds.

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58 308 Limitation also exists in that the participants in WL group and acupuncturists
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4 309 cannot be blinded, which might induce performance and detection bias into the trial.
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6 310 To decrease influence towards the results, the outcome assessment will be undertaken
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8 311 by an independent research assistant who know nothing about the allocation.
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4 312 **Ethical Approval and Consent to participate:** The study has received approval
5
6 313 from the Guang'anmen Hospital Institution of Review Board (2019-241-KY). Written
7
8 314 informed content will be obtained from every participant.

9
10 315 **Consent for publication:** Not applicable.

11
12 316 **Authors' contributions:** Zhishun Liu conceived the study, initiated the design, and
13
14 317 revised the manuscript; Yan Liu is responsible for statistical analysis plan and drafted
15
16 318 the manuscript; Yuanjie Sun participated the design and drafted the manuscript; Huan
17
18 319 Chen participated the design and revised the manuscript; Yan Yan helped to draft the
19
20 320 manuscript. All authors have read and approved the final manuscript.

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27
28 324 They have no role in study design and will have no role in collection, management,
29
30 325 analysis, and interpretation of data; writing of the report; and the decision to submit
31
32 326 the report for publication.

33
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35
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37
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4 **Figure legends**

5 Figure 1. Flow chart

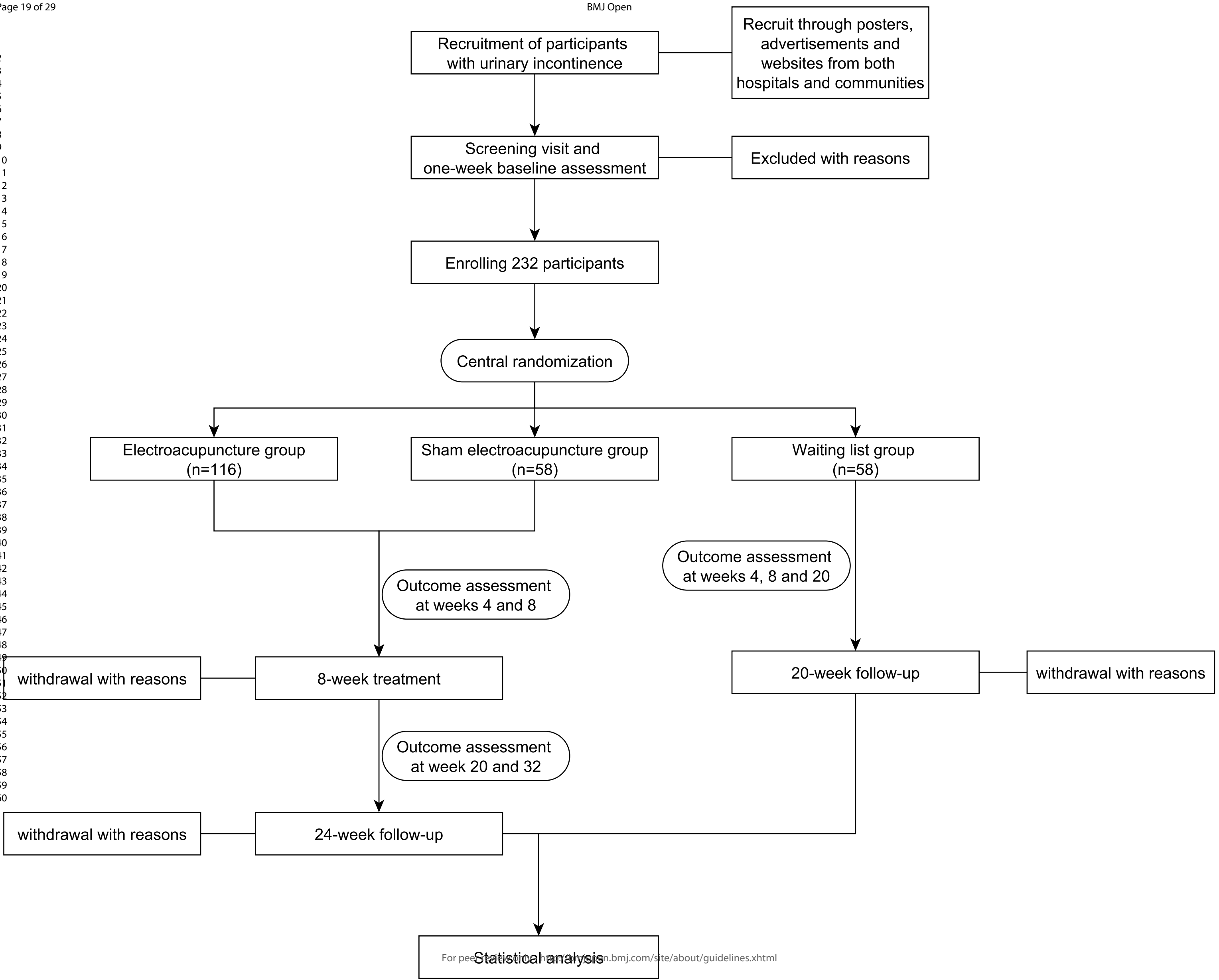
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7 Figure 2. Study schedule

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9 * Only for participants in electroacupuncture and sham electroacupuncture groups

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TIMEPOINT		Week -1	Week 0	Week 4	Week 8	Week 20	Week 32*
ENROLMENT	Eligibility screen	×					
	Informed consent	×					
	Allocation		×				
INTERVENTIONS	Electroacupuncture			×	×		
	Sham electroacupuncture			×	×		
	Waiting list			×	×	×	
ASSESSMENTS	Demography information	×					
	3-day voiding diary	×		×	×	×	×
	1-hour pad test	×			×		
	International Consultation on Incontinence Questionnaire short form	×		×	×	×	×
	Patient global impression of improvement			×		×	
	Adverse events	×	×	×	×	×	×
	Blindness assessment*				×		
	Expectation assessment*	×					
	Belief assessment*	×		×			

Testimonials of sponsor

This study was supported by “The 13th Five-year” National Science and Technology Pillar Program (grant number 2017YFC1703602) by the Ministry of Science and Technology of the People’s Republic of China.

We provide the cover page and signature and seal pages of project assignment paper as testimonials.

Attachment 1: Cover page of project assignment paper

Attachment 2: Signature and seal pages of project assignment paper

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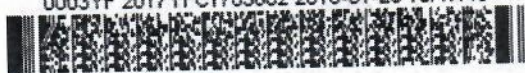
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11
12 国家重点研发计划
13 课题任务书
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22 课题名称： 电针治疗神经源性尿潴留、膀胱过度活动症的疗效评
23 价
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25 所属项目： 针灸优势病种疗效评价国际合作研究
26
27 所属专项： 中医药现代化研究
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29 项目牵头承担单位： 中国中医科学院中医临床基础医学研究所
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31 课题承担单位： 中国中医科学院广安门医院
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33 课题负责人： 刘志顺
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35 执行期限： 2018年03月至2021年12月
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中华人民共和国科学技术部制

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任务书签署

甲乙双方根据《国务院关于改进加强中央财政科研项目和资金管理的若干意见》（国发[2014]11号）、《国务院印发关于深化中央财政科技计划（专项、基金）管理改革方案的通知》（国发[2014]64号）、《科技部 财政部关于印发〈国家重点研发计划管理暂行办法〉的通知》（国科发资[2017]152号）、《财政部 科技部关于印发〈国家重点研发计划资金管理办法〉的通知》（财科教[2016]113号）、《科技部财政部关于印发〈中央财政科技计划（专项、基金等）监督工作暂行规定〉的通知》（国科发政[2015]471号）等有关文件规定，以及有关法律、政策和管理要求，依据项目立项通知，签署本任务书。

项目牵头承担单位（甲方）：

法定代表人签字（签章）：



项目负责人签字 (签章): 何丽云

2018年3月15日

课题承担单位 (乙方):

法定代表人签字 (签章):

王阶



课题负责人签字 (签章):

刘建

2018年3月15日



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Table 1



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
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5		18b	Plans to promote participant retention and complete follow-up, including list 8
6			of any outcome data to be collected for participants who discontinue or
7			deviate from intervention protocols
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10	Data	19	Plans for data entry, coding, security, and storage, including any related 10
11	management		processes to promote data quality (eg, double data entry; range checks for
12			data values). Reference to where details of data management procedures
13			can be found, if not in the protocol
14			
15	Statistical	20a	Statistical methods for analysing primary and secondary outcomes. 11
16	methods		Reference to where other details of the statistical analysis plan can be
17			found, if not in the protocol
18			
19			
20		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) NA
21			
22		20c	Definition of analysis population relating to protocol non-adherence (eg, as
23			randomised analysis), and any statistical methods to handle missing data 11
24			(eg, multiple imputation)
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27	Methods: Monitoring		
28			
29	Data	21a	Composition of data monitoring committee (DMC); summary of its role and NA
30	monitoring		reporting structure; statement of whether it is independent from the sponsor
31			and competing interests; and reference to where further details about its
32			charter can be found, if not in the protocol. Alternatively, an explanation of
33			why a DMC is not needed
34			
35			
36		21b	Description of any interim analyses and stopping guidelines, including who NA
37			will have access to these interim results and make the final decision to
38			terminate the trial
39			
40	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and 10
41			spontaneously reported adverse events and other unintended effects of
42			trial interventions or trial conduct
43			
44			
45	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether NA
46			the process will be independent from investigators and the sponsor
47			
48			
49	Ethics and dissemination		
50			
51	Research	24	Plans for seeking research ethics committee/institutional review board 11-12,14
52	ethics		(REC/IRB) approval
53	approval		
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5	Protocol	25	Plans for communicating important protocol modifications (eg, changes to	12
6	amendments		eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,	
7			REC/IRBs, trial participants, trial registries, journals, regulators)	
8				
9	Consent or	26a	Who will obtain informed consent or assent from potential trial participants	14
10	assent		or authorised surrogates, and how (see Item 32)	
11				
12		26b	Additional consent provisions for collection and use of participant data and	NA
13			biological specimens in ancillary studies, if applicable	
14				
15				
16	Confidentiality	27	How personal information about potential and enrolled participants will be	10
17			collected, shared, and maintained in order to protect confidentiality before,	
18			during, and after the trial	
19				
20	Declaration of	28	Financial and other competing interests for principal investigators for the	14
21	interests		overall trial and each study site	
22				
23				
24	Access to	29	Statement of who will have access to the final trial dataset, and disclosure	10
25	data		of contractual agreements that limit such access for investigators	
26				
27	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for compensation to	NA
28	post-trial care		those who suffer harm from trial participation	
29				
30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	10
31	policy		participants, healthcare professionals, the public, and other relevant groups	
32			(eg, via publication, reporting in results databases, or other data sharing	
33			arrangements), including any publication restrictions	
34				
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36		31b	Authorship eligibility guidelines and any intended use of professional	NA
37			writers	
38				
39		31c	Plans, if any, for granting public access to the full protocol, participant-level	10
40			dataset, and statistical code	
41				
42				
43	Appendices			
44				
45	Informed	32	Model consent form and other related documentation given to participants	8
46	consent		and authorised surrogates	
47	materials			
48				
49	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
50	specimens		specimens for genetic or molecular analysis in the current trial and for	
51			future use in ancillary studies, if applicable	
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5 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation &
6 Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.
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8 NonCommercial-NoDerivs 3.0 Unported](#)" license.
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BMJ Open

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038452.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Sep-2020
Complete List of Authors:	Sun, Yuanjie; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture Liu, Yan; Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital, Key Laboratory of Chinese Internal Medicine of Ministry of Education Chen, Huan; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture Yan, Yan; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture Liu, zhishun; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Urology, Complementary medicine
Keywords:	Urinary incontinences < UROLOGY, Bladder disorders < UROLOGY, COMPLEMENTARY MEDICINE

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8 3 Article title:

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10 4 **Electroacupuncture for stress-predominant mixed urinary**
11 **incontinence: a protocol for a three-armed randomized controlled**
12 **trial**

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16 7 Yuanjie Sun, MD^{1*}; Yan Liu, MD^{2*}; Huan Chen, MD, MSc¹; Yan Yan, BS¹; Zhishun
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18 8 Liu, MD, PhD^{1†}

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32 15 *Yuanjie Sun and Yan Liu contributed equally to this work and shared the first author
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34 16 position.

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43
44 21 **Running title:** acupuncture for stress-predominant mixed urinary incontinence

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46 22 **Word count:** abstract 197; main text 3164

1
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4 23 **Abstract**

5 24 **Introduction:** Evidence targeted at stress-predominant mixed urinary incontinence is
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7 still lack at present, and acupuncture might help to relieve the symptoms. We plan to
8
9 conduct this multi-center, three-armed, randomized controlled trial to investigate the
10
11 efficacy and safety of electroacupuncture on women with stress-predominant mixed
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13 urinary incontinence.
14

15 29 **Methods and analysis:** The trial will be conducted in 5 hospitals in China. 232
16
17 eligible women will be randomly assigned to electroacupuncture, sham
18
19 electroacupuncture or waiting list group, at 2:1:1 ratio, to receive 24-session
20
21 acupuncture or sham acupuncture treatment over 8 weeks and 24-week follow-up, or
22
23 20-week watchful waiting. The primary outcome is the proportion of participants with
24
25 at least 50% reduction in mean 24-hour stress incontinence episode frequencies from
26
27 baseline to week 8. The outcome will be analyzed in intention to treat population
28
29 (defined as participants randomized) with a two-sided *P* value of less than .05
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31 considered significant.
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34 38 **Ethics and dissemination:** The protocol was approved by Guang'anmen Hospital
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36 Institution of Review Board (2019-241-KY). Detailed information of the trial will be
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38 informed to the participants and written informed content will be obtained from every
39
40 participant before randomization. Results of the trial will be expected to be published
41
42 on a peer-reviewed journal.
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44 43 **Key words:** Acupuncture; Mixed urinary incontinence; Female; Stress urinary
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46 incontinence
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48 45 **Trial registration:** Clinicaltrials.gov identifier: NCT04299932
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4 **46 Strengths and limitations of this study**

- 5
6 47 ➤ The first randomized controlled trial to investigate the efficacy and safety of
7
8 48 acupuncture on stress-predominant mixed urinary incontinence.
- 9
10 49 ➤ Sham control and waiting-list control are designed to eliminate the influence of
11
12 50 placebo effects and disease's natural course on the efficacy of acupuncture;
- 13
14 51 ➤ Minimal electroacupuncture serves as a sham intervention to blind participants in
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16 52 the electroacupuncture and sham electroacupuncture groups.
- 17
18 53 ➤ One limitation is that acupuncturists and participants in the waiting list group
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20 54 cannot be blinded.
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55 INTRODUCTION

56 Mixed urinary incontinence (MUI) is a complaint of involuntary loss of urinary
57 associated with both physical exertion and urgency.¹ Compared with pure urinary
58 incontinence (UI), MUI presents with more severe symptoms and puts greater burden
59 on the health of individuals and economy of the society.² An estimate of 21%-33%
60 females in the world³ and 9.4% females in China⁴ are troubled with MUI, while less
61 than fifty percent of such population report it to doctors and receive treatment⁵.

62 Stress-predominant MUI constitutes mainly of stress component. It features leakage
63 on increased abdominal pressure, which can be induced by exertion, sneeze, cough,
64 etc. Despite the existence of leakage with urgency, stress incontinence episode
65 frequency (IEF) outnumbered 50% of total IEF.⁶

66 Current European Association of Urology (EAU) guideline on incontinence
67 recommends to initiate treatment targeted at predominant component of MUI.⁷
68 However, no strong evidence supported that the interventions for stress urinary
69 incontinence (SUI) is as effective when treating stress-predominant MUI.⁶ The effects
70 of pelvic floor muscle training (PFMT), first-line therapy for pure SUI, decrease
71 among MUI patients.⁸ About half of patients practicing PFMT will seek help from
72 surgery eventually in long-term follow-up⁹, and surgery might be more useful than
73 PFMT for moderate to severe symptoms¹⁰. When surgery is considered for MUI,
74 other therapies might need to be combined with to control the urgency component.¹¹
75 In addition, the existence of urgency symptoms might be aggravated after surgery¹²,
76 and even reduce the success rate of stress incontinence operation¹³. Therefore, it is
77 necessary to seek for interventions specific to stress-predominant MUI.

78 Results of previous studies indicates that acupuncture may help to relieve the
79 incontinence symptoms.^{14 15} It is proven effective in reducing leakage amount of pure
80 SUI¹⁴ and total IEF of MUI.¹⁵ Further analysis of the two trials suggests EA might
81 relieve the symptoms of stress-related UI.¹⁶ Since the two trials didn't focus on stress-
82 predominant MUI specifically, this multi-center, three-armed, randomized controlled

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4 83 is designed to evaluate the efficacy and safety of EA in participants with stress-
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6 84 predominant MUI.

7 8 85 **Hypotheses**

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10 86 Our primary hypothesis is that the effects of EA is superior to sham
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12 87 electroacupuncture (SA) and waiting list (WL) in improving proportion of stress-
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14 88 predominant MUI participants with at least 50% reduction of mean 24-hour stress IEF
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16 89 from baseline to week 8.

17 18 90 **METHODS AND ANALYSIS**

19 20 91 **Study design**

21
22 92 This is a three-armed, randomized, SA and WL-controlled trial conducted in five
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24 93 recruitment sites, which are Guang'anmen Hospital, China Academy of Chinese
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26 94 Medical Sciences; Hengyang Hospital Affiliated to Hunan University of Chinese
27
28 95 Medicine; Yantai Hospital of Traditional Chinese Medicine; The third affiliated
29
30 96 hospital of Beijing university of Chinese Medicine and Jiangxi Provincial Hospital of
31
32 97 traditional Chinese Medicine.

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34 98 The study durations are 33 weeks for participants in the EA and SA groups with
35
36 99 one-week baseline assessment, 8-week treatment and 24-week follow-up; while 21
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38 100 weeks for participants in the WL group, with one-week baseline assessment and 20-
39
40 101 week watchful waiting (Figure 1. Flow Chart). The study will start recruitment on
41
42 102 October 9, 2020, and is anticipated to finish the treatment and follow-up on
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44 103 September 30, 2023. Participations in the EA and SA groups, outcome assessors, data
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46 104 managers and statisticians will be blind to the group allocation, while acupuncturists
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48 105 and participants in the WL group will not be blind for obvious reasons.

49 50 106 **Patient and public involvement**

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52 107 Patients or the public are not involved in the design, or conduct, or reporting, or
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54 108 dissemination plans of our research.

55 56 109 **Inclusion criteria**

57
58 110 1) Diagnosis of MUI by the coexistence of SUI and UUI symptoms in accordance
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4 111 with EAU guideline⁷;
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6 112 2) Female participants aged between 35 and 75;
- 7
8 113 3) Stress index > urge index in accordance with Medical, epidemiologic, and social
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10 114 aspects of Aging(MESA) questionnaire¹⁷;
- 11
12 115 4) Symptoms of MUI for at least three months, and SUI episodes outnumber 50%
13
14 116 total IEF documented in 3-day voiding diary;
- 15
16 117 5) Less than 12 micturition episodes in average 24 hours documented in 3-day
17
18 118 voiding diary;
- 19
20 119 6) Positive cough stress test;
- 21
22 120 7) Urine leakage > 1 g in 1-hour pad test¹⁸;
- 23
24 121 8) Voluntary participation in the trial and signed written informed content.
- 25
26 122 Participants meeting all these eight criteria might be able to be recruited in the trial.

27
28 **123 Exclusion criteria**

- 29
30 124 1) Urgency-predominant MUI, pure SUI, pure UUI, overflow UI and neurogenic
31
32 125 bladder;
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34 126 2) Uncontrolled symptomatic urinary tract infection;
- 35
36 127 3) Tumor in urinary system and pelvic organ;
- 37
38 128 4) Pelvic organ prolapse \geq degree II ;
- 39
40 129 5) Residual urine volume \geq 100ml;
- 41
42 130 6) History of treatments targeted at UI, such as acupuncture, PFMT and medications
43
44 131 in the previous one month;
- 45
46 132 7) History of surgery targeted at UI or in pelvic floor, including hysterectomy;
- 47
48 133 8) Uncontrolled diabetes or severe high blood pressure;
- 49
50 134 9) Nervous system diseases that may hamper the function of urinary system, such as
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52 135 Multiple sclerosis, Alzheimer's disease, Parkinson's disease, spinal cord injury,
53
54 136 cauda equina nerve injury, or multiple system atrophy;
- 55
56 137 10) Severe heart, lung, brain, liver, kidney, mental illness, coagulation dysfunction or
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58 138 with obvious cognitive dysfunction
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4 139 11) Installed cardiac pacemaker;
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6 140 12) Inconvenient or unable to walk, run, go up and down stairs;
7
8 141 13) Allergy to metal, severely fear of acupuncture needles or unbearable to EA;
9
10 142 14) Pregnant at present, plan to conceive in future one year, at lactation period or
11
12 143 within 12 months after childbirth.

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14 144 Participants with either situation mentioned above will not be enrolled in the trial.

15 145 **Randomization and allocation concealment**

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17
18 146 The randomization allocation sequence will be produced by a third independent
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20 147 party (Linkermed Technology Co., Ltd. [Beijing, China]). Eligible participants will be
21
22 148 randomly assigned into the EA, SA or WL group at 2:1:1 ratio, stratified by
23
24 149 recruitment sites and using varied blocks. The randomization number and group
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26 150 allocation will be acquired by acupuncturists in each recruitment site by logging in the
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28 151 Central Randomization System and typing in basic information of eligible
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30 152 participants.

31 153 **Interventions**

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34 154 The acupoint regimen and administration protocol are both based on the results of
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36 155 previous studies and specialist consensus^{14 15}. Participants in the EA group will
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38 156 receive stimulation at bilateral BL33 (Zhongliao), BL35 (Huiyang) and SP6
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40 157 (Sanyinjiao). BL 33 is located in the third posterior sacral foramen; BL35, 0.5 cun (\approx
41
42 158 10mm) lateral to the extremity of the coccyx; and SP6 posterior to the medial border
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44 159 of the tibia, 3 cun superior to the prominence of the medial malleolus.¹⁹ Bilateral
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46 160 BL33 will be inserted by acupuncture needles (Huatuo, Suzhou Medical Appliance)
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48 161 of 0.30×75mm size at the angle of 45° , inward and downward, till the depth of 60-
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50 162 70mm. Bilateral BL35 will be inserted by needles of 0.30×75mm size, slightly
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52 163 outward and upward, till the depth of 60-70mm. Bilateral SP6 will be inserted by
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54 164 needles of 0.30×40mm till the depth of 25-30mm. All the needles will be lifted,
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56 165 thrust and twisted evenly for three times, right after insertion, to induce the
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58 166 sensation of *deqi*. Electronic acupuncture apparatus (Yingdi KWD 808 I electro pulse
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4 167 acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical Device
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6 168 Co., Ltd) will be connected to the three pairs of needles transversally, with continuous
7
8 169 wave of 20Hz, electric current of 2mA-6.5mA for BL33 and BL35, and 1mA-3.5mA
9
10 170 for SP6. The EA stimulation will last 30mins for each session, 3 sessions a week
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12 171 (ideally every other day) for a succession of 8 weeks.

13
14 172 Participants in the SA group will receive superficial insertion at bilateral sham
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16 173 BL33 (Zhongliao), sham BL35 (Huiyang) and sham SP6 (Sanyinjiao). Sham BL33 is
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18 174 in the area 1 cun (≈ 20 mm) horizontally outside of BL33; sham BL35, 1 cun (\approx
19
20 175 20mm) horizontally outside of BL35; Sham SP6, in the middle of SP6 and tendons.
21
22 176 The three pairs of acupoints will be inserted by acupuncture needles of 0.30 \times 40mm
23
24 177 size to a depth of 2-3mm till the needles can stand still. No manipulations will be
25
26 178 conducted, and the sensation of *deqi* will not be induced. Electronic acupuncture
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28 179 apparatus will be connected to the three pairs of needles transversally, with
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30 180 continuous wave of 20Hz and minimal electric current (ideally at a degree which
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32 181 participant can just percept). In about 30 seconds, the electric current will be turned
33
34 182 down, leaving the indicator light and ticking sound on. The treatment sessions are
35
36 183 similar to those in the EA group.

37
38 184 Participants in the EA and SA groups will be blind to the group allocations.
39
40 185 Acupuncturists and research assistants will be instructed not to tell the group
41
42 186 allocation to participants. Addition, to avoid the occurrence of inadvertent unblinding,
43
44 187 the contacts between participants and project staff during treatment will be reduced as
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46 188 much as possible, and the manipulation of acupuncture, connecting to electronic
47
48 189 apparatus and withdrawal of needles will be separately undertaken by acupuncturists
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50 190 and another research assistant. Participants will be treated separately with curtain
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52 191 drawing and their companions waiting outside the clinic, if any. Before manipulation,
53
54 192 participants will be told that during the treatment they may feel the electrical
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56 193 stimulation fade down gradually, even to the degree that they cannot percept. That is
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58 194 because the body has built up a tolerance to the electrical stimulation during the
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4 195 treatment process. Within 5 minutes after either treatment at week 8, participants will
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6 196 be told that they may have received EA treatment with deep insertion, or SA
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8 197 treatment with shallow insertion, and asked to answer the question do you think you
9
10 198 have received EA treatment, and choose the answer between the options of Yes and
11
12 199 No.

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14 200 Participants in the WL group will not receive active treatments. After the trial, they
15
16 201 will receive 24-session EA treatment mentioned above as compensation.

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18 202 Participants in all the three groups will receive handbook of healthcare education
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20 203 and lifestyle modification advice, concerning exercise, fluid intake, weight loss,
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22 204 smoking and respiratory symptoms, constipation, heavy lifting and urinary tract
23
24 205 infection. During the process of the trial, participants are not allowed to take other
25
26 206 specialized medication and treatments for UI, such as PFMT or antimuscarinic agents;
27
28 207 details should be recorded in CRF if used. Any medications that might influence the
29
30 208 function of lower urinary tract function should also be documented in CRF.

31 32 209 **Outcomes**

33 34 210 Primary outcome

35
36 211 The primary outcome is the proportion of participants with at least 50% reduction
37
38 212 in mean 24-hour stress IEF from baseline to week 8, measured by 3-day voiding
39
40 213 diary. At least 50% reduction in IEF is regarded as successful treatment in clinic,²⁰
41
42 214 and 3-day voiding diary is a reliable and validated tool for UI in both clinic and
43
44 215 research, without much burden placed on participants.²¹ In 3-day voiding diary, IEF
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46 216 of different types, micturition and nocturia episodes, fluid intake, and pad
47
48 217 consumptions will be documented.

49 50 218 Secondary outcomes

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52 219 Secondary outcomes will be measured by 3-day voiding diary, International
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54 220 Consultation on Incontinence Questionnaire-short form (ICIQ-SF) and Overactive
55
56 221 Bladder Questionnaire short form (OAB-q SF) at weeks 4, 8, 20 and 32; 1-hour pad
57
58 222 test at week 8; and Patient Global Impression of Improvement (PGI-I) at weeks 8 and
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60

223 20 (Figure 2. Study schedule). The specific secondary outcome measures and time
224 frame are displayed in Table 1. Secondary outcome measures.

225 ICIQ-SF is a validated tool to assess the frequency, severity and influence on QoL
226 of UI in the past 4 weeks^{22 23}. The total score of the questionnaire ranges from 1 to 21,
227 with higher score indicating greater severity.

228 OAB-q SF is used to assess the OAB symptom bother and the health-related quality
229 of life (HRQL) in the past 4 weeks^{24 25}. The domains include coping, concern, sleep
230 and emotional interactions. The scores are transformed to a 0- to 100-point scale, with
231 higher scores indicating severe symptoms and better HRQL.

232 One-hour pad test is the only tool standardized with a set protocol to measure the
233 urinary leakage¹⁸. Participants will be instructed to drink 500 ml solid-free water, and
234 perform a series of activities including standing and sitting, coughing, running,
235 picking up a coin and putting hands under water. The leakage amount in one hour will
236 be measured via pad.²⁶

237 PGI-I is a global index, with only one item, used to rate the participants' subject
238 perception on symptom improvement. Participants will describe their impression from
239 very much better to very much worse.²⁷ Improvement was considered to be clinically
240 significant if the participant's response is "Much better" or "Very much better".

241 To assess participants' expectations of improvement in UI, at baseline, participants
242 will be asked how do they expect the UI to be in two months. They will choose the
243 answer form the options of "Much better", "Better", "Don't know", "Same", and
244 "Worse".

245 To assess participants' belief that acupuncture might help, both at baseline and
246 week 4, participants in the EA and SA groups will be asked how do they think their
247 incontinence problem may be helped by acupuncture. They will choose the answer
248 from the options of "Very ineffective", "Fairly ineffective", "Can't decide",
249 "Effective", and "Very effective".

250 Safety assessment

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4 251 Adverse events (AEs), associated with the intervention or not, will be monitored
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6 252 and documented by participants and research assistants in Adverse Event Record
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8 253 Form and CRF throughout the trial. Whether the events are related to the treatments
9
10 254 will be decided by acupuncturists and related specialists in each site within 24 hours
11
12 255 of occurrence. Acupuncture related AEs are defined as following: broken needle,
13
14 256 needle phobia, intense pain that is unbearable, bleeding, hematoma, infection or
15
16 257 abscess at the needling site, and other discomfort induced by acupuncture, such as
17
18 258 pain, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, or insomnia
19
20 259 that lasts for one hour or longer after treatment.

21 22 260 **Quality control**

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24 261 To ensure consistency of the study, personnel in recruitment sites will receive
25
26 262 exactly the same training from the principal investigator (ZS Liu) concerning the
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28 263 protocol, manipulating methods of acupuncture and blinding of participants, etc.

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30 264 At least two acupuncturists (with no less than two-year clinical experience) are
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32 265 needed for rotation in each site, while the 24-session treatment of each participant
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34 266 should be completed by one specific acupuncturist. Additionally, the same
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36 267 participants should be taken charge of by the same research assistant/outcome
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38 268 assessor throughout the trial. They will instruct participants to complete voiding diary,
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40 269 explain the contents of handbook if necessary, and remind the participants of their
41
42 270 schedule by phone or we-chat.

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44 271 To promote the adherence on lifestyle modification, the research assistants will
45
46 272 remind the participants to adjust their lifestyle per the suggestions and record the
47
48 273 changes of condition and lifestyle on Lifestyle Record Form every week. On each
49
50 274 outcome assessment visit, the forms will be collected and examined by outcome
51
52 275 assessors, and recorded in CRF in time.

53
54 276 All the data collected will be documented in paper CRF first, and typed into EDC
55
56 277 system within one week. This rule is set to ensure the data be traced back, monitored
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58 278 by the system automatically and CRA, and supplemented without delay, if missing or
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4 279 inaccuracy. In follow-up period, missing data in voiding diary can be asked by phone
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6 280 rather than in person. The database will be protected by a password and only the
7
8 281 principal investigator will have access to the final dataset. Data are available upon
9
10 282 reasonable request to the principal investigator, excluding the private information of
11
12 283 patients.

13 14 284 **Sample size**

15
16 285 Based on our previous study^{14 15}, we assume that 25% participants in the SA group
17
18 286 will have at least 50% reduction of mean stress IEF from baseline to week 8. To
19
20 287 detect a difference of 23% between the EA and SA group, a sample size of 232
21
22 288 participants will need to provide the trial with 80% power with a two-sided
23
24 289 significance level of 0.05 and 10% dropouts.

25 26 290 **Statistical analysis**

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28 291 For primary hypothesis, we will compare the proportion of participants with at least
29
30 292 50% reduction in mean 24-hour stress IEF at week 8 among the three groups. The
31
32 293 primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test to
33
34 294 compare the rate of participants with at least 50% reduction in stress IEF at week 8
35
36 295 between the EA group and the WL group. If this analysis is significant, the
37
38 296 hierarchical testing will be used the EA group versus the SA group.

39
40 297 For other categorical variables, comparisons between treatment groups will be
41
42 298 assessed using the Fisher exact test or Chi-squared test as appropriate. We will use the
43
44 299 *t* test or Wilcoxon rank-sum test to analyze change of urinary leakage amount from
45
46 300 baseline, change of mean 24-hour IEF from baseline, change of total and sub-score of
47
48 301 ICIQ-SF from baseline, change of 24-h urgency episodes from baseline, and other
49
50 302 continuous variables. Chi-square or Fisher's exact tests will be used to compare the
51
52 303 frequency of AEs between groups.

53
54 304 All outcomes will be analyzed in intention to treat (ITT) population (defined as
55
56 305 participants randomized). Analysis will be performed using SAS version 9.4 (SAS
57
58 306 Institute Inc) with a two-sided *P* value of less than .05 considered significant.

307 **Ethics and dissemination**

308 The protocol was approved by Guang'anmen Hospital Institution of Review Board
309 (2019-241-KY). It is registered on Clinicaltrials.gov (NCT04299932), and any
310 revision of the protocol will be reported on the website. The trial will be conducted
311 according to the Declaration of Helsinki and the International Conference on
312 Harmonization Good Clinical Practice E6 Guidance for Good Clinical Practice.
313 Detailed information of the trial will be informed to the participants and written
314 informed content will be obtained from every participant before randomization.
315 Participants in WL group will receive 24-session EA treatment for compensation.
316 Results of the trial will be expected to be published on a peer-reviewed journal.

317 **DISCUSSION**

318 MUI is a condition frustrating almost thirty percent of women globally, while about
319 half of them feel embarrassed to report^{3 5}. The physiology underlying MUI remains
320 unclear. Intrinsic urethral sphincter deficiency caused by weak pelvic floor muscles
321 have been proposed as the main pathophysiology of SUI²⁸ and detrusor overactivity is
322 one of the main reasons leading to UUI¹¹. Via acupuncture point BL33 and BL35,
323 electroacupuncture may stimulate the S3 nerve and both motor and afferent fibers of
324 the pudendal nerve, which can not only strengthen the pelvic muscles and raise the
325 patient's awareness of these muscles, but also decrease the sensation of urgency and
326 inhibit parasympathetic activity and involuntary detrusor contractions²⁹.

327 Since plenty of patients in China have received acupuncture before, the form of
328 superficial insertion at non-acupoint area with minimal and transient electric current is
329 applied as sham control to eliminate placebo effects. The superficial insertion enables
330 participants to promptly percept the stimulation and electric current, which may
331 further enhance the blinding even if it lasts only about 30 seconds. It is argued that
332 minimal acupuncture may evoke physiologic effects³⁰, especially for pain and
333 depression^{31 32}. However, the pathology of MUI is mainly sphincter insufficiency and
334 detrusor overactivity. Studies indicates the rheobase of the normal bladder was 1-

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4 335 5mA³³. The transient and minimal current output may not produce effects on the
5
6 336 function of bladder. In the WL group, participants only receive healthcare education
7
8 337 and lifestyle modification. The WL-control is applied to eliminate the influence of
9
10 338 disease's natural cause.

11 339 Limitation also exists in the design of this trial. Participants in WL group and
12
13 340 acupuncturists cannot be blinded, which might induce performance and detection bias
14
15 341 into the trial. However, large bias is unlikely to be induced to the results since the
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17 342 primary outcome of stress IEF is subjective; and to decrease influence towards the
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19 343 results, the outcome assessment will be undertaken by an independent research
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21 344 assistant who know nothing about the allocation.
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4 345 **Ethical Approval and Consent to participate:** The study has received approval
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6 346 from the Guang'anmen Hospital Institution of Review Board (2019-241-KY). Written
7
8 347 informed content will be obtained from every participant.

9
10 348 **Consent for publication:** Not applicable.

11
12 349 **Authors' contributions:** Zhishun Liu conceived the study, initiated the design, and
13
14 350 revised the manuscript; Yan Liu is responsible for statistical analysis plan and drafted
15
16 351 the manuscript; Yuanjie Sun participated the design and drafted the manuscript; Huan
17
18 352 Chen participated the design and revised the manuscript; Yan Yan helped to draft the
19
20 353 manuscript. All authors have read and approved the final manuscript.

21
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25
26 356 Ministry of Science and Technology of the People's Republic of China. They have no
27
28 357 role in study design and will have no role in collection, management, analysis, and
29
30 358 interpretation of data; writing of the report; and the decision to submit the report for
31
32 359 publication.

33
34 360 **Competing interests:** The author declare that they have no competing interests.

35
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37
38 362 personnel in recruitment centers for their contributions.
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Figure legends

Figure 1. Flow chart

Figure 2. Study schedule

* Only for participants in the electroacupuncture and sham electroacupuncture groups
 ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

Table

Table 1. Secondary outcome measures

No	Outcome measure	Time Frame
1	Proportion of participants with at least 50% reduction of urinary leakage amount from baseline.	week 8
2	Change of urinary leakage amount from baseline	week 8
3	Proportion of participants with at least 50% reduction of mean 24-hour stress IEF from baseline.	weeks 4, 20 and 32
4	Change of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
5	Change of mean 24-hour stress IEF from baseline	weeks 4, 8, 20 and 32
6	Proportion of participants with at least 50% reduction of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
7	Change of total and sub-score of International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) from baseline	weeks 4, 8, 20 and 32
8	Change of total and sub-score of Overactive Bladder Questionnaire short form (OAB-q SF) from baseline	weeks 4, 8, 20 and 32
9	Change of mean 24-hour pad consumption from baseline	weeks 4, 8, 20 and 32
10	Proportion of participants with adequate improvement assessed by Patient global impression improvement (PGI-I)	weeks 8 and 20
11	Change of mean 24-hour urgency episodes from baseline	weeks 4, 8, 20 and 32
12	Change of mean 24-hour micturition episodes from baseline	weeks 4, 8, 20 and 32
13	Participants' expectations of improvement to urinary incontinence	Baseline
14	Participants' belief that acupuncture might help	Baseline and week 4
15	Blinding assessment	Week 8

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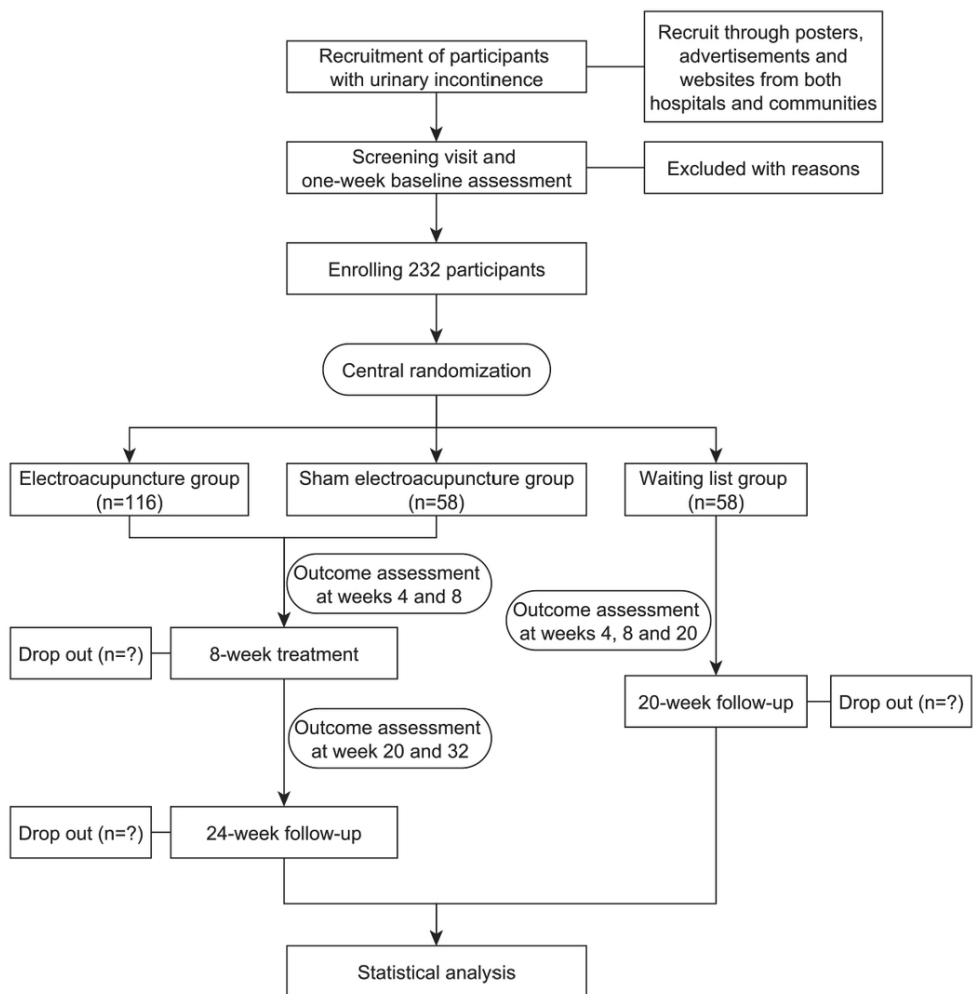


Figure 1. Flow chart

91x93mm (300 x 300 DPI)

TIMEPOINT (W, week)	W -1	W 0	W 4	W 8	W 20	W 32*
ENROLMENT						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
Demography characteristics	×					
Medical history	×					
Urine routine	×					
Residual urine volume	×					
Urine pregnancy test	×					
INTERVENTIONS						
Electroacupuncture			×	×		
Sham electroacupuncture			×	×		
Waiting list			×	×	×	
ASSESSMENTS						
3-day voiding diary	×		×	×	×	×
1-hour pad test	×			×		
ICIQ-SF		×	×	×	×	×
OAB-q SF		×	×	×	×	×
PGI-I				×	×	
Adverse events	×	×	×	×	×	×
Expectation assessment		×				
Belief assessment*		×	×			
Blindness assessment*				×		

Figure 2. Study schedule

* Only for participants in the electroacupuncture and sham electroacupuncture groups
 ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

91x94mm (300 x 300 DPI)

Table 1



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	5-12
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11, Table 1

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
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	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13,15
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5	Protocol	25	Plans for communicating important protocol modifications (eg, changes to	13
6	amendments		eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,	
7			REC/IRBs, trial participants, trial registries, journals, regulators)	
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9	Consent or	26a	Who will obtain informed consent or assent from potential trial participants	13
10	assent		or authorised surrogates, and how (see Item 32)	
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12		26b	Additional consent provisions for collection and use of participant data and	NA
13			biological specimens in ancillary studies, if applicable	
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16	Confidentiality	27	How personal information about potential and enrolled participants will be	11-12
17			collected, shared, and maintained in order to protect confidentiality before,	
18			during, and after the trial	
19				
20	Declaration of	28	Financial and other competing interests for principal investigators for the	15
21	interests		overall trial and each study site	
22				
23	Access to	29	Statement of who will have access to the final trial dataset, and disclosure	11-12
24	data		of contractual agreements that limit such access for investigators	
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27	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for compensation to	9,13
28	post-trial care		those who suffer harm from trial participation	
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30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	12
31	policy		participants, healthcare professionals, the public, and other relevant groups	
32			(eg, via publication, reporting in results databases, or other data sharing	
33			arrangements), including any publication restrictions	
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36		31b	Authorship eligibility guidelines and any intended use of professional	NA
37			writers	
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39		31c	Plans, if any, for granting public access to the full protocol, participant-level	11-12
40			dataset, and statistical code	
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43	Appendices			
44				
45	Informed	32	Model consent form and other related documentation given to participants	Content
46	consent		and authorised surrogates	inform
47	materials			
48				
49	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
50	specimens		specimens for genetic or molecular analysis in the current trial and for	
51			future use in ancillary studies, if applicable	
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5 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation &
6 Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.
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8 NonCommercial-NoDerivs 3.0 Unported](#)" license.
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BMJ Open

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038452.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Dec-2020
Complete List of Authors:	Sun, Yuanjie; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture Liu, Yan; Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital, Key Laboratory of Chinese Internal Medicine of Ministry of Education Chen, Huan; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture Yan, Yan; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture Liu, zhishun; China Academy of Traditional Chinese Medicine Guanganmen Hospital, Department of Acupuncture
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Urology, Complementary medicine
Keywords:	Urinary incontinences < UROLOGY, Bladder disorders < UROLOGY, COMPLEMENTARY MEDICINE

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8 3 Article title:

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10 4 **Electroacupuncture for stress-predominant mixed urinary**
11 **incontinence: a protocol for a three-armed randomized controlled**
12 **trial**

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16 7 Yuanjie Sun, MD^{1*}; Yan Liu, MD^{2*}; Huan Chen, MD, MSc¹; Yan Yan, BS¹; Zhishun
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18 8 Liu, MD, PhD^{1†}

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32 15 *Yuanjie Sun and Yan Liu contributed equally to this work and shared the first author
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34 16 position.

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40 19 Academy of Chinese Medical Sciences, Beijing, China. Tel. +86 10 88002331; Fax:
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42 20 +86 10 88001241; E-mail address: zhishunjournal@163.com (Zhishun Liu).

43
44 21 **Running title:** acupuncture for stress-predominant mixed urinary incontinence

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46 22 **Word count:** abstract 191; main text 3388

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3
4 23 **Abstract**

5 24 **Introduction:** Evidence specific for stress-predominant mixed urinary incontinence is
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7 still lack at present, and acupuncture may relieve the symptoms. We plan to conduct
8 25
9 this multi-center, three-armed, randomized controlled trial to investigate the efficacy
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11 and safety of electroacupuncture among women with stress-predominant mixed
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13 urinary incontinence.
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15 29 **Methods and analysis:** The trial will be conducted at 5 hospitals in China. 232
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17 eligible women will be randomly assigned (2:1:1) to the electroacupuncture, sham
18 30
19 electroacupuncture or waiting list group to receive either 24-session
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21 acupuncture/sham acupuncture treatment over 8 weeks and 24-week follow-up, or 20-
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23 week watchful waiting. The primary outcome is the proportion of participants with at
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25 least 50% reduction in mean 24-hour stress incontinence episode frequencies from
26 34
27 baseline to week 8. The outcome will be analyzed in intention to treat population
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29 (defined as participants randomized) with a two-sided *P* value of less than .05
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31 considered significant.
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33 38 **Ethics and dissemination:** The protocol has been approved by Guang'anmen
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35 Hospital Institutional Review Board (2019-241-KY). Detailed information of the trial
36 39
37 will be informed to the participants and written informed consent will be obtained
38 40
39 from every participant. Results of the trial are expected to be published in a peer-
40 41
41 reviewed journal.
42 42

43 43 **Key words:** Acupuncture; Mixed urinary incontinence; Female; Stress urinary
44 44
45 incontinence
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48 45 **Trial registration:** Clinicaltrials.gov identifier: NCT04299932
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4 **46 Strengths and limitations of this study**

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6 47 ➤ The first randomized controlled trial to investigate the efficacy and safety of
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8 48 acupuncture on stress-predominant mixed urinary incontinence.
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10 49 ➤ Sham control and waiting-list control are designed to eliminate the influence of
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12 50 placebo effects and the disease's natural course on the results.
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14 51 ➤ Minimal electroacupuncture serves as a sham control to blind participants in the
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16 52 electroacupuncture and sham electroacupuncture groups.
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18 53 ➤ One limitation is that acupuncturists and participants in the waiting list group
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20 54 cannot be blinded.
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55 INTRODUCTION

56 Mixed urinary incontinence (MUI) is a complaint of involuntary loss of urine
57 associated with both physical exertion and urgency.¹ It presents with more severe
58 symptoms in comparison with pure urinary incontinence (UI), and thus puts greater
59 burden on health of individuals and economy of the society.² Approximately 21%-
60 33% of females in the world³ and 9.4% of females in China⁴ are troubled with MUI,
61 while less than 50% of such population reports it to doctors and receives treatment⁵.

62 Stress-predominant MUI constitutes mainly of stress component. It features leakage
63 on increased abdominal pressure, which can be induced by exertion, sneeze, cough
64 etc. Despite the existence of leakage with urgency, stress incontinence episode
65 frequencies (IEFs) outnumber 50% of total IEFs.⁶

66 Current European Association of Urology (EAU) guideline on incontinence
67 recommends to initiate treatment for predominant component of MUI.⁷ However, no
68 strong evidence supports that the interventions for stress urinary incontinence (SUI) is
69 as effective when used to treat stress-predominant MUI.⁶ The effects of pelvic floor
70 muscle training (PFMT), first-line therapy for pure SUI, decrease among MUI
71 patients.⁸ About half of patients practicing PFMT will seek help from surgery
72 eventually in long-term follow-up⁹, and surgery might be more useful than PFMT for
73 moderate to severe symptoms¹⁰. When surgery is considered for MUI, other therapies
74 might need to be combined with to control the urgency component.¹¹ In addition, the
75 existence of urgency symptoms might be aggravated after surgery¹², and even reduce
76 the success rate of stress incontinence operation¹³. Therefore, it is necessary to seek
77 for interventions specific for stress-predominant MUI.

78 Previous studies indicates acupuncture may relieve the incontinence symptoms.^{14 15}
79 It is proven effective in reducing leakage amount of pure SUI¹⁴ and total IEFs of
80 MUI.¹⁵ Further analysis of the two trials suggests EA might relieve the symptoms of
81 stress-related UI.¹⁶ Since the two trials didn't focus on stress-predominant MUI
82 specifically, this multi-center, three-armed, randomized controlled is designed to

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3
4 83 evaluate the efficacy and safety of EA among participants with stress-predominant
5
6 84 MUI.

7 8 85 **Hypotheses**

9
10 86 Our primary hypothesis is that the effects of EA is superior to sham
11
12 87 electroacupuncture (SA) and waiting list (WL) in improving proportion of stress-
13
14 88 predominant MUI participants with at least 50% reduction of mean 24-hour stress
15
16 89 IEFs from baseline to week 8.

17 18 90 **METHODS AND ANALYSIS**

19 20 91 **Study design**

21
22 92 This is a three-armed, randomized, SA and WL-controlled trial conducted at five
23
24 93 recruitment sites, which are Guang'anmen Hospital, China Academy of Chinese
25
26 94 Medical Sciences; Hengyang Hospital Affiliated to Hunan University of Chinese
27
28 95 Medicine; Yantai Hospital of Traditional Chinese Medicine; The third affiliated
29
30 96 hospital of Beijing university of Chinese Medicine; and Jiangxi Provincial Hospital of
31
32 97 traditional Chinese Medicine.

33
34 98 The study duration is 33 weeks for participants in the EA and SA groups, with one-
35
36 99 week baseline assessment, 8-week treatment and 24-week follow-up; while 21 weeks
37
38 100 for participants in the WL group, with one-week baseline assessment and 20-week
39
40 101 watchful waiting (Figure 1. Flow Chart). The study will start recruitment on October
41
42 102 9, 2020, and is anticipated to finish the treatment and follow-up on September 30,
43
44 103 2023. Participations in the EA and SA groups, outcome assessors, data managers and
45
46 104 statisticians will be blinded to the group allocation, while acupuncturists and
47
48 105 participants in the WL group will not be blinded for obvious reasons.

49 50 106 **Patient and public involvement**

51
52 107 Patients or the public are not involved in the design, conduct, report or
53
54 108 dissemination of our research.

55 56 109 **Inclusion criteria**

57
58 110 1) Diagnosis of MUI by the coexistence of SUI and UUI symptoms in accordance
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4 111 with EAU guideline⁷;
- 5
6 112 2) Female participants aged between 35 and 75;
- 7
8 113 3) Stress index > urge index in accordance with Medical, epidemiologic, and social
9
10 114 aspects of Aging(MESA) questionnaire¹⁷;
- 11
12 115 4) Symptom of MUI for at least three months, and SUI episodes outnumber 50%
13
14 116 total IEFs documented in 3-day voiding diary;
- 15
16 117 5) Less than 12 micturition episodes in average 24 hours documented in 3-day
17
18 118 voiding diary;
- 19
20 119 6) Positive cough stress test;
- 21
22 120 7) Urine leakage > 1 g in 1-hour pad test¹⁸;
- 23
24 121 8) Voluntary participation in the trial and signed written informed consent.

25
26 122 Participants meeting all these eight inclusion criteria might be able to be enrolled.

27
28 123 **Exclusion criteria**

- 29
30 124 1) Urgency-predominant MUI, pure SUI, pure UUI, overflow UI and neurogenic
31
32 125 bladder;
- 33
34 126 2) Uncontrolled symptomatic urinary tract infection;
- 35
36 127 3) Tumor in urinary system and pelvic organ;
- 37
38 128 4) Pelvic organ prolapse \geq degree II ;
- 39
40 129 5) Residual urine volume \geq 100ml;
- 41
42 130 6) History of treatments specific for UI, such as acupuncture, PFMT and medications
43
44 131 in the previous one month;
- 45
46 132 7) History of surgery specific UI or in pelvic floor, including hysterectomy;
- 47
48 133 8) Uncontrolled diabetes or severe high blood pressure;
- 49
50 134 9) Nervous system diseases that may hamper the function of urinary system, such as
51
52 135 Multiple sclerosis, Alzheimer's disease, Parkinson's disease, spinal cord injury,
53
54 136 cauda equina nerve injury, or multiple system atrophy;
- 55
56 137 10) Severe heart, lung, brain, liver, kidney, mental illness, coagulation dysfunction or
57
58 138 obvious cognitive dysfunction;
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4 139 11) Installed cardiac pacemaker;
5
6 140 12) Inconvenient or unable to walk, run, go up and down stairs;
7
8 141 13) Allergy to metal, dreadfully fear of acupuncture needles or unbearable to EA;
9
10 142 14) Pregnant at present, plan to conceive in future one year, at lactation period or
11
12 143 within 12 months after childbirth.

13
14 144 Participants with either situation mentioned above will not be enrolled in the trial.

15 16 145 **Randomization and allocation concealment**

17
18 146 The random sequence will be produced by a third independent party (Linkermed
19
20 147 Technology Co., Ltd. [Beijing, China]). Eligible participants will be randomly
21
22 148 assigned into the EA, SA or WL group at 2:1:1 ratio, stratified by recruitment sites
23
24 149 and using variable blocks. The random number and group allocation will be acquired
25
26 150 by acupuncturists in each recruitment site by logging in the Central Randomization
27
28 151 System and typing in basic information of eligible participants.

29 30 152 **Interventions**

31
32 153 The acupuncture point regimen and administration protocol are both based on the
33
34 154 results of previous studies and specialist consensus^{14 15}. Participants in the EA group
35
36 155 will receive stimulation at bilateral BL33 (Zhongliao), BL35 (Huiyang) and SP6
37
38 156 (Sanyinjiao). BL 33 is located in the third posterior sacral foramen; BL35, 0.5
39
40 157 proportional bone (skeletal) cun (B-cun) ($\approx 10\text{mm}$) lateral to the extremity of the
41
42 158 coccyx; and SP6, posterior to the medial border of the tibia, 3 B-cun superior to the
43
44 159 prominence of the medial malleolus.¹⁹ Bilateral BL33 will be inserted by acupuncture
45
46 160 needles (Huatuo, Suzhou Medical Appliance) of 0.30×75mm size at an angle of 45° ,
47
48 161 inward and downward, till the depth of 60-70mm. Bilateral BL35 will be inserted by
49
50 162 needles of 0.30×75mm size, slightly outward and upward, till the depth of 60-70mm.
51
52 163 Bilateral SP6 will be inserted by needles of 0.30×40mm till the depth of 25-30mm.
53
54 164 All the needles will be lifted, thrust and twisted evenly for three times, right after
55
56 165 insertion, to induce the sensation of *deqi*. Electronic acupuncture apparatus (Yingdi
57
58 166 KWD 808 I electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi

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4 167 Electronic Medical Device Co., Ltd) will be connected to the three pairs of needles
5
6 168 transversally, with a continuous wave of 20Hz, electric current of 2mA-6.5mA for
7
8 169 BL33 and BL35, and 1mA-3.5mA for SP6. The EA stimulation will last 30mins for
9
10 170 each session, 3 sessions a week (ideally every other day) for a succession of 8 weeks.

11
12 171 Participants in the SA group will receive superficial insertion at bilateral sham
13
14 172 BL33 (Zhongliao), sham BL35 (Huiyang) and sham SP6 (Sanyinjiao). Sham BL33 is
15
16 173 in the area 1 B-cun (≈ 20 mm) horizontally outside of BL33; sham BL35, 1 B-cun (\approx
17
18 174 20mm) horizontally outside of BL35; Sham SP6, in the middle of SP6 and tendons.
19
20 175 Acupuncture needles of 0.30 \times 40mm size will be inserted at a depth of 2-3mm till the
21
22 176 needles can stand still. No manipulation will be conducted, and the sensation of *deqi*
23
24 177 will not be induced. Electronic acupuncture apparatus (Yingdi KWD 808 I electro
25
26 178 pulse acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical
27
28 179 Device Co., Ltd) will be connected to the three pairs of needles transversally, with a
29
30 180 continuous wave of 20Hz and minimal electric current (ideally at a degree which
31
32 181 participant can just percept). In about 30 seconds, the electric current will be turned
33
34 182 down, leaving the indicator light and ticking sound on. The treatment sessions are
35
36 183 similar to those in the EA group.

37
38 184 Participants in the EA and SA groups will be blinded to the group allocation.
39
40 185 Acupuncturists and research assistants will be instructed not to tell the group
41
42 186 allocation to participants. Additionally, to avoid inadvertent unblinding, contact
43
44 187 between participants and project staff will be reduced as much as possible during
45
46 188 treatment. The manipulation of acupuncture, connecting to electronic apparatus and
47
48 189 withdrawal of needles will be separately undertaken by acupuncturists and another
49
50 190 research assistant. Participants will be treated separately with curtain drawn and their
51
52 191 companions waiting outside the clinic, if any. Before manipulation, participants will
53
54 192 be told they may feel the electrical stimulation fade down gradually, even to the
55
56 193 degree that they cannot percept, and that is because the body has built up a tolerance
57
58 194 to the electrical stimulation during the treatment process. Within 5 minutes after either
59
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4 195 treatment session at week 8, participants will be told they may have received EA
5
6 196 treatment with deep insertion, or SA treatment with shallow insertion. Then, the
7
8 197 participants will be asked to answer the question do you think you have received EA
9
10 198 treatment, and choose answer between the options of Yes or No.

11
12 199 Participants in the WL group will not receive active treatment. After the trial, they
13
14 200 will receive 24-session EA treatment mentioned above as compensation.

15
16 201 Participants in all the three groups will receive handbook of advice on healthcare
17
18 202 education and lifestyle modification, concerning exercise, fluid intake, weight loss,
19
20 203 smoking and respiratory symptoms, constipation, heavy lifting and urinary tract
21
22 204 infection. During the process of the trial, participants are not allowed to take other
23
24 205 specialized medication or therapies for UI, such as PFMT or antimuscarinic agents;
25
26 206 details should be recorded in case report form (CRF), if used. Any medications that
27
28 207 might influence the function of lower urinary tract should also be documented in
29
30 208 CRF.

31 32 209 **Outcomes**

33 34 210 **Primary outcome**

35
36 211 The primary outcome is the proportion of participants with at least 50% reduction
37
38 212 in mean 24-hour stress IEFs from baseline to week 8, measured by 3-day voiding
39
40 213 diary. Reduction of at least 50% in IEF is regarded as successful treatment in clinic,²⁰
41
42 214 and 3-day voiding diary is a reliable and validated tool for UI in both clinic and
43
44 215 research, without much burden placed on participants.²¹ In 3-day voiding diary, IEF
45
46 216 of different types, micturition and nocturia episodes, fluid intake, and pad
47
48 217 consumptions will be documented.

49 50 218 **Secondary outcomes**

51
52 219 Secondary outcomes will be measured by 3-day voiding diary, International
53
54 220 Consultation on Incontinence Questionnaire-short form (ICIQ-SF) and Overactive
55
56 221 Bladder Questionnaire short form (OAB-q SF) at weeks 4, 8, 20 and 32; 1-hour pad
57
58 222 test at week 8; and Patient Global Impression of Improvement (PGI-I) at weeks 8 and
59
60

223 20 (Figure 2. Study schedule). The specific secondary outcome measures and time
224 frame are displayed in Table 1 Secondary outcome measures.

225 ICIQ-SF is a validated tool to assess the frequency and severity of UI, and its
226 influence on QoL in the past 4 weeks^{22 23}. The total score of the questionnaire ranges
227 from 1 to 21, with higher score indicating greater severity of symptoms.

228 OAB-q SF is used to assess the OAB symptom bother and the health-related quality
229 of life (HRQOL) in the past 4 weeks^{24 25}. The domains include coping, concern, sleep
230 and emotional interactions. The scores are transformed to 0- to 100-point scales, with
231 higher scores on the symptom bother scale indicating severe symptoms and higher
232 scores on the HRQOL indicating a better HRQOL.

233 One-hour pad test is the only tool standardized with a set protocol to measure the
234 urinary leakage¹⁸. Participants will be instructed to drink 500 ml sodium-free water,
235 and perform a series of activities including standing and sitting, coughing, running,
236 picking up a coin and putting hands under water. The leakage amount in one hour will
237 be measured via pad.²⁶

238 PGI-I is a global index, with only one item, used to rate the participants' subjective
239 perception on symptom improvement. Participants will describe their impression from
240 very much better to very much worse.²⁷ Improvement was considered to be clinically
241 significant if the participant's response is "Much better" or "Very much better".

242 To assess participants' expectations of improvement in UI, at baseline, participants
243 will be asked how do they expect the UI to be in two months. They will choose the
244 answer form the options of "Much better", "Better", "Don't know", "Same", and
245 "Worse".

246 To assess participants' belief that acupuncture might help, both at baseline and
247 week 4, participants in the EA and SA groups will answer how do they think their
248 incontinence problem may be helped by acupuncture. They will choose the answer
249 from the options of "Very ineffective", "Fairly ineffective", "Can't decide",
250 "Effective", and "Very effective".

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4 251 **Safety assessment**

5 252 Adverse events (AEs), associated with the intervention or not, will be monitored
6
7 253 and documented by participants and research assistants in Adverse Event Record
8
9 254 Form and CRF throughout the trial. Whether the events are related to the treatments
10
11 255 will be decided by acupuncturists and related specialists in each site within 24 hours
12
13 256 of occurrence. Acupuncture related AEs are defined as following: broken needle,
14
15 257 needle phobia, intense pain that is unbearable, bleeding, hematoma, infection or
16
17 258 abscess at the needling site, and other discomfort induced by acupuncture, such as
18
19 259 pain, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, or insomnia
20
21 260 that lasts for one hour or longer after treatment.

22
23
24 261 **Quality control**

25
26 262 To ensure consistency of the study, personnel in recruitment sites will receive
27
28 263 extensive training from the principal investigator (ZS Liu) concerning the protocol,
29
30 264 manipulating methods of acupuncture and blinding of participants, etc.

31
32 265 At least two certified acupuncturists (with no less than two-year clinical
33
34 266 experience) are needed for rotation in each site, while the 24-session treatment of each
35
36 267 participant should be completed by one specific acupuncturist. Additionally, the same
37
38 268 participants should be taken charge of by the same research assistant/outcome
39
40 269 assessor throughout the trial. They will instruct participants to complete voiding diary,
41
42 270 explain the contents of handbook if necessary, and remind the participants of their
43
44 271 schedule by phone or we-chat.

45
46 272 To promote the adherence on lifestyle modification, the research assistants will
47
48 273 remind the participants to adjust their lifestyle per the suggestions and record the
49
50 274 changes of condition and lifestyle on Lifestyle Record Form every week. On each
51
52 275 outcome assessment visit, the forms will be collected and examined by outcome
53
54 276 assessors, and recorded in CRF in time.

55
56 277 All the data collected will be documented in paper CRF first, and typed into EDC
57
58 278 system within one week by clinical research coordinator. This rule is set to ensure the
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4 279 date be traced back, monitored by the system automatically and clinical research
5
6 280 associate, and supplemented without delay, if missing or inaccuracy. In follow-up
7
8 281 period, missing data in voiding diary can be asked by phone rather than in person. The
9
10 282 database will be protected by a password and only the principal investigator will have
11
12 283 access to the final dataset. Data are available upon reasonable request to the principal
13
14 284 investigator, excluding the private information of patients.

15 16 285 **Sample size**

17
18 286 Based on our previous study^{14 15}, we assume that 25% participants in the SA group
19
20 287 will have at least 50% reduction of mean stress IEF from baseline to week 8. To
21
22 288 detect a difference of 23% between the EA and SA group, a sample size of 232
23
24 289 participants will need to provide the trial with 80% power with a two-sided
25
26 290 significance level of 0.05 and 10% dropouts.

27 28 291 **Statistical analysis**

29
30 292 For the primary hypothesis, we will compare the proportion of participants with at
31
32 293 least 50% reduction in mean 24-hour stress IEF at week 8 among the three groups.
33
34 294 The primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test to
35
36 295 compare the rate of participants with at least 50% reduction in stress IEF at week 8
37
38 296 between the EA group and the WL group. If this analysis is significant, the
39
40 297 hierarchical testing will be used the EA group versus the SA group.

41
42 298 For other categorical variables, comparisons between treatment groups will be
43
44 299 assessed using the Fisher exact test or Chi-squared test as appropriate. We will use the
45
46 300 *t* test or Wilcoxon rank-sum test to analyze change of urinary leakage amount from
47
48 301 baseline, change of mean 24-hour IEF from baseline, change of total and sub-score of
49
50 302 ICIQ-SF from baseline, change of 24-h urgency episodes from baseline, and other
51
52 303 continuous variables. Chi-square or Fisher's exact tests will be used to compare the
53
54 304 frequency of AEs between groups.

55
56 305 All the outcomes will be analyzed in intention to treat (ITT) population (defined as
57
58 306 participants randomized). Analysis will be performed using SAS version 9.4 (SAS

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4 307 Institute Inc) with a two-sided P value of less than .05 considered significant.

5
6 308 **Ethics and dissemination**

7
8 309 The protocol has been approved by Guang'anmen Hospital Institutional Review
9
10 310 Board (2019-241-KY). It is registered on Clinicaltrials.gov (NCT04299932), and any
11
12 311 revision of the protocol will be reported on the website. The trial will be conducted
13
14 312 according to the Declaration of Helsinki and the International Conference on
15
16 313 Harmonization Good Clinical Practice E6 Guidance for Good Clinical Practice.
17
18 314 Detailed information of the trial will be informed to the participants and written
19
20 315 informed consent will be obtained from every participant. Participants in the WL
21
22 316 group will receive 24-session EA treatment for compensation. Results of the trial are
23
24 317 expected to be published on a peer-reviewed journal.

25
26 318 **DISCUSSION**

27
28 319 MUI is a condition frustrating almost thirty percent of women globally, while about
29
30 320 half of them feel embarrassed to report³⁻⁵. The physiology underlying MUI remains
31
32 321 unclear. UUI is closely associated with physiological perturbations to bladder
33
34 322 function, such as detrusor overactivity, poor detrusor compliance and bladder
35
36 323 hypersensitivity¹¹, while urethral hypermobility resulting from weak pelvic floor or
37
38 324 poorly supported urethral sphincter, or intrinsic urethral sphincter deficiency have
39
40 325 been proposed as the main pathophysiology of SUI²⁸. Electroacupuncture may relieve
41
42 326 the symptoms of MUI by modulate the function of related nerves. Acupuncture points
43
44 327 of BL 33, BL35 and SP6 are located in the lumbosacral region and posterior tibial
45
46 328 region, in the distribution area of sacral plexus and pudendal nerves. Either by direct
47
48 329 stimulation or indirect stimulation via sacral roots or plexus, the pudendal afferent can
49
50 330 be activated to induce a strong inhibition of the detrusor hyperreflexia and cause
51
52 331 detrusor relaxation²⁹. Additionally, stimulation of pudendal nerves can contract the
53
54 332 pelvic floor muscle and simulate PFMT³⁰, which can improve urethral function and
55
56 333 relieve SUI symptoms³¹.

57
58 334 Since plenty of Chinese have received acupuncture before, superficial insertion at
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4 335 non-acupuncture point area with minimal and transient electric current is applied as
5
6 336 sham control to eliminate placebo effects. The superficial insertion enables
7
8 337 participants to percept the stimulation and electric current promptly, and the transient
9
10 338 electric current can enhance the blinding even if it lasts only about 30 seconds. It is
11
12 339 argued that minimal acupuncture may evoke physiologic effects³², especially for pain
13
14 340 and depression^{33 34}. However, the pathology of MUI is mainly sphincter insufficiency
15
16 341 and detrusor overactivity. Studies indicates the rheobase of the normal bladder was 1-
17
18 342 5mA³⁵. The transient and minimal current output may not produce effects on the
19
20 343 function of bladder. In the WL group, participants only receive healthcare education
21
22 344 and lifestyle modification. The WL-control is applied to eliminate the influence of
23
24 345 disease's natural cause.

25
26 346 Limitation also exists in the design of this trial. Participants in the WL group and
27
28 347 acupuncturists cannot be blinded, which might induce performance and detection bias.
29
30 348 However, large bias is unlikely to be attached to the results since the primary outcome
31
32 349 of stress IEF is objective. In addition, the outcome assessors will be blinded to group
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34 350 allocation.
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4 351 **Ethical Approval and Consent to participate:** The study has received approval
5
6 352 from the Guang'anmen Hospital Institutional Review Board (2019-241-KY). Written
7
8 353 informed consent will be obtained from every participant.

9
10 354 **Consent for publication:** Not applicable.

11
12 355 **Authors' contributions:** Zhishun Liu conceived the study, initiated the design, and
13
14 356 revised the manuscript; Yan Liu was responsible for statistical analysis plan and
15
16 357 drafted the manuscript; Yuanjie Sun participated the design and drafted the
17
18 358 manuscript; Huan Chen participated the design and revised the manuscript; Yan Yan
19
20 359 helped to draft the manuscript. All authors have read and approved the final
21
22 360 manuscript.

23
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27
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29
30 364 role in study design and will have no role in collection, management, analysis, and
31
32 365 interpretation of data; writing of the report; and the decision to submit the report for
33
34 366 publication.

35
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37
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39
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Figure legends

Figure 1. Flow chart

Figure 2. Study schedule

* Only for participants in electroacupuncture and sham electroacupuncture groups

ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

Table

Table 1. Secondary outcome measures

No	Outcome measure	Time Frame
1	Proportion of participants with at least 50% reduction of urinary leakage amount from baseline.	week 8
2	Change of urinary leakage amount from baseline	week 8
3	Proportion of participants with at least 50% reduction of mean 24-hour stress IEF from baseline.	weeks 4, 20 and 32
4	Change of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
5	Change of mean 24-hour stress IEF from baseline	weeks 4, 8, 20 and 32
6	Proportion of participants with at least 50% reduction of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
7	Change of total and sub-score of International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) from baseline	weeks 4, 8, 20 and 32
8	Change of total and sub-score of Overactive Bladder Questionnaire short form (OAB-q SF) from baseline	weeks 4, 8, 20 and 32
9	Change of mean 24-hour pad consumption from baseline	weeks 4, 8, 20 and 32
10	Proportion of participants with adequate improvement assessed by Patient global impression improvement (PGI-I)	weeks 8 and 20
11	Change of mean 24-hour urgency episodes from baseline	weeks 4, 8, 20 and 32
12	Change of mean 24-hour micturition episodes from baseline	weeks 4, 8, 20 and 32
13	Participants' expectations of improvement to urinary incontinence	Baseline
14	Participants' belief that acupuncture might help	Baseline and week 4

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15	Blinding assessment	Week 8
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For peer review only

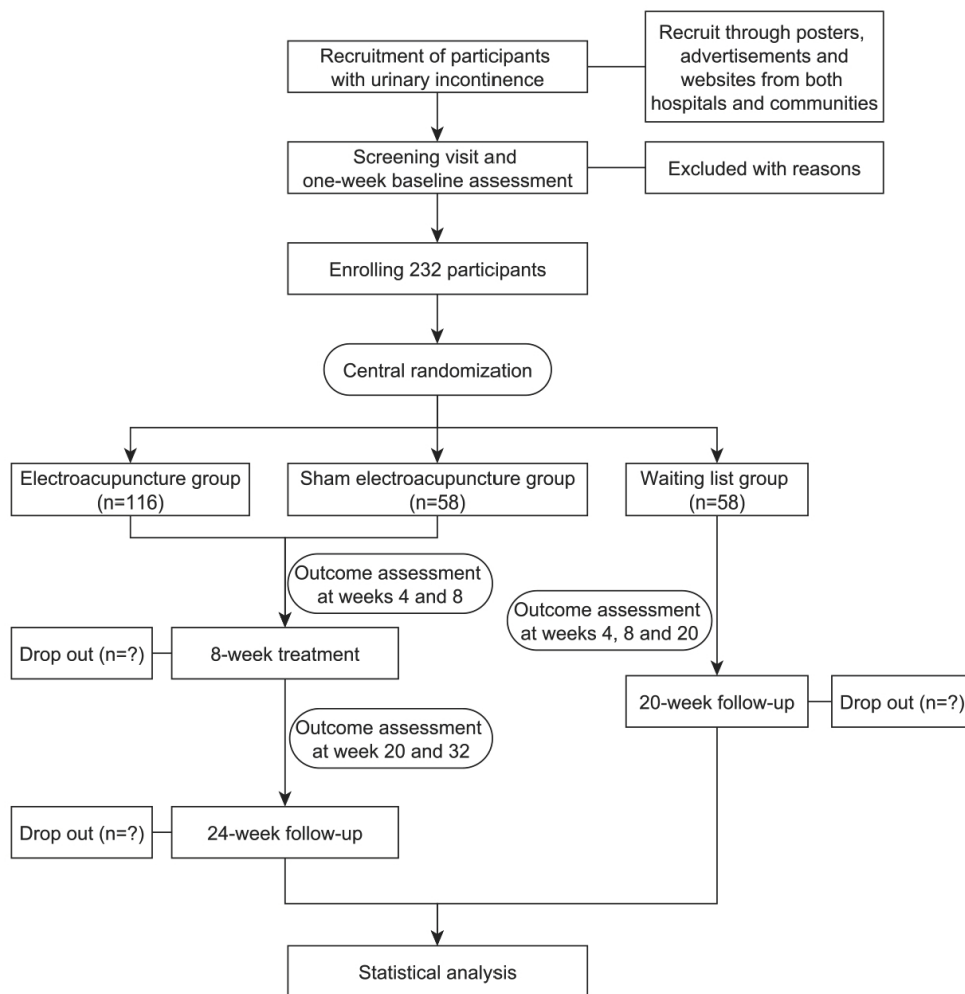


Figure 1. Flow chart

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TIMEPOINT (W, week)	W -1	W 0	W 4	W 8	W 20	W 32*
ENROLMENT						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
Demography characteristics	×					
Medical history	×					
Urine routine	×					
Residual urine volume	×					
Urine pregnancy test	×					
INTERVENTIONS						
Electroacupuncture			×	×		
Sham electroacupuncture			×	×		
Waiting list			×	×	×	
ASSESSMENTS						
3-day voiding diary	×		×	×	×	×
1-hour pad test	×			×		
ICIQ-SF		×	×	×	×	×
OAB-q SF		×	×	×	×	×
PGI-I				×	×	
Adverse events	×	×	×	×	×	×
Expectation assessment		×				
Belief assessment*		×	×			
Blindness assessment*				×		

Figure 2. Study schedule

* Only for participants in the electroacupuncture and sham electroacupuncture groups
 ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

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Table 1



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	5-12
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11, Table 1

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
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5		18b	Plans to promote participant retention and complete follow-up, including list 11-12
6			of any outcome data to be collected for participants who discontinue or
7			deviate from intervention protocols
8			
9			
10	Data	19	Plans for data entry, coding, security, and storage, including any related 11-12
11	management		processes to promote data quality (eg, double data entry; range checks for
12			data values). Reference to where details of data management procedures
13			can be found, if not in the protocol
14			
15	Statistical	20a	Statistical methods for analysing primary and secondary outcomes. 12
16	methods		Reference to where other details of the statistical analysis plan can be
17			found, if not in the protocol
18			
19			
20		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) NA
21			
22		20c	Definition of analysis population relating to protocol non-adherence (eg, as
23			randomised analysis), and any statistical methods to handle missing data 12
24			(eg, multiple imputation)
25			
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Methods: Monitoring

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29	Data	21a	Composition of data monitoring committee (DMC); summary of its role and NA
30	monitoring		reporting structure; statement of whether it is independent from the sponsor
31			and competing interests; and reference to where further details about its
32			charter can be found, if not in the protocol. Alternatively, an explanation of
33			why a DMC is not needed
34			
35			
36		21b	Description of any interim analyses and stopping guidelines, including who NA
37			will have access to these interim results and make the final decision to
38			terminate the trial
39			
40	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and 10-11
41			spontaneously reported adverse events and other unintended effects of
42			trial interventions or trial conduct
43			
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45	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether NA
46			the process will be independent from investigators and the sponsor
47			

Ethics and dissemination

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50	Research	24	Plans for seeking research ethics committee/institutional review board 13,15
51	ethics		(REC/IRB) approval
52	approval		
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5	Protocol	25	Plans for communicating important protocol modifications (eg, changes to	13
6	amendments		eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,	
7			REC/IRBs, trial participants, trial registries, journals, regulators)	
8				
9	Consent or	26a	Who will obtain informed consent or assent from potential trial participants	13
10	assent		or authorised surrogates, and how (see Item 32)	
11				
12		26b	Additional consent provisions for collection and use of participant data and	NA
13			biological specimens in ancillary studies, if applicable	
14				
15				
16	Confidentiality	27	How personal information about potential and enrolled participants will be	11-12
17			collected, shared, and maintained in order to protect confidentiality before,	
18			during, and after the trial	
19				
20	Declaration of	28	Financial and other competing interests for principal investigators for the	15
21	interests		overall trial and each study site	
22				
23				
24	Access to	29	Statement of who will have access to the final trial dataset, and disclosure	11-12
25	data		of contractual agreements that limit such access for investigators	
26				
27	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for compensation to	9,13
28	post-trial care		those who suffer harm from trial participation	
29				
30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	12
31	policy		participants, healthcare professionals, the public, and other relevant groups	
32			(eg, via publication, reporting in results databases, or other data sharing	
33			arrangements), including any publication restrictions	
34				
35				
36		31b	Authorship eligibility guidelines and any intended use of professional	NA
37			writers	
38				
39		31c	Plans, if any, for granting public access to the full protocol, participant-level	11-12
40			dataset, and statistical code	
41				
42				
43	Appendices			
44				
45	Informed	32	Model consent form and other related documentation given to participants	Content
46	consent		and authorised surrogates	inform
47	materials			
48				
49	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
50	specimens		specimens for genetic or molecular analysis in the current trial and for	
51			future use in ancillary studies, if applicable	
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5 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation &
6 Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.
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