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## Transcutaneous electrical acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing laparoscopic colon surgery: Study protocol for a randomized controlled trial

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| Keywords:                     | Transcutaneous electrical acupoint stimulation (TEAS), postoperative ileus (POI), Pretreatment   |
|                               |  |

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4 1 **Transcutaneous electrical acupoint stimulation pretreatment for prevention of**  
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6 2 **postoperative ileus in patients undergoing laparoscopic colon surgery: Study protocol for**  
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8 3 **a randomized controlled trial**  
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4 22 **Abstract**

5 23 **Introduction:** Postoperative ileus (POI) is a common complication after surgery, which  
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7 24 severely affects postoperative recovery. It is not clear whether pretreatment with transcutaneous  
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9 25 electrical acupoint stimulation (TEAS) can improve recovery of POI. This trial will evaluate  
10  
11 26 the effects of TEAS pretreatment for POI.

12  
13 27 **Methods and analysis:** This will be a prospective, randomized, controlled trial. ASA I-II level  
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15 28 patients aged 18-65 years and scheduled for laparoscopic colon surgery will be included. It is  
16  
17 29 planned that 146 subjects will be randomized to the TEAS and sham TEAS (STEAS) groups  
18  
19 30 underwent 2 sessions of TEAS/STEAS treatment daily for 3 days before surgery and a last  
20  
21 31 TEAS/STEAS treatment for 30 minutes before anesthesia. The primary endpoint is the first  
22  
23 32 defecation time. The secondary endpoints include postoperative anal exhaust time,  
24  
25 33 time for dieting, time beginning to walk alone, length of hospital stay, postoperative pain VAS  
26  
27 34 score of the first 3 days after operation, analgesic requirements, complications, inflammatory  
28  
29 35 mediators in blood including IFN- $\beta$ , IFN - $\gamma$ , IL-6, IL-1.

30  
31 36 **Ethics and dissemination:** This study has been approved by the Chinese registered clinical  
32  
33 37 trial ethics review committee (NO.ChiECRCT-20170084). The result of the trial will be  
34  
35 38 published in an internationally peer-reviewed journal.

36  
37 39 **Trial registration:** This study has been registered with the Chinese clinical trial register (NO.  
38  
39 40 ChiCTR-INR-17013184).

40  
41 41 **Trial status:** The study was in the recruitment phase at the time of manuscript submission.

42  
43 42 **Abbreviations:** POI = Postoperative ileus, TCM = traditional Chinese medicine, EA = electro-  
44  
45 43 acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index,  
46  
47 44 PACU = post anaesthesia care unit, ERAS= Enhanced Recovery After Surgery.

48  
49 45 **Key words:** Transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI);  
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51 46 Pretreatment.  
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4 47 **Strengths and limitations of the study**

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6 48 ➤ This study aims to evaluate the influence of pretreatment with transcutaneous electrical  
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8 49 acupuncture stimulation (TEAS) in preventing of postoperative ileus (POI) after surgery.  
9  
10 50 ➤ The intervention is simple, non-invasive and easy acceptance therapy.  
11  
12 51 ➤ This study will be possible to verify the mechanism of inflammatory response reduction  
13  
14 52 by TEAS pretreatment in preventing postoperative ileus.  
15  
16 53 ➤ It is a single-center study, the generalization and application may be limited. To reduce  
17  
18 54 this potential bias, large sample, multicenter, multiracial studies are still needed.  
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## 55 **Introduction**

56 Postoperative ileus (POI) is a transient gastrointestinal propulsion dysfunction following  
57 surgery. It often occurs after abdominal surgery and may also occur following surgery at other  
58 sites [1]. The main symptom is abdominal pain, abdominal distention, nausea, vomiting, stop  
59 exhaust defecation, intolerance to solid food, etc. Postoperative ileus is usually temporary, but  
60 if it prolonged, may lead to surgical incision dehiscence, intestinal anastomotic fistula,  
61 abdominal cavity infection, intestinal ischemia, aspiration pneumonia and other serious  
62 complications [2-4]. A retrospective cohort study involving nearly 500 U.S. hospitals has  
63 shown that postoperative ileus is a key reason for prolonged hospitalization and increased  
64 medical costs for patients with abdominal surgery [1]. The United States spends more than  
65 \$1.46 billion on POI treatments every year [5]. At present, methods used in treatment of  
66 postoperative ileus mainly include: perioperative rational use of narcotic drugs and opioids,  
67 eating as soon as possible, avoidance to use nasogastric tube after operation, early ambulation,  
68 postoperative epidural analgesia, restrict fluid intake, the minimally invasive surgery (such as  
69 laparoscopic), drug therapy, chewing gum, etc. However, despite the numerous treatment  
70 strategies, the current clinical treatment effect is still not ideal. POI is still a difficult clinical  
71 problem that affects the rapid recovery of postoperative patients. It is necessary to find more  
72 effective, convenient and economical treatment methods [6-10].

73 The main mechanism that causes POI may be the activation of macrophages in the external  
74 muscular layer during surgical operation [11]. Intestinal manipulation during operation can  
75 activate the macrophages cells outside layer muscle of small intestine, the cells can release  
76 inflammatory factors (IL-6, IL-1 $\beta$ ) and chemokine (MIP-1 $\alpha$ ), and increase the expression of  
77 adhesion molecules (ICAM-1) on the endothelial cells, induction of neutrophils and monocytes  
78 in the circulation into the small intestine muscle layer. These cells and activating macrophages  
79 can release a large amount of the inducible nitric oxide synthase (iNOS) and prostaglandin,  
80 inhibits the movement and contraction of the gastrointestinal tract in the end[12, 13]. Further,  
81 the inflammatory mediators were migrated with the blood flow, and further activation of  
82 macrophages in the distal gastrointestinal tract caused the whole gastrointestinal paralysis [14].

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4 83 It was confirmed by a large number of animal experiments that the reduction of inflammatory  
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6 84 response was effective for POI treatment [15-17].  
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8 85 Clinical doctors of traditional Chinese medicine (TCM) have long history using acupuncture to  
9  
10 86 treat functional gastrointestinal disease. In recent years, doctors around the world have also  
11  
12 87 been increasingly concerned about the significant effect of acupuncture on POI. Therefore, the  
13  
14 88 effect of EA on postoperative ileus is clear and promising. Ng, S.S., *et al.* applied electro-  
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16 89 acupuncture (EA) in the treatment postoperative intestinal paralysis of patients under  
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18 90 laparoscopic colon surgery [18]. The results showed that compared with patients without  
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20 91 electro-acupuncture treatment, the defecation time, length of hospital stay were significantly  
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22 92 shortened in the EA group. You, X.M., *et al.* found that significant reduction of the incidence  
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24 93 of POI in patients with hepatic resection by acupuncture combined with Chinese herbal  
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26 94 medicine, and the time of hospitalization was also significantly shortened ( $14.0\pm 4.9d$  vs  
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28 95  $16.5\pm 6.8d$ ,  $P=0.014$ ) [19].  
29

30 96 Our previous studies proved that the pretreatment of acupuncture could regulate the excessive  
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32 97 activation of the innate immune system, and inhibit inflammatory response. This effect may be  
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34 98 achieved by activating the vagus nerve system [20, 21]. Studies have shown that transcutaneous  
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36 99 electrical acupoint stimulation and EA therapy have similar effects in pain treatment and  
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38 100 alleviating inflammatory response [22, 23].  
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40 101 Traditional Chinese medicine holds that the best treatment for disease is precaution. Based on  
41  
42 102 all of the above studies, we hypothesize that using transcutaneous electrical acupoint  
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44 103 stimulation (TEAS) as pretreatment, before the operation, may reduce the incidence of  
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46 104 postoperative ileus. Until now, there is no research report on this.  
47

48 105 We design this randomized, controlled trial, which intends to find whether the pretreatment of  
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50 106 transcutaneous electrical acupoint stimulation can reduce the incidence of postoperative ileus  
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52 107 in laparoscopic colon resection patients. Further to verify that this anti-inflammatory effect is  
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54 108 associated with the immunomodulation function of TEAS.  
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4 111 **Methods and analysis**

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6 112 **Study objective**

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8 113 The primary objective is to investigate whether the pretreatment of percutaneous acupuncture  
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10 114 can improve gastrointestinal motor function after laparoscopic colon surgery. The secondary  
11  
12 115 objective is to verify the suppression of overactivation of innate immune system and reduction  
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14 116 of inflammatory response as the mechanism of pretreatment of percutaneous acupuncture to  
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16 117 prevent POI.

17  
18 118 **Study location**

19  
20 119 A prospective, single-centre, single-blinded, randomized, controlled trial will be conducted at  
21  
22 120 Shuguang hospital affiliated to Shanghai university of traditional Chinese medicine, China.

23  
24 121 **Study population**

25  
26 122 Participants will be recruited according to the following inclusion and exclusion criteria.

27  
28 123 **Inclusion criteria**

- 29  
30 124 1. Aged 18 ~ 75 years old male and female patients.  
31  
32 125 2. Patients undergoing laparoscopic descending colon and rectal cancer surgery.  
33  
34 126 3. Weight index BMI 18 to 31 kg/m<sup>2</sup>.  
35  
36 127 4. The ASA is I-II level.  
37  
38 128 5. Patients signed informed consent.

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40 129 **Exclusion criteria**

- 41  
42 130 1. The middle and lower segment rectal cancer, the whole colon, complete rectal resection,  
43  
44 131 or need of a complex endoscopic surgery.  
45  
46 132 2. It is necessary for abdominal wall fistula, gastrointestinal fistula or fistula surgery.  
47  
48 133 3. Operation history of abdominal, pelvic or complication.  
49  
50 134 4. Patients to receive epidural or epidural analgesic.  
51  
52 135 5. Patients with skin infections, surgical incision or scar on the point.  
53  
54 136 6. Patients with limbs, spinal surgery or nerve injury.  
55  
56 137 7. Patients participated in other clinical trials or received other acupuncture therapy in the  
57  
58 138 near four weeks.

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4 139 8. Patients with cardiac pacemakers.  
5  
6 140 9. Patients with preoperative combined pain, patients with central analgesic drugs, opioid  
7  
8 141 addiction, dependents, or patients with a history of alcoholism.  
9  
10 142 10. Patients with preoperative combination of severe central nervous system disease and  
11  
12 143 severe mental illness.

13  
14 144 **Endpoints**

15  
16 145 **Primary endpoint**

17  
18 146 The first defecation time (h): the time to observe the first anal defecation after laparoscopic  
19  
20 147 surgery.

21  
22 148 **Secondary endpoints**

23  
24 149 Postoperative anal exhaust time (h), time that the patients tolerated a solid diet (h), time to walk  
25  
26 150 independently (h), length of hospital stay (d), postoperative pain VAS score day1,day2,day3 (0  
27  
28 151 to 10, 0 points represent entirely painless, 10 points represent the worst pain intensity),  
29  
30 152 postoperative analgesic requirements, postoperative complications, detected inflammatory  
31  
32 153 mediators IFN- $\beta$ , IFN- $\gamma$ , IL-6, IL-1 in blood before TEAS/STEAS intervention and 1d, 3d, 5d  
33  
34 154 after operation respectively.

35  
36 155 **Randomization and blinding**

37  
38 156 Patients were randomized to receive either TEAS or STEAS treatment by stratified  
39  
40 157 randomization according to sex, in a 1:1 ratio (Figure1). According to the computer-generated  
41  
42 158 random sequence, a sealed nonopaque envelope would be opened to determine the group of  
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44 159 entry. The acupuncturist was aware of treatment allocation. A nurse anaesthetist as outcome  
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46 160 investigator was blinded to the treatment allocation.

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4 162 ***Current sample size justification***

5 163 According to our previous pilot study, mean time to first defecation in the laparoscopic colon  
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7 164 surgery was 62±19h. With assumption that the clinically meaningful difference in mean time  
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9 165 to first defecation between TEAS and STEAS groups is 1 day or 24 hours, 66 patients in each  
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11 166 group were needed to reach a power of 80% and 5% Type I error rate. Suppose the drop-out  
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13 167 rate is 10%, a sample size of 146 patients for 2 groups was needed in this study.

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16 168 ***Statistical analysis***

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18 169 All data will be analysed using SPSS17.0 or other statistical software packages as needed. The  
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20 170 statistical methods will include descriptive statistics, the t-test,  $\chi^2$  test, analysis of variance,  
21  
22 171 univariate logistic regression analysis and multivariate linear regression analysis. The  
23  
24 172 significance level will be set at 5%.

25  
26 173 ***Pretreatment***

27  
28 174 The patients randomized to TEAS and STEAS groups underwent 2 sessions of TEAS/STEAS  
29  
30 175 treatment daily for three consecutive days before surgery. And the patients were administered  
31  
32 176 a last TEAS/STEAS treatment for 30 minutes before anesthesia.

33  
34 177 The perioperative management of all patients was standardized. Early ambulation was  
35  
36 178 encouraged. Oral feeding was resumed as early as possible. All patients will be followed up  
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38 179 until discharge from the hospital.

39  
40 180 In TEAS group, the acupoints including Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4), and  
41  
42 181 Neiguan (P-6), were identified before electrical stimulation with surface electrodes (Figure 2).

43  
44 182 Selection of these acupoints was based on a consensus between the acupuncturists of the study.

45  
46 183 No electrical stimulation sensation was performed in STEAS group. Electric stimulation was  
47  
48 184 used in TEAS group with the Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng  
49  
50 185 Medical Technology Co., Ltd., Nanjing, China). Frequency of the electric stimulation was set  
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52 186 at 100 Hz. In STEAS group, pseudo-stimulation was provided by deliberately connecting the  
53  
54 187 electrodes to the incorrect output socket of EA device, and thus there was no flow of electric  
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56 188 current. Patients could see the output light flashing but no current was transmitted throughout  
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189 the procedure. Patients were told that the stimulation frequency selected was not perceivable  
190 by human beings. Each session of EA treatment last for 30 minutes.

191 All operations were under general anesthesia, according to standardized anesthesia procedures.  
192 Patients would be fasting for 12 hours before operation. Right upper extremity venous access  
193 would be established before the patients entering the operation room. 8ml/kg of lactate ringer's  
194 was intravenous infusion for compensatory expansion before induction. Patients would then  
195 intravenously receive midazolam (0.04 mg/kg), fentanyl (3  $\mu$ g/kg), vecuronium bromide (0.1  
196 mg/kg), propofol (1.5-2.0mg/kg) for anesthesia induction. Maintaining anesthesia used CP-600  
197 anaesthesia delivery system (Slgo medical technology co., LTD, Beijing, china). Adjustment  
198 of propofol was performed in order to maintain the bispectral index (BIS) reaching 40 ~ 60.  
199 After operation, all patients would be remained in the post anaesthesia care unit (PACU) and  
200 would return to the ward for recovery procedure until discharge.

#### 201 *Adverse events*

202 All adverse reactions would be recorded and closely monitored through spontaneous reports by  
203 patients or direct observation by clinicians or by non-inducing methods to ask patients about  
204 their adverse events. Taking appropriate treatment if necessary. Serious adverse events should  
205 be reported to the ethics committee.

#### 206 *Data collection and management*

207 Demographic variables and clinical data will be collected from all patients. Furthermore, during  
208 the procedure, blood pressure, heart rate and oxygen saturation will be monitored. Any adverse  
209 events will be recorded. Data will be collected throughout the study and will be securely  
210 managed under conditions of confidentiality. Data collection will be performed by a nurse  
211 anaesthetist. The participants will be referred to by their participant number rather than their  
212 name throughout the study unless otherwise specified. All relevant documents and files will be  
213 archived for 5 years. Data can be only accessed by the investigators who sign the confidential  
214 disclosure agreement and by institutional or governmental auditors during the study. Data  
215 without patient identifiers will be publicly accessible after the study. The process will be  
216 monitored by the Institutional Ethics Committee for Clinical Research of Shuguang Hospital.

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4 217 ***Patient and public involvement***

5 218 Patient and Public Involvement (PPI) has been considered over the course of the trial design.  
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7 219 we organized a Clinical Experience Advisory Panel (CEAP). Our CEAP is made up of staff  
8  
9 220 with expertise in management of complications after abdominal surgery and nursing. CEAP  
10  
11 221 staff will meet twice a year and track the progress of the study and offer advice to the research  
12  
13 222 team. The relationship of CEAP and our research team is coordinated by our hospital clinical  
14  
15 223 trial management committee. Patients will be invited to request study results if interested.  
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18 224 **Discussion**

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20 225 Prevention of postoperative bowel paralysis is of great importance to reduce perioperative  
21  
22 226 complications and reduce hospitalization costs. It has been proved that acupuncture and EA can  
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24 227 effectively treat postoperative bowel paralysis and shorten the time of POI. However, there are  
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26 228 few studies on whether the pretreatment of TEAS can prevent POI. Previous studies have  
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28 229 shown that TEAS are similar to handle acupuncture and EA in pain treatment, reducing  
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30 230 inflammation and so on.

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32 231 It is necessary to verify the efficacy and effectiveness of POI prevention by using  
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34 232 TEAS through clinical trial. This study will evaluate on the occurrence of POI for patients after  
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36 233 using pretreatment with TEAS. There are still some limitations to this study. This study is a  
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38 234 single-centre trial, and therapeutic effect of TEAS may be ethnic and regional, so it is necessary  
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40 235 to conduct multi-center and large sample study in future. In addition, it is difficult to apply the  
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42 236 blind method to the treatment of TEAS, which is hard to distinguish the psychological factors  
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44 237 and placebo effect of the patients, and more methodological improvements are needed.

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46 238 TEAS is treatment that combines percutaneous neurostimulation therapy and acupuncture point  
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48 239 together. In comparison with EA or acupuncture, it has the advantages of non-invasive, simple  
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50 240 operation and easy acceptance. The successful implementation of our clinical trial will help  
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52 241 provide an effective technical means for improving gastrointestinal function recovery in  
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54 242 patients undergoing laparoscopic surgery. It can provide optimized option for postoperative  
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56 243 rehabilitation treatment such as Enhanced Recovery After Surgery (ERAS). In particular, it can  
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58 244 also decrease the economic burden of intensive care units as well as recovery institutions.  
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7  
8 247 statistical design of this study.

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15  
16 251 Ltd.

17  
18 252 ***Availability of data and materials***

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20 253 The dataset to be generated during the present designed study will be available from the  
21  
22 254 corresponding author on reasonable request via email.

23  
24 255 ***Authors' contributions***

25  
26 256 Jian Wang conceived of the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu  
27  
28 257 participated in its design and coordination. Wen-ting Chen, Yue Yong and Jun Guo collected  
29  
30 258 references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistics analysis.  
31  
32 259 Rui Feng will follow up patients and record data. Jian Wang, Li-hua Fan and Jian-gang Song  
33  
34 260 drafted the manuscript. All authors read and approved the final manuscript.

35  
36 261 ***Competing interests***

37  
38 262 The authors declare that they have no competing interests.

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4 344 **Figure Legend**

5 345 Figure 1. Flow chart of the study

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7 346 Figure 2. Acupoints selected in this trial. (a) shows he gu (IL-4), neiguan(P-6). (b) shows zu

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9 347 sanli(ST-36), Shang juxu(ST-37). (c) Han's acupoint nerve stimulator.  
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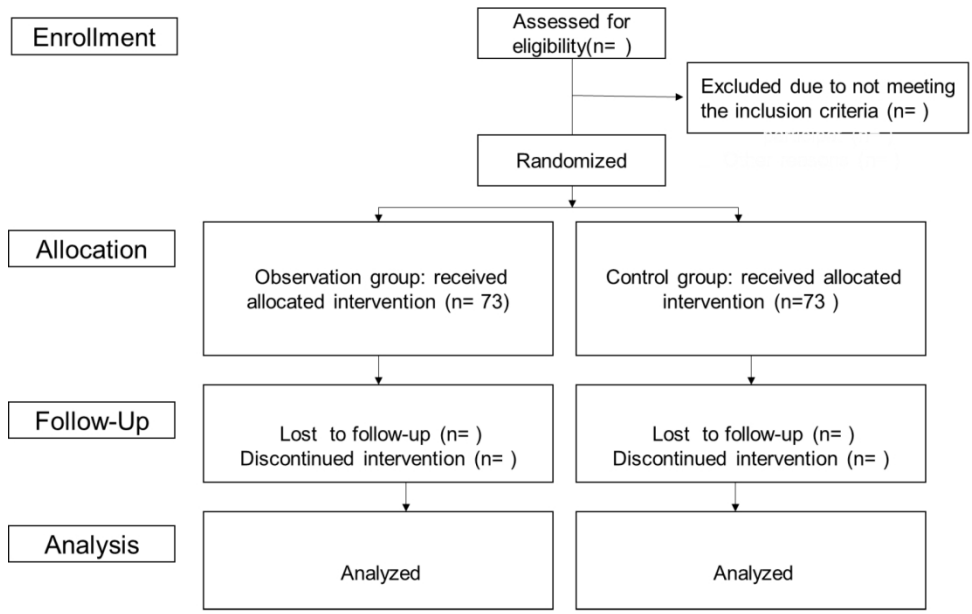


Figure 1. Flow chart of the study

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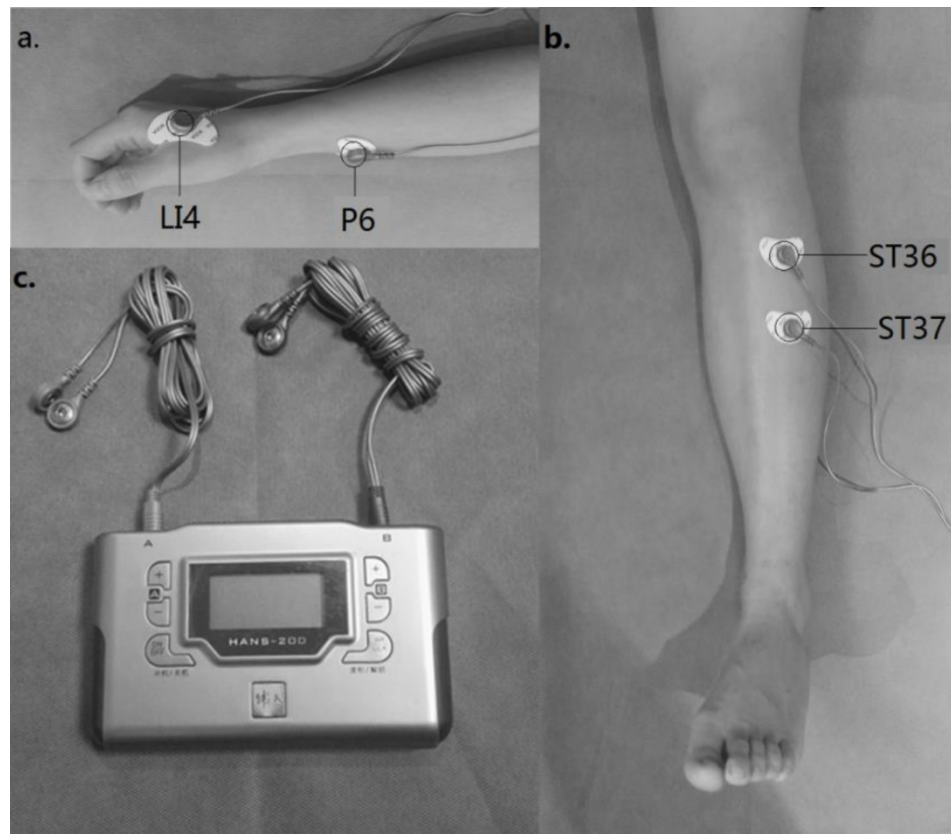


Figure 2. Acupoints selected in this trial. (a) shows he gu (IL-4), neiguan(P-6). (b) shows zu sanli(ST-36), Shang juxu(ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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   | _____ 2 _____            |
| Protocol version                  | 3       | Date and version identifier  | _____ 2 _____            |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____ 11 _____           |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____ 1&11 _____         |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____ 11 _____           |
|                                   | 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 | _____ 11 _____           |
|                                   | 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)                         | _____ 9 _____            |

1 **Introduction**

2

3 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

4

5

6 6b Explanation for choice of comparators \_\_\_\_\_

7

8 Objectives 7 Specific objectives or hypotheses 5

9

10 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

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12

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14 **Methods: Participants, interventions, and outcomes**

15

16 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 6

17

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19 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) 6

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 8&9

23

24

25 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) \_\_\_\_\_

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) \_\_\_\_\_

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_

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34 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 7

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40 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) 7

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including \_\_\_\_\_ 8 \_\_\_\_\_  
 2 clinical and statistical assumptions supporting any sample size calculations

3  
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size \_\_\_\_\_ 8 \_\_\_\_\_  
 5

6 **Methods: Assignment of interventions (for controlled trials)**

7  
 8 Allocation:

9  
 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any \_\_\_\_\_ 7 \_\_\_\_\_  
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
 13 or assign interventions  
 14

15  
 16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, \_\_\_\_\_ 7 \_\_\_\_\_  
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
 18 mechanism  
 19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to \_\_\_\_\_ 7 \_\_\_\_\_  
 21 interventions  
 22

23  
 24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome \_\_\_\_\_ 7 \_\_\_\_\_  
 25 assessors, data analysts), and how  
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's \_\_\_\_\_ 7 \_\_\_\_\_  
 28 allocated intervention during the trial  
 29

30  
 31 **Methods: Data collection, management, and analysis**

32  
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related \_\_\_\_\_ 9 \_\_\_\_\_  
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
 36 Reference to where data collection forms can be found, if not in the protocol  
 37

38  
 39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_ 9 \_\_\_\_\_  
 40 collected for participants who discontinue or deviate from intervention protocols  
 41

|    |                                 |     |   |    |
|----|---------------------------------|-----|---|----|
| 1  | 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   | 9  |
| 2  |                                 |     |   |    |
| 3  |                                 |     |   |    |
| 4  |                                 |     |   |    |
| 5  | 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  | 8  |
| 6  |                                 |     |   |    |
| 7  |                                 |     |   |    |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8  |
| 9  |                                 |     |   |    |
| 10 |                                 | 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)   | 8  |
| 11 |                                 |     |   |    |
| 12 |                                 |     |   |    |
| 13 |                                 |     |   |    |
| 14 | <b>Methods: Monitoring</b>      |     |   |    |
| 15 |                                 |     |   |    |
| 16 | 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 | 9  |
| 17 |                                 |     |   |    |
| 18 |                                 |     |   |    |
| 19 |                                 |     |   |    |
| 20 |                                 |     |   |    |
| 21 |                                 |     |   |    |
| 22 |                                 | 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   | 9  |
| 23 |                                 |     |   |    |
| 24 |                                 |     |   |    |
| 25 | 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   | 9  |
| 26 |                                 |     |   |    |
| 27 |                                 |     |   |    |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 10 |
| 29 |                                 |     |   |    |
| 30 |                                 |     |   |    |
| 31 |                                 |     |   |    |
| 32 | <b>Ethics and dissemination</b> |     |   |    |
| 33 |                                 |     |   |    |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 2  |
| 35 |                                 |     |   |    |
| 36 |                                 |     |   |    |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | 10 |
| 38 |                                 |     |   |    |
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| 40 |                                 |     |   |    |
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|----|-------------------------------|-----|---|--------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | _____6_____  |
| 2  |                               |     |   |              |
| 3  |                               |     |   |              |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | _____6_____  |
| 5  |                               |     |   |              |
| 6  |                               |     |   |              |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | _____9_____  |
| 8  |                               |     |   |              |
| 9  |                               |     |   |              |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | _____11_____ |
| 11 |                               |     |   |              |
| 12 |                               |     |   |              |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | _____9_____  |
| 14 |                               |     |   |              |
| 15 |                               |     |   |              |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | _____9_____  |
| 17 |                               |     |   |              |
| 18 |                               |     |   |              |
| 19 |                               |     |   |              |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____2_____  |
| 21 |                               |     |   |              |
| 22 |                               |     |   |              |
| 23 |                               |     |   |              |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | _____2_____  |
| 25 |                               |     |   |              |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | _____2_____  |
| 27 |                               |     |   |              |
| 28 |                               |     |   |              |
| 29 | <b>Appendices</b>             |     |   |              |
| 30 |                               |     |   |              |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | _____NA_____ |
| 32 |                               |     |   |              |
| 33 |                               |     |   |              |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | _____NA_____ |
| 35 |                               |     |   |              |
| 36 |                               |     |   |              |

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
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# BMJ Open

## Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2019-030694.R1   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 03-Dec-2019  |
| Complete List of Authors:       | <p>Wang, Jian; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine</p> <p>Li, Dongli; Wenzhou Medical University, the sixth Affiliated Hospital, Anesthesiology</p> <p>Tang, Wei; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Guo, Jun; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Chen, Wenting; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Yong, Yue; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Yu, Guijie; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Feng, Rui; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Yuan, Lan; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Fu, Guoqiang; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Song, Jiangang; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Fan, Lihua; Wenzhou Medical University, the sixth Affiliated Hospital, Anesthesiology</p> |
| <b>Primary Subject Heading</b>: | Complementary medicine   |
| Secondary Subject Heading:      | Anaesthesia, Gastroenterology and hepatology, Surgery  |
| Keywords:                       | Transcutaneous electrical acupoint stimulation (TEAS), postoperative ileus (POI), Pretreatment   |
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4 1 **Pretreatment with transcutaneous electrical acupoint stimulation to prevent**  
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6 2 **postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for**  
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8 3 **a randomized controlled trial**  
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10 4

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4 22 **Abstract**

5 23 **Introduction:** Postoperative ileus (POI), a common complication after surgery, severely affects  
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8 24 postoperative recovery. It is unclear whether pretreatment with transcutaneous electrical  
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10 25 acupoint stimulation (TEAS) can improve recovery from POI. This trial will evaluate the effects  
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12 26 of pretreatment with TEAS on POI.

13  
14 27 **Methods and analysis:** This will be a prospective, randomized, controlled trial. ASA I–III  
15  
16 28 level patients, aged 18–75 years and scheduled for laparoscopic colon surgery, will be included  
17  
18 29 in the study. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS  
19  
20 30 (STEAS) groups. The groups will undergo two sessions of TEAS/STEAS daily for three days  
21  
22 31 before surgery, with a final TEAS/STEAS treatment 30 minutes before anesthesia. The primary  
23  
24 32 endpoint of the study will be time to first defecation. Secondary endpoints will include time to  
25  
26 33 first flatus, time to tolerance of oral diet, GI-2 (composite outcome of time to first defecation  
27  
28 34 and time to tolerance of oral diet), time to independent walking , length of hospital stay,  
29  
30 35 postoperative pain VAS score on the first three days after surgery, analgesic requirements,  
31  
32 36 complications, and plasma concentrations of IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ . Multiple linear  
33  
34 37 regression will be used to identify independent predictors of outcome measures.

35  
36 38 **Ethics and dissemination:** This study has been approved by the Chinese Registered Clinical  
37  
38 39 Trial Ethics Review Committee (NO.ChiECRCT-20170084). The results of the trial will be  
39  
40 40 published in an international peer-reviewed journal.

41 41 **Trial registration:** This study has been registered with the Chinese Clinical Trial Registry (NO.  
42  
43 42 ChiCTR-INR-17013184).

44 43 **Trial status:** The study was in the recruitment phase at the time of manuscript submission.

45 44 **Abbreviations:** POI = postoperative ileus, TCM = traditional Chinese medicine, EA = electro-  
46  
47 45 acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index,  
48  
49 46 PACU = post anesthesia care unit, ERAS= enhanced recovery after surgery.

50  
51 47 **Key words:** transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI);  
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53 48 pretreatment.  
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4 49 Strengths and limitations of the study

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6  
7 51 ➤ This study aims to evaluate whether pretreatment with transcutaneous electrical  
8 52 acupoint stimulation (TEAS) can prevent postoperative ileus (POI).

9 53 ➤ TEAS is a safe, noninvasive and easily accepted adjunctive intervention.

10  
11 54 ➤ This study will provide deeper insights into the mechanism by which TEAS  
12 55 pretreatment reduces the inflammatory response.

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14 56 ➤ This is a single-center study, which is a potential limitation.  
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## 57 **Introduction**

58 Postoperative ileus (POI) is a transient dysfunction of gastrointestinal propulsion that often  
59 occurs after abdominal surgery and may also occur following surgery at other sites<sup>1</sup>. The main  
60 symptoms of POI include abdominal pain and distention, nausea, vomiting, difficult  
61 defecation and intolerance to solid food. POI is usually temporary, but if prolonged, may lead  
62 to surgical incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection,  
63 intestinal ischemia, aspiration pneumonia and other serious complications<sup>2-4</sup>. A retrospective  
64 cohort study involving nearly 500 hospitals in the United States showed that POI is a key reason  
65 for prolonged hospitalization and increased medical costs for patients undergoing abdominal  
66 surgery<sup>1</sup>. The United States spends more than \$1.46 billion treating POI every year<sup>5</sup>. At present,  
67 the most common methods used to treat POI include: rational perioperative use of narcotic  
68 drugs and opioids, eating as soon as possible after surgery, avoidance of nasogastric tubes after  
69 the operation, early ambulation, postoperative epidural analgesia, restriction of fluid intake, the  
70 use of minimally invasive surgery (such as laparoscopic), drug therapy and the use of chewing  
71 gum. Despite the numerous treatment strategies, POI remains a difficult clinical challenge that  
72 compromises the rapid recovery of postoperative patients. It is, therefore, necessary to find  
73 more effective, convenient and economical treatment methods<sup>6-10</sup>.

74 The main mechanism underlying POI may be activation of macrophages in the external  
75 muscular layer during the surgical procedure<sup>11</sup>. Intestinal manipulation during surgery can  
76 activate macrophages in the outer muscle layer of the small intestine, leading to release of  
77 inflammatory factors (IL-6, IL-1 $\beta$ ) and the chemokine MIP-1 $\alpha$ , together with increased  
78 expression of the adhesion molecule ICAM-1 on endothelial cells and induction of neutrophils  
79 and monocytes in the circulation into the small intestine muscle layer. These cells, and activated  
80 macrophages, can release a large amount of inducible nitric oxide synthase (iNOS) and  
81 prostaglandin, which inhibit the movement and contraction of the gastrointestinal tract<sup>12,13</sup>.  
82 Transport of these inflammatory mediators in the blood stream causes activation of  
83 macrophages in the distal gastrointestinal tract, leading to total gastrointestinal paralysis<sup>14</sup>. It



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4 84 has been confirmed by a large number of animal experiments that reducing the inflammatory  
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6 85 response is an effective way to treat POI<sup>15-17</sup>.

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8 86 There is a long history in traditional Chinese medicine (TCM) of using acupuncture to treat  
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10 87 functional gastrointestinal diseases and, in recent years, there has been significant global  
11  
12 88 interest in the beneficial effects of acupuncture on POI. The positive effect of  
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14 89 electroacupuncture (EA) on POI has been clearly demonstrated. Ng *et al.* used EA to treat  
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16 90 postoperative intestinal paralysis in patients undergoing laparoscopic colon surgery<sup>18</sup>.  
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18 91 Defecation time and length of hospital stay were significantly shortened in patients who  
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20 92 received EA compared with those who did not receive the treatment. In patients undergoing  
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22 93 hepatic resection, You *et al.* found a significant reduction in the incidence of POI in patients  
23  
24 94 treated with a combination of acupuncture and Chinese herbal medicine. The length of  
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26 95 hospitalization was also significantly shortened in the treated group ( $14.0 \pm 4.9$  d vs  $16.5 \pm 6.8$   
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28 96 d,  $P = 0.014$ )<sup>19</sup>.

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30 97 In previous studies, we proved that pretreatment with acupuncture could reduce excessive  
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32 98 activation of the innate immune system and inhibit the inflammatory response. This effect may  
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34 99 be achieved by activation of the vagal nervous system<sup>20,21</sup>. Other studies have shown that  
35  
36 100 transcutaneous electrical acupoint stimulation (TEAS) and EA have similar effects in the  
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38 101 treatment of pain and alleviating the inflammatory response<sup>22,23</sup>.

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40 102 Traditional Chinese medicine holds that the best treatment for disease is prevention . Based on  
41  
42 103 all of the above studies, we hypothesize that the use of TEAS as a preoperative treatment may  
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44 104 reduce the incidence of POI. There have, so far, not been any studies that address this question.  
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46 105 We have, therefore, designed a randomized, controlled trial to investigate whether pretreatment  
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48 106 with TEAS can reduce the incidence of POI in patients undergoing laparoscopic colon resection.  
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50 107 The study is also designed to verify that the anti-inflammatory effect is associated with the  
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52 108 immunomodulatory function of TEAS.

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## 56 110 **Methods and analysis**

### 57 58 111 ***Study objective***

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4 112 The primary objective is to assess the effect of TEAS on clinical recovery of bowel function  
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6 113 after laparoscopic colon surgery. The secondary objective is to verify that suppression of  
7  
8 114 overactivation of the innate immune system and reduction of the inflammatory response are the  
9  
10 115 mechanisms underlying the ability of pretreatment of percutaneous acupuncture to prevent POI.

### 116 ***Study location***

117 A prospective, single-center, single-blinded, randomized, controlled trial will be conducted at  
118 Shuguang Hospital, which is affiliated to the Shanghai University of Traditional Chinese  
119 Medicine, China.

### 120 ***Study population***

121 Participants will be recruited according to the inclusion and exclusion criteria.

### 122 **Inclusion criteria**

- 123 1. Male and female patients aged 18–75 years
- 124 2. Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such  
125 as left colectomy, right colectomy, and anterior resection of the upper part of the rectum  
126 and lower part of the sigmoid)
- 127 3. Body mass index (BMI) 18–31 kg/m<sup>2</sup>
- 128 4. ASA classification I–III
- 129 5. Patients provide signed informed consent

### 130 **Exclusion criteria**

- 131 1. Middle and lower rectal resection, total/proctocolectomy or the need for complex  
132 endoscopic surgery
- 133 2. Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation
- 134 3. History of abdominal/pelvic operations or complications
- 135 4. Patients receiving epidural anesthesia or epidural analgesia
- 136 5. Patients with skin infections, surgical incision or scar at the point of application of  
137 acupuncture
- 138 6. Patients with limbs, spinal surgery or nerve injury

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4 139 7. Patients who participated in other clinical trials, or received other acupuncture therapy, in  
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6 140 the previous four weeks  
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8 141 8. Patients with cardiac pacemakers  
9  
10 142 9. Patients with preoperative combined pain, patients using centrally active analgesic drugs,  
11  
12 143 opioid addiction or dependency, patients with a history of alcoholism  
13  
14 144 10. Patients with preoperative combination of severe central nervous system disease and  
15  
16 145 severe mental illness

17  
18 146 **Endpoints**

19  
20 147 **Primary endpoint**

21  
22 148 First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.

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24 149 **Secondary endpoints**

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26 150 Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time  
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28 151 to first defecation and time to tolerance of oral diet), time to walk independently (h), length of  
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30 152 hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital  
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32 153 discharge include stability of vital signs with no fever, achievement of flatus or defecation,  
33  
34 154 ability to tolerate solid food without vomiting, control of postoperative pain, absence of other  
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36 155 postoperative complications and ability to function at home independently or with home care  
37  
38 156 provided. Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1,  
39  
40 157 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the  
41  
42 158 worst pain intensity). Postoperative requirements for analgesia will also be assessed.  
43  
44 159 Inflammatory mediators (IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ ) in blood will be measured before  
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46 160 TEAS/STEAS intervention and on days 1, 3 and 5 after the operation. Postoperative  
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48 161 complications will be recorded using the Clavien - Dindo classification for complication  
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50 162 assessment<sup>24</sup>. The follow-up period will be at least 6 months.

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52 163 **Randomization and blinding**

53  
54 164 Patients will be randomized to receive either TEAS or STEAS by stratified randomization  
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56 165 according to sex, in a 1:1 ratio (Figure 1). Using a computer-generated random sequence, a  
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58 166 sealed envelope will be opened to determine to which group the patient has been assigned. The

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4 167 acupuncturist will be aware of the treatment group, but the nurse anesthetist, as outcome  
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6 168 investigator, will be blinded to the treatment allocation.

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8 169 ***Current sample size justification***

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10 170 According to Wang Jian and Song Jiangan's preliminary study of transcutaneous electrical  
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12 171 acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing  
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14 172 laparoscopic colon surgery in Shuguang Hospital, the mean time to first defecation following  
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16 173 laparoscopic colon surgery was  $62 \pm 19$  h ( $M \pm SD$ ). Working on the assumption that a clinically  
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18 174 meaningful difference in mean time to first defecation between the TEAS and STEAS groups  
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20 175 is 1 day or 24 h, 66 patients would be needed in each group to reach a power of 80% and a 5%  
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22 176 Type I error rate. If the drop-out rate is 10%, a total sample size of 146 patients for the two  
23  
24 177 groups is needed for this study.

25  
26 178 ***Statistical analysis***

27  
28 179 Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance  
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30 180 of oral diet, time to walking independently, length of hospital stay) will be reported using the  
31  
32 181 mean and standard deviation ( $M \pm SD$ ) for normally distributed data or median (range) for  
33  
34 182 skewed data. Data for categorical variables will be expressed as a number (percentage).  
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36 183 Intergroup differences will be assessed using the Student's t-test or Mann-Whitney U test.  
37  
38 184 Outcomes such as time to first flatus, time to tolerance of oral diet, GI-2 and time to walking  
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40 185 independently will be included in multiple linear regression to identify independent predictors  
41  
42 186 that affect length of hospital stay. The significance level will be set at 5%. All data will be  
43  
44 187 analyzed using SPSS 17.0 software or other appropriate statistical software packages.

45  
46 188 ***Pretreatment***

47  
48 189 Patients randomized to the TEAS and STEAS groups will undergo two treatment sessions daily  
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50 190 for three consecutive days before surgery. The patients will then be treated for a final time 30  
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52 191 minutes before anesthesia.

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54 192 For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and  
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56 193 Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes  
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58 194 (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists

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4 195 carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint  
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6 196 nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China),  
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8 197 at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight  
9  
10 198 twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness,  
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12 199 distention and heaviness. The STEAS group will receive a strong, but comfortable current for  
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14 200 30 s, and the current will then gradually vanish over the next 15 s. The participants will be told  
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16 201 that they are receiving TEAS, but that sensation thresholds differ and that there may be no  
17  
18 202 precise perception of current stimulation. Each session of acupoints treatment will last for 30  
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20 203 min. During the application of TEAS, patients will be required not to change the current settings  
21  
22 204 themselves. A prompt beep at the end of TEAS will indicate the end of treatment.

23  
24 205 All surgery will be carried out under general anesthesia, using standardized anesthetic  
25  
26 206 procedures. Patients will be fasted for 12 h before surgery. Right upper extremity venous access  
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28 207 will be established before the patients entering the operating theater. Ringer's lactate solution  
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30 208 (8 mL/kg) will be administered by intravenous infusion for compensatory expansion before  
31  
32 209 induction of anesthesia. Patients will then receive midazolam (0.04 mg/kg), fentanyl (3 µg/kg),  
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34 210 vecuronium bromide (0.1 mg/kg) and propofol (1.5–2.0 mg/kg) intravenously for induction of  
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36 211 anesthesia. Anesthesia will be maintained using a CP-600 anesthesia delivery system (Slgo  
37  
38 212 Medical Technology Co., Ltd., Beijing, China). The dose of propofol will be adjusted to  
39  
40 213 maintain the bispectral index (BIS) in the range 40–60. After surgery, all patients will remain  
41  
42 214 in the post anesthesia care unit and then return to the ward for recovery until discharge.

43  
44 215 The perioperative management of all patients will be standardized. Early ambulation will be  
45  
46 216 encouraged and oral feeding will be resumed as early as possible. All patients will be followed-  
47  
48 217 up for at least 6 months after discharge from the hospital.

#### 49 218 *Adverse events*

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51 219 All adverse reactions will be closely monitored through spontaneous reports by patients or  
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53 220 direct observation by clinicians, or by asking the patients about adverse events using open  
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55 221 questions. All adverse reactions will be recorded and appropriate treatment will be provided if  
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57 222 necessary. Serious adverse events will be reported to the ethics committee.  
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4 223 ***Data collection and management***

5 224 Demographic variables and clinical data will be collected from all patients. During the study,  
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7 225 blood pressure, heart rate and oxygen saturation will also be monitored. Any adverse events  
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9 226 will be recorded. Data will be collected throughout the study and will be securely managed  
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11 227 under conditions of confidentiality. Data collection will be performed by a nurse anesthetist.  
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13 228 The participants will be referred to by their participant number rather than by their name  
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15 229 throughout the study, unless otherwise specified. All relevant documents and files will be  
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17 230 archived for 5 years. The data will be accessible only by investigators who sign the confidential  
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19 231 disclosure agreement and by institutional or governmental auditors during the study. Data  
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21 232 without patient identifiers will be publicly accessible after the study. Data collection and  
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23 233 management will be monitored by the Institutional Ethics Committee for Clinical Research of  
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25 234 Shuguang Hospital.

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28 235 ***Patient and public involvement***

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30 236 This study is currently in the recruitment phase. The participants will be able to access the study  
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32 237 results through social media.

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34 238 **Discussion**

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36 239 POI continues to represent an important cause of morbidity following colon surgery. The  
37  
38 240 prevention of postoperative bowel paralysis is thus of great importance in reducing  
39  
40 241 perioperative complications and reducing hospitalization costs. Although it has been shown  
41  
42 242 that EA can shorten the duration of POI<sup>18</sup>, the effectiveness of TEAS, which is a similar  
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44 243 technique, in preventing POI has not been investigated. It is, therefore, important to assess the  
45  
46 244 effectiveness of TEAS in preventing POI through a clinical study.

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48 245 This study has several strengths. Firstly, the intervention strategy of the protocol will be  
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50 246 pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic  
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52 247 effect. For example, pretreatment with TEAS has been shown to improve pain treatment<sup>25,26</sup>  
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54 248 and to improve resuscitation after anesthesia, with reduction of postoperative nausea and  
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56 249 vomiting<sup>27</sup>. It is, however, unclear whether preoperative TEAS can prevent POI. Studies  
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58 250 suggest that early preoperative intervention may be more beneficial in regulating physiological  
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4 251 functions and preventing gastrointestinal paralysis<sup>28</sup>. In an extension to these findings, the  
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6 252 present study will help to determine whether TEAS pretreatment could improve  
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8 253 postoperative bowel paralysis.

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10 254 Secondly, the effectiveness of TEAS will be evaluated by assessing clinical function and by  
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12 255 serological examination. In this randomized controlled trial of patients undergoing laparoscopic  
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14 256 colorectal surgery, our aim is to assess the effects of preoperative TEAS on POI using relevant  
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16 257 clinical parameters associated with bowel function. These include time to first defecation, time  
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18 258 to first flatus, time to tolerance of oral diet and GI-2. Importantly, we will also measure serum  
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20 259 concentrations of inflammatory mediators associated with POI, such as IFN- $\beta$ , IFN- $\gamma$ , IL-6 and  
21  
22 260 IL-1 $\beta$ . Our findings may, thus, provide deeper insights into the mechanisms by which TEAS  
23  
24 261 improves POI.

25  
26 262 There are also limitations to this protocol. Various clinical indicators have been used in studies  
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28 263 for the diagnosis of POI, but there is no consensus on which clinical parameter is the best for  
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30 264 assessment of gastrointestinal (GI) transit<sup>9,29,30</sup>. Two indicators that are widely used to assess  
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32 265 bowel movement will be used in this study. Time to first defecation will be the primary outcome  
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34 266 and time to first flatus will be one of the secondary outcomes. There is a possibility that we  
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36 267 may observe conflicting results (i.e., significant improvement in time to flatus, but not  
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38 268 defecation). Because flatus can vary considerably between patients, clinical trials support the  
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40 269 time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to  
41  
42 270 first tolerance of solid food and time to first bowel movement) as supplementary  
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44 271 secondary outcomes to measure the recovery time of GI function and these will be used in this  
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46 272 study<sup>31,32</sup>. Other limitations of these indicators are that they require objective measurement of  
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48 273 motility and are time consuming to measure<sup>33,34</sup>. Recently, this situation has been improved by  
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50 274 the use of in vivo monitoring techniques to assess the function of gastrointestinal movements.  
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52 275 Innovative devices, such as Sitz markers, have been used to evaluate postoperative recovery of  
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54 276 small bowel movement by counting the number of Sitz markers that did not pass through the  
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56 277 ileocecal valve, but remained in the small intestine using radiography<sup>35</sup>. The SmartPill is a  
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58 278 swallowable device that records parameters within the GI tract. Indicators, such as pH,  
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4 279 temperature and intracavitary pressure, can be collected to analyze gastrointestinal transit times  
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6 280 in vivo<sup>36</sup>. These devices acquire objective parameters to evaluate bowel movement and could  
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8 281 save time. Research into the satisfaction of both doctors and patients with these device needs  
9  
10 282 to be carried out. Furthermore, this study is a single-center trial and, because the therapeutic  
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12 283 effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-  
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14 284 center and large sample studies in the future.

15  
16 285 Notwithstanding its limitations, this study can clearly indicate the overall effects of TEAS on  
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18 286 postoperative recovery. We hypothesize that pretreatment with TEAS could improve recovery  
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20 287 of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides  
21  
22 288 positive results, it will be possible to recommend this pretreatment strategy for patients  
23  
24 289 undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of  
25  
26 290 consideration.

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29  
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31  
32 293 statistical design of this study.

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37  
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39  
40 297 Ltd.

#### 41 42 298 ***Availability of data and materials***

43  
44 299 The dataset to be generated during the study will be available from the corresponding author  
45  
46 300 on reasonable request via email.

#### 47 48 301 ***Author contributions***

49  
50 302 Jian Wang conceived the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated  
51  
52 303 in its design and coordination. Wen-ting Chen, Yue Yong, Jia-qun He and Jun Guo collected  
53  
54 304 references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistical  
55  
56 305 analyses. Rui Feng will follow-up with patients and record data. Jian Wang, Li-hua Fan and  
57  
58 306 Jian-gang Song drafted the manuscript. All authors have read and approved the final manuscript.



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307 ***Competing interests***

308 None declared.

For peer review only

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### 455 **Figure Legend**

456 Figure 1. Flow chart of the study protocol

457 Figure 2. Acupoints selected in this trial (a) Hegu (IL-4) and Neiguan (P-6); (b) Zusanli (ST-  
458 36) and Shangjuxu (ST-37); (c) Han's acupoint nerve stimulator

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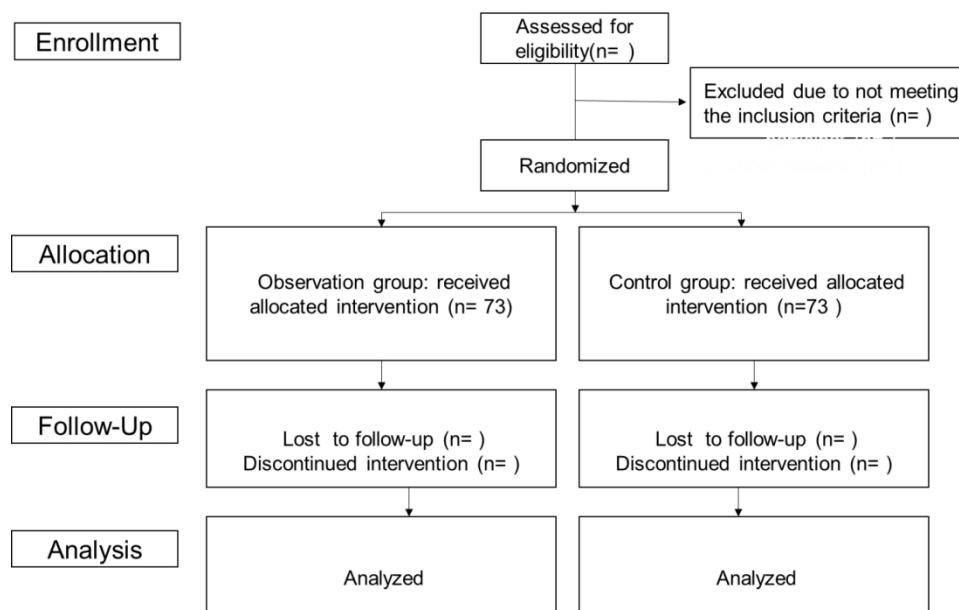


Figure 1. Flow chart of the study

177x109mm (300 x 300 DPI)

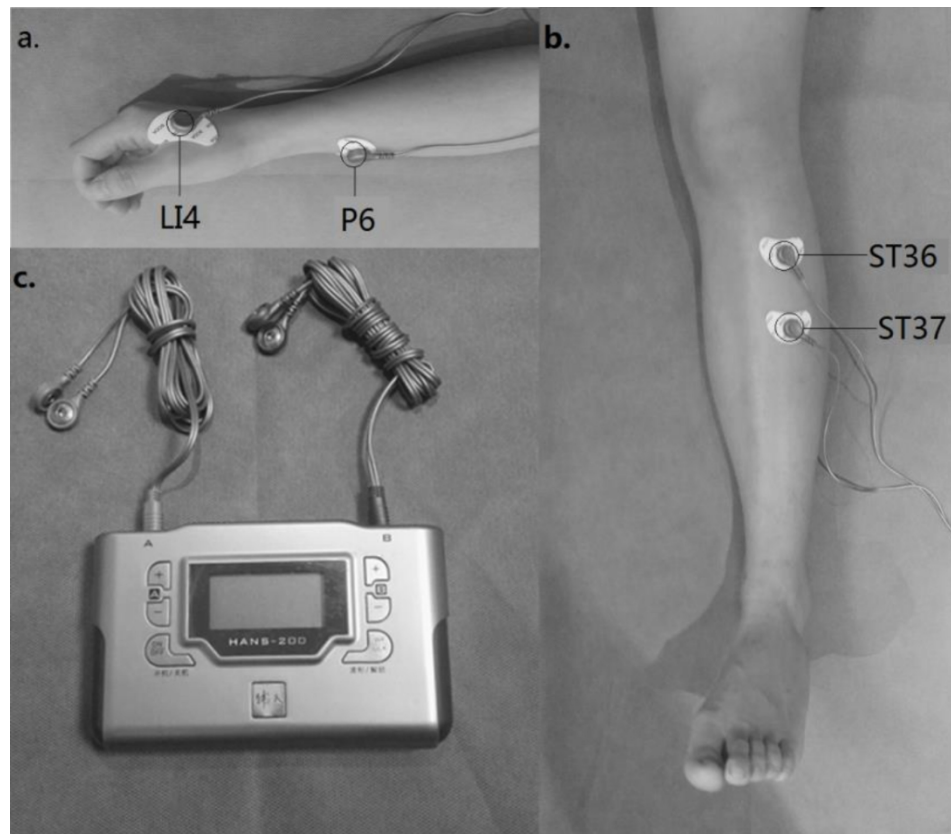


Figure 2. Acupoints selected in this trial. (a) shows Hegu (LI-4), Neiguan (P-6). (b) shows Zusanli (ST-36), Shangjuxu (ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)



SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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   | _____ 2 _____            |
| Protocol version                  | 3       | Date and version identifier  | _____ 2 _____            |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____ 11 _____           |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____ 1&11 _____         |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____ 11 _____           |
|                                   | 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 | _____ 11 _____           |
|                                   | 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)                         | _____ 9 _____            |



|    |   |     |   |                 |
|----|---|-----|---|-----------------|
| 1  | <b>Introduction</b>                                       |     |   |                 |
| 2  |   |     |   |                 |
| 3  | Background and  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant   | _____ 4&5 _____ |
| 4  | rationale   |     | studies (published and unpublished) examining benefits and harms for each intervention                        |                 |
| 5  |   |     |   |                 |
| 6  |   | 6b  | Explanation for choice of comparators   | _____           |
| 7  |   |     |   |                 |
| 8  | Objectives  | 7   | Specific objectives or hypotheses   | _____ 5 _____   |
| 9  |   |     |   |                 |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), | _____ 5 _____   |
| 11 |   |     | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   |                 |
| 12 |   |     |   |                 |
| 13 |   |     |   |                 |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |   |                 |
| 15 |   |     |   |                 |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will | _____ 6 _____   |
| 17 |   |     | be collected. Reference to where list of study sites can be obtained  |                 |
| 18 |   |     |   |                 |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  | _____ 6 _____   |
| 20 |   |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |                 |
| 21 |   |     |   |                 |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be | _____ 8&9 _____ |
| 23 |   |     | administered  |                 |
| 24 |   |     |   |                 |
| 25 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  | _____           |
| 26 |   |     | change in response to harms, participant request, or improving/worsening disease)                             |                 |
| 27 |   |     |   |                 |
| 28 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        | _____           |
| 29 |   |     | (eg, drug tablet return, laboratory tests)  |                 |
| 30 |   |     |   |                 |
| 31 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 | _____           |
| 32 |   |     |   |                 |
| 33 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       | _____ 7 _____   |
| 34 |   |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, |                 |
| 35 |   |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |                 |
| 36 |   |     | efficacy and harm outcomes is strongly recommended  |                 |
| 37 |   |     |   |                 |
| 38 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   | _____ 7 _____   |
| 39 |   |     | participants. A schematic diagram is highly recommended (see Figure)  |                 |
| 40 |   |     |   |                 |
| 41 |   |     |   |                 |
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|---|-------------|----|---|-------------|
| 1 | 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 | _____8_____ |
| 2 |             |    |   |             |
| 3 |             |    |   |             |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | _____8_____ |
| 5 |             |    |   |             |

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

|    |                    |     |  |             |
|----|--------------------|-----|--|-------------|
| 8  |                    |     |  |             |
| 9  |                    |     |  |             |
| 10 | Sequence           | 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_____ |
| 11 | generation         |     |  |             |
| 12 |                    |     |  |             |
| 13 |                    |     |  |             |
| 14 |                    |     |  |             |
| 15 |                    |     |  |             |
| 16 | Allocation         | 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_____ |
| 17 | concealment        |     |  |             |
| 18 | mechanism          |     |  |             |
| 19 |                    |     |  |             |
| 20 | Implementation     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | _____7_____ |
| 21 |                    |     |  |             |
| 22 |                    |     |  |             |
| 23 |                    |     |  |             |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | _____7_____ |
| 25 |                    |     |  |             |
| 26 |                    |     |  |             |
| 27 |                    | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | _____7_____ |
| 28 |                    |     |  |             |
| 29 |                    |     |  |             |
| 30 |                    |     |  |             |

### 31 **Methods: Data collection, management, and analysis**

|    |                 |     |  |             |
|----|-----------------|-----|--|-------------|
| 32 |                 |     |  |             |
| 33 | Data collection | 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_____ |
| 34 | methods         |     |  |             |
| 35 |                 |     |  |             |
| 36 |                 |     |  |             |
| 37 |                 |     |  |             |
| 38 |                 |     |  |             |
| 39 |                 | 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  | _____9_____ |
| 40 |                 |     |  |             |
| 41 |                 |     |  |             |
| 42 |                 |     |  |             |

|    |                                 |     |   |              |
|----|---------------------------------|-----|---|--------------|
| 1  | 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   | _____9_____  |
| 2  |                                 |     |   |              |
| 3  |                                 |     |   |              |
| 4  |                                 |     |   |              |
| 5  | 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  | _____8_____  |
| 6  |                                 |     |   |              |
| 7  |                                 |     |   |              |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | _____8_____  |
| 9  |                                 |     |   |              |
| 10 |                                 | 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)   | _____8_____  |
| 11 |                                 |     |   |              |
| 12 |                                 |     |   |              |
| 13 |                                 |     |   |              |
| 14 | <b>Methods: Monitoring</b>      |     |   |              |
| 15 |                                 |     |   |              |
| 16 | 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 | _____9_____  |
| 17 |                                 |     |   |              |
| 18 |                                 |     |   |              |
| 19 |                                 |     |   |              |
| 20 |                                 |     |   |              |
| 21 |                                 |     |   |              |
| 22 |                                 | 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   | _____9_____  |
| 23 |                                 |     |   |              |
| 24 |                                 |     |   |              |
| 25 | 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   | _____9_____  |
| 26 |                                 |     |   |              |
| 27 |                                 |     |   |              |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | _____10_____ |
| 29 |                                 |     |   |              |
| 30 |                                 |     |   |              |
| 31 |                                 |     |   |              |
| 32 | <b>Ethics and dissemination</b> |     |   |              |
| 33 |                                 |     |   |              |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | _____2_____  |
| 35 |                                 |     |   |              |
| 36 |                                 |     |   |              |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | _____10_____ |
| 38 |                                 |     |   |              |
| 39 |                                 |     |   |              |
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|    |                               |     |   |              |
|----|-------------------------------|-----|---|--------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | _____6_____  |
| 2  |                               |     |   |              |
| 3  |                               |     |   |              |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | _____6_____  |
| 5  |                               |     |   |              |
| 6  |                               |     |   |              |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | _____9_____  |
| 8  |                               |     |   |              |
| 9  |                               |     |   |              |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | _____11_____ |
| 11 |                               |     |   |              |
| 12 |                               |     |   |              |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | _____9_____  |
| 14 |                               |     |   |              |
| 15 |                               |     |   |              |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | _____9_____  |
| 17 |                               |     |   |              |
| 18 |                               |     |   |              |
| 19 |                               |     |   |              |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____2_____  |
| 21 |                               |     |   |              |
| 22 |                               |     |   |              |
| 23 |                               |     |   |              |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | _____2_____  |
| 25 |                               |     |   |              |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | _____2_____  |
| 27 |                               |     |   |              |
| 28 |                               |     |   |              |
| 29 | <b>Appendices</b>             |     |   |              |
| 30 |                               |     |   |              |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | _____NA_____ |
| 32 |                               |     |   |              |
| 33 |                               |     |   |              |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | _____NA_____ |
| 35 |                               |     |   |              |
| 36 |                               |     |   |              |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

# BMJ Open

## Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2019-030694.R2   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 26-Feb-2020  |
| Complete List of Authors:       | <p>Wang, Jian; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine</p> <p>Li, Dongli; Wenzhou Medical University, the sixth Affiliated Hospital, Anesthesiology</p> <p>Tang, Wei; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Guo, Jun; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Chen, Wenting; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Yong, Yue; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Song, Wei; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine</p> <p>Yu, Guijie; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Feng, Rui; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Yuan, Lan; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Fu, Guoqiang; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Song, Jiangang; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Anesthesiology</p> <p>Fan, Lihua; Wenzhou Medical University, the sixth Affiliated Hospital, Anesthesiology</p> |
| <b>Primary Subject Heading</b>: | Complementary medicine   |
| Secondary Subject Heading:      | Anaesthesia, Gastroenterology and hepatology, Surgery  |
| Keywords:                       | Transcutaneous electrical acupoint stimulation (TEAS), postoperative ileus (POI), Pretreatment   |
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4 1 **Pretreatment with transcutaneous electrical acupoint stimulation to prevent**  
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6 2 **postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for**  
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8 3 **a randomized controlled trial**  
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4 22 **Abstract**

5 23 **Introduction:** Postoperative ileus (POI), a common complication after surgery, severely affects  
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8 24 postoperative recovery. It is unclear whether pretreatment with transcutaneous electrical  
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10 25 acupoint stimulation (TEAS) can improve recovery from POI. This trial will evaluate the effects  
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12 26 of pretreatment with TEAS on POI.

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14 27 **Methods and analysis:** This will be a prospective, randomized, controlled trial. ASA I–III  
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16 28 level patients, aged 18–75 years and scheduled for laparoscopic colon surgery, will be included  
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18 29 in the study. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS  
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20 30 (STEAS) groups. The groups will undergo two sessions of TEAS/STEAS daily for three days  
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22 31 before surgery, with a final TEAS/STEAS treatment 30 minutes before anesthesia. The primary  
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24 32 endpoint of the study will be time to first defecation. Secondary endpoints will include time to  
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26 33 first flatus, time to tolerance of oral diet, GI-2 (composite outcome of time to first defecation  
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28 34 and time to tolerance of oral diet), time to independent walking , length of hospital stay,  
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30 35 postoperative pain VAS score on the first three days after surgery, analgesic requirements,  
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32 36 complications, and plasma concentrations of IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ . Multiple linear  
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34 37 regression will be used to identify independent predictors of outcome measures.

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36 38 **Ethics and dissemination:** This study has been approved by the Chinese Registered Clinical  
37  
38 39 Trial Ethics Review Committee (NO.ChiECRCT-20170084). The results of the trial will be  
39  
40 40 published in an international peer-reviewed journal.

41 41 **Trial registration:** This study has been registered with the Chinese Clinical Trial Registry (NO.  
42  
43 42 ChiCTR-INR-17013184).

44 43 **Trial status:** The study was in the recruitment phase at the time of manuscript submission.

45 44 **Abbreviations:** POI = postoperative ileus, TCM = traditional Chinese medicine, EA = electro-  
46  
47 45 acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index,  
48  
49 46 PACU = post anesthesia care unit, ERAS= enhanced recovery after surgery.

50  
51 47 **Key words:** transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI);  
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53 48 pretreatment.  
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4 49 Strengths and limitations of the study

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7 51 ➤ This study aims to evaluate whether pretreatment with transcutaneous electrical  
8 52 acupoint stimulation (TEAS) can prevent postoperative ileus (POI).

9 53 ➤ TEAS is a safe, noninvasive and easily accepted adjunctive intervention.

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11 54 ➤ This study will provide deeper insights into the mechanism by which TEAS  
12 55 pretreatment reduces the inflammatory response.

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14 56 ➤ This is a single-center study, which is a potential limitation.  
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## 57 Introduction

58 Postoperative ileus (POI) is a transient dysfunction of gastrointestinal propulsion that often  
59 occurs after abdominal surgery and may also occur following surgery at other sites<sup>1</sup>. The main  
60 symptoms of POI include abdominal pain and distention, nausea, vomiting, difficult defecation  
61 and intolerance to solid food. POI is usually temporary, but if prolonged, may lead to surgical  
62 incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection, intestinal  
63 ischemia, aspiration pneumonia and other serious complications<sup>2-4</sup>. A retrospective cohort study  
64 involving nearly 500 hospitals in the United States showed that POI is a key reason for  
65 prolonged hospitalization and increased medical costs for patients undergoing abdominal  
66 surgery<sup>1</sup>. The United States spends more than \$1.46 billion treating POI every year<sup>5</sup>. At present,  
67 the most common methods used to treat POI include: rational perioperative use of narcotic  
68 drugs and opioids, eating as soon as possible after surgery, avoidance of nasogastric tubes after  
69 the operation, early ambulation, postoperative epidural analgesia, restriction of fluid intake, the  
70 use of minimally invasive surgery (such as laparoscopic), drug therapy and the use of chewing  
71 gum. Despite the numerous treatment strategies, POI remains a difficult clinical challenge that  
72 compromises the rapid recovery of postoperative patients. It is, therefore, necessary to find  
73 more effective, convenient and economical treatment methods<sup>6-10</sup>.

74 The main mechanism underlying POI may be activation of macrophages in the external  
75 muscular layer during the surgical procedure<sup>11</sup>. Intestinal manipulation during surgery can  
76 activate macrophages in the outer muscle layer of the small intestine, leading to release of  
77 inflammatory factors (IL-6, IL-1 $\beta$ ) and the chemokine MIP-1 $\alpha$ , together with increased  
78 expression of the adhesion molecule ICAM-1 on endothelial cells and induction of neutrophils  
79 and monocytes in the circulation into the small intestine muscle layer. These cells, and activated  
80 macrophages, can release a large amount of inducible nitric oxide synthase (iNOS) and  
81 prostaglandin, which inhibit the movement and contraction of the gastrointestinal tract<sup>12,13</sup>.  
82 Transport of these inflammatory mediators in the blood stream causes activation of  
83 macrophages in the distal gastrointestinal tract, leading to postoperative ileus over the entire

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4 84 intestinal tract<sup>14</sup>. It has been confirmed by a large number of animal experiments that reducing  
5 85 the inflammatory response is an effective way to treat POI<sup>15-17</sup>.

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7 86 There is a long history in traditional Chinese medicine (TCM) of using acupuncture to treat  
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9 87 functional gastrointestinal diseases and, in recent years, there has been significant global  
10 88 interest in the beneficial effects of acupuncture on POI. The positive effect of  
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12 89 electroacupuncture (EA) on POI has been clearly demonstrated. Ng *et al.* used EA to treat POI  
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14 90 in patients undergoing laparoscopic colon surgery<sup>18</sup>. Defecation time and length of hospital stay  
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16 91 were significantly shortened in patients who received EA compared with those who did not  
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18 92 receive the treatment. In patients undergoing hepatic resection, You *et al.* found a significant  
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20 93 reduction in the incidence of POI in patients treated with a combination of acupuncture and  
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22 94 Chinese herbal medicine. The length of hospitalization was also significantly shortened in the  
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24 95 treated group ( $14.0 \pm 4.9$  d vs  $16.5 \pm 6.8$  d,  $P = 0.014$ )<sup>19</sup>.

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27 96 In previous studies, we proved that pretreatment with acupuncture could reduce excessive  
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29 97 activation of the innate immune system and inhibit the inflammatory response. This effect may  
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31 98 be achieved by activation of the vagal nervous system<sup>20,21</sup>. Other studies have shown that  
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33 99 transcutaneous electrical acupoint stimulation (TEAS) and EA have similar effects in the  
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35 100 treatment of pain and alleviating the inflammatory response<sup>22,23</sup>.

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38 101 Traditional Chinese medicine holds that the best treatment for disease is prevention. Based on  
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40 102 all of the above studies, we hypothesize that the use of TEAS as a preoperative treatment may  
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42 103 reduce the incidence of POI. There have, so far, not been any studies that address this question.  
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44 104 We have, therefore, designed a randomized, controlled trial to investigate whether pretreatment  
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46 105 with TEAS can reduce the incidence of POI in patients undergoing laparoscopic colon resection.  
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48 106 The study is also designed to verify that the anti-inflammatory effect is associated with the  
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50 107 immunomodulatory function of TEAS.

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## 53 54 109 **Methods and analysis**

### 55 56 110 ***Study objective***

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4 111 The primary objective is to assess the effect of TEAS on clinical recovery of bowel function  
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6 112 after laparoscopic colon surgery. The secondary objective is to verify that suppression of  
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8 113 overactivation of the innate immune system and reduction of the inflammatory response are the  
9  
10 114 mechanisms underlying the ability of pretreatment of percutaneous acupuncture to prevent POI.

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12 115 ***Study location***

13  
14 116 A prospective, single-center, double-blinded, randomized, controlled trial will be conducted at  
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16 117 Shuguang Hospital, which is affiliated to the Shanghai University of Traditional Chinese  
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18 118 Medicine, China.

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20 119 ***Study population***

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22 120 Participants will be recruited according to the inclusion and exclusion criteria.

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24 121 **Inclusion criteria**

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26 122 1. Male and female patients aged 18–75 years  
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28 123 2. Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such  
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30 124 as left colectomy, right colectomy, and anterior resection of the upper part of the rectum  
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32 125 and lower part of the sigmoid)  
33  
34 126 3. Body mass index (BMI) 18–31 kg/m<sup>2</sup>  
35  
36 127 4. ASA classification I–III  
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38 128 5. Patients provide signed informed consent

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40 129 **Exclusion criteria**

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42 130 1. Middle and lower rectal resection, total/proctocolectomy or the need for complex  
43  
44 131 endoscopic surgery  
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46 132 2. Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation  
47  
48 133 3. History of abdominal/pelvic operations or complications  
49  
50 134 4. Patients receiving epidural anesthesia or epidural analgesia  
51  
52 135 5. Patients with skin infections, surgical incision or scar at the point of application of  
53  
54 136 acupuncture  
55  
56 137 6. Patients have a history of limb surgery, spinal surgery or nerve injury  
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4 138 7. Patients who participated in other clinical trials, or received other acupuncture therapy, in  
5  
6 139 the previous four weeks  
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8 140 8. Patients with cardiac pacemakers  
9  
10 141 9. Patients have one of the following conditions before surgery: chronic pain, drug  
11  
12 142 addiction or alcohol dependence  
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14 143 10. Patients with preoperative combination of severe central nervous system disease and  
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16 144 severe mental illness

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18 145 **Endpoints**

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20 146 **Primary endpoint**

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22 147 First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.

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24 148 **Secondary endpoints**

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26 149 Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time  
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28 150 to first defecation and time to tolerance of oral diet), time to walk independently (h), length of  
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30 151 hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital  
31  
32 152 discharge include stability of vital signs with no fever, achievement of flatus or defecation,  
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34 153 ability to tolerate solid food without vomiting, control of postoperative pain, absence of other  
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36 154 postoperative complications and ability to function at home independently or with home care  
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38 155 provided. Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1,  
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40 156 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the  
41  
42 157 worst pain intensity). Postoperative requirements for analgesia will also be assessed.  
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44 158 Inflammatory mediators (IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ ) in blood will be measured before  
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46 159 TEAS/STEAS intervention and on days 1, 3 and 5 after the operation. Postoperative  
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48 160 complications will be recorded using the Clavien - Dindo classification for complication  
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50 161 assessment<sup>24</sup>. The follow-up period will be at least 6 months.

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52 162 **Randomization and blinding**

53  
54 163 Patients will be randomized to receive either TEAS or STEAS by stratified randomization  
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56 164 according to sex, in a 1:1 ratio (Figure 1). Using a computer-generated random sequence, a  
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58 165 sealed envelope will be opened to determine to which group the patient has been assigned. The  
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4 166 acupuncturist will be aware of the treatment group. Patients as well as the outcome investigator  
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6 167 (nurse anesthetist) , will be blinded to the treatment allocation.  
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#### 8 168 ***Current sample size justification***

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10 169 According to Wang Jian and Song Jiangan's preliminary study of transcutaneous electrical  
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12 170 acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing  
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14 171 laparoscopic colon surgery in Shuguang Hospital, the mean time to first defecation following  
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16 172 laparoscopic colon surgery was  $62 \pm 19$  h ( $M \pm SD$ ). Working on the assumption that a clinically  
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18 173 meaningful difference in mean time to first defecation between the TEAS and STEAS groups  
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20 174 is 1 day or 24 h, 66 patients would be needed in each group to reach a power of 80% and a 5%  
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22 175 Type I error rate. If the drop-out rate is 10%, a total sample size of 146 patients for the two  
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24 176 groups is needed for this study.  
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#### 26 177 ***Statistical analysis***

27  
28 178 Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance  
29  
30 179 of oral diet, time to walking independently, length of hospital stay) will be reported using the  
31  
32 180 mean and standard deviation ( $M \pm SD$ ) for normally distributed data or median (range) for  
33  
34 181 skewed data. Data for categorical variables will be expressed as a number (percentage).  
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36 182 Intergroup differences will be assessed using the Student's t-test or Mann-Whitney U test.  
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38 183 Intergroup differences in inflammatory mediators (at time points of pre-TEAS/STEAS  
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40 184 treatment, and on post-operative days 1, 3, and 5) were assessed by two-way repeated measures  
41  
42 185 analysis of variance with Bonferroni post hoc test. The significance level will be set at 5%. All  
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44 186 data will be analyzed using SPSS 17.0 software or other appropriate statistical software  
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46 187 packages.  
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#### 48 188 ***Pretreatment***

49  
50 189 Patients randomized to the TEAS and STEAS groups will undergo two treatment sessions daily  
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52 190 for three consecutive days before surgery. The patients will then be treated for a final time 30  
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54 191 minutes before anesthesia.  
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56 192 For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and  
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58 193 Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes  
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4 194 (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists  
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6 195 carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint  
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8 196 nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China),  
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10 197 at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight  
11  
12 198 twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness,  
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14 199 distention and heaviness. The STEAS group will receive a strong, but comfortable current for  
15  
16 200 30 s, and the current will then gradually vanish over the next 15 s<sup>25</sup>. The participants of both  
17  
18 201 groups will be told that they are receiving current stimulation. Each session of acupoints  
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20 202 treatment will last for 30 min. During the application of TEAS, patients will be required not to  
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22 203 change the current settings themselves. A prompt beep at the end of TEAS will indicate the end  
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24 204 of treatment.

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26 205 All surgery will be carried out under general anesthesia, using standardized anesthetic  
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28 206 procedures. Patients will be fasted for 12 h before surgery. Right upper extremity venous access  
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30 207 will be established before the patients entering the operating theater. Ringer's lactate solution  
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32 208 (8 mL/kg) will be administered by intravenous infusion for compensatory expansion before  
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34 209 induction of anesthesia. Patients will then receive midazolam (0.04 mg/kg), fentanyl (3 µg/kg),  
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36 210 vecuronium bromide (0.1 mg/kg) and propofol (1.5–2.0 mg/kg) intravenously for induction of  
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38 211 anesthesia. Anesthesia will be maintained using a CP-600 anesthesia delivery system (Slgo  
39  
40 212 Medical Technology Co., Ltd., Beijing, China). The dose of propofol will be adjusted to  
41  
42 213 maintain the bispectral index (BIS) in the range 40–60. After surgery, all patients will remain  
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44 214 in the post anesthesia care unit and then return to the ward for recovery until discharge.

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46 215 The perioperative management of all patients will be standardized. Early ambulation will be  
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48 216 encouraged and oral feeding will be resumed as early as possible. All patients will be followed-  
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50 217 up for at least 6 months after discharge from the hospital.

#### 51 52 218 *Adverse events*

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54 219 All adverse reactions will be closely monitored through spontaneous reports by patients or  
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56 220 direct observation by clinicians, or by asking the patients about adverse events using open  
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221 questions. All adverse reactions will be recorded and appropriate treatment will be provided if  
222 necessary. Serious adverse events will be reported to the ethics committee.

### 223 ***Data collection and management***

224 Demographic variables and clinical data will be collected from all patients. During the study,  
225 blood pressure, heart rate and oxygen saturation will also be monitored. Any adverse events  
226 will be recorded. Data will be collected throughout the study and will be securely managed  
227 under conditions of confidentiality. Data collection will be performed by a nurse anesthetist.  
228 The participants will be referred to by their participant number rather than by their name  
229 throughout the study, unless otherwise specified. All relevant documents and files will be  
230 archived for 5 years. The data will be accessible only by investigators who sign the confidential  
231 disclosure agreement and by institutional or governmental auditors during the study. Data  
232 without patient identifiers will be publicly accessible after the study. Data collection and  
233 management will be monitored by the Institutional Ethics Committee for Clinical Research of  
234 Shuguang Hospital.

### 235 ***Patient and public involvement***

236 This study is currently in the recruitment phase. The participants will be able to access the study  
237 results through social media.

### 238 **Discussion**

239 POI continues to represent an important cause of morbidity following colon surgery. The  
240 prevention of POI is thus of great importance in reducing perioperative complications and  
241 reducing hospitalization costs. Although it has been shown that EA can shorten the duration of  
242 POI<sup>18</sup>, the effectiveness of TEAS, which is a similar technique, in preventing POI has not been  
243 investigated. It is, therefore, important to assess the effectiveness of TEAS in preventing POI  
244 through a clinical study.

245 This study has several strengths. Firstly, the intervention strategy of the protocol will be  
246 pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic  
247 effect. For example, pretreatment with TEAS has been shown to improve pain treatment<sup>26,27</sup>  
248 and to improve resuscitation after anesthesia, with reduction of postoperative nausea and

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4 249 vomiting<sup>28</sup>. It is, however, unclear whether preoperative TEAS can prevent POI. Studies  
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6 250 suggest that early preoperative intervention may be more beneficial in regulating physiological  
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8 251 functions and preventing POI<sup>29</sup>. In an extension to these findings, the present study will help to  
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10 252 determine whether TEAS pretreatment could improve POI.

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12 253 Secondly, the effectiveness of TEAS will be evaluated by assessing clinical function and by  
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14 254 serological examination. In this randomized controlled trial of patients undergoing laparoscopic  
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16 255 colorectal surgery, our aim is to assess the effects of preoperative TEAS on POI using relevant  
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18 256 clinical parameters associated with bowel function. These include time to first defecation, time  
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20 257 to first flatus, time to tolerance of oral diet and GI-2. Importantly, we will also measure serum  
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22 258 concentrations of inflammatory mediators associated with POI, such as IFN- $\beta$ , IFN- $\gamma$ , IL-6 and  
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24 259 IL-1 $\beta$ . Our findings may, thus, provide deeper insights into the mechanisms by which TEAS  
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26 260 improves POI.

27  
28 261 There are also limitations to this protocol. Various clinical indicators have been used in studies  
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30 262 for the diagnosis of POI, but there is no consensus on which clinical parameter is the best for  
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32 263 assessment of gastrointestinal (GI) transit<sup>9,30,31</sup>. Two indicators that are widely used to assess  
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34 264 bowel movement will be used in this study. Time to first defecation will be the primary outcome  
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36 265 and time to first flatus will be one of the secondary outcomes. There is a possibility that we  
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38 266 may observe conflicting results (i.e., significant improvement in time to flatus, but not  
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40 267 defecation). Because flatus can vary considerably between patients, clinical trials support the  
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42 268 time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to  
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44 269 first tolerance of solid food and time to first bowel movement) as supplementary  
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46 270 secondary outcomes to measure the recovery time of GI function and these will be used in this  
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48 271 study<sup>32,33</sup>. Other limitations of these indicators are that they require objective measurement of  
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50 272 motility and are time consuming to measure<sup>34,35</sup>. Recently, this situation has been improved by  
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52 273 the use of in vivo monitoring techniques to assess the function of gastrointestinal movements.  
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54 274 Innovative devices, such as Sitz markers, have been used to evaluate postoperative recovery of  
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56 275 small bowel movement by counting the number of Sitz markers that did not pass through the  
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58 276 ileocecal valve, but remained in the small intestine using radiography<sup>36</sup>. The SmartPill is a  
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4 277 swallowable device that record parameters within the GI tract. Indicators, such as pH,  
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6 278 temperature and intracavitary pressure, can be collected to analyze gastrointestinal transit times  
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8 279 in vivo<sup>37</sup>. These devices acquire objective parameters to evaluate bowel movement and could  
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10 280 save time. Research into the satisfaction of both doctors and patients with these device needs  
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12 281 to be carried out. Furthermore, this study is a single-center trial and, because the therapeutic  
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14 282 effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-  
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16 283 center and large sample studies in the future.

17  
18 284 Notwithstanding its limitations, this study can clearly indicate the overall effects of TEAS on  
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20 285 postoperative recovery. We hypothesize that pretreatment with TEAS could improve recovery  
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22 286 of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides  
23  
24 287 positive results, it will be possible to recommend this pretreatment strategy for patients  
25  
26 288 undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of  
27  
28 289 consideration.

#### 30 ***Acknowledgements***

31  
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33  
34 292 statistical design of this study.

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41  
42 296 of SINCH Pharmaceuticals Tech. Co., Ltd.

#### 44 ***Availability of data and materials***

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47 298 The dataset to be generated during the study will be available from the corresponding author  
48  
49 299 on reasonable request via email.

#### 50 ***Author contributions***

51  
52 301 Jian Wang conceived the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated  
53  
54 302 in its design and coordination. Wen-ting Chen, Yue Yong, Wei Song and Jun Guo collected  
55  
56 303 references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistical  
57  
58 304 analyses. Rui Feng will follow-up with patients and record data. Jian Wang, Li-hua Fan and  
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305 Jian-gang Song drafted the manuscript. All authors have read and approved the final manuscript.

306 ***Competing interests***

307 None declared.

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## 458 **Figure Legend**

459 Figure 1. Flow chart of the study protocol

460 Figure 2. Acupoints selected in this trial (a) Hegu (IL-4) and Neiguan (P-6); (b) Zusanli (ST-  
461 36) and Shangjuxu (ST-37); (c) Han's acupoint nerve stimulator



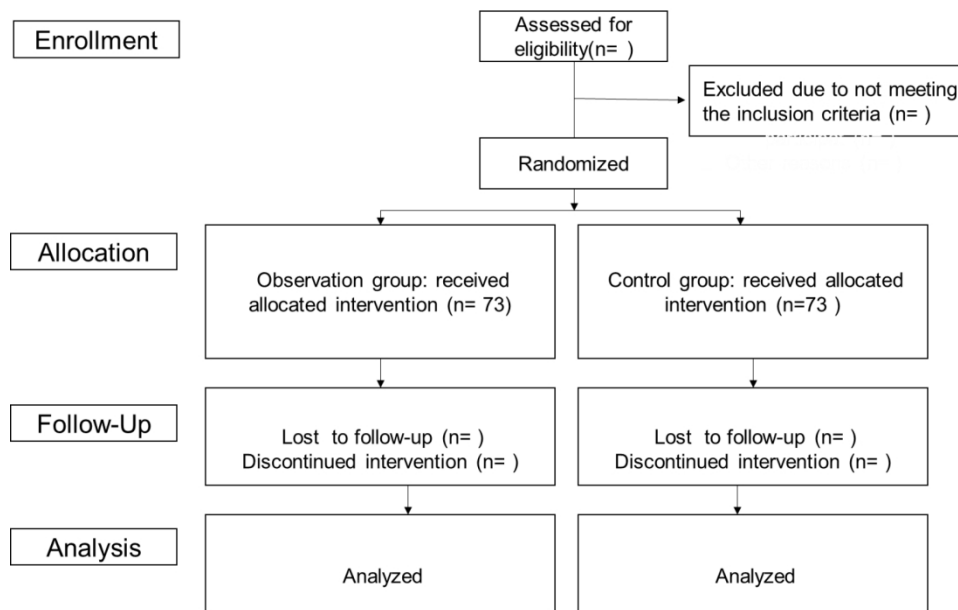


Figure 1. Flow chart of the study

177x109mm (300 x 300 DPI)

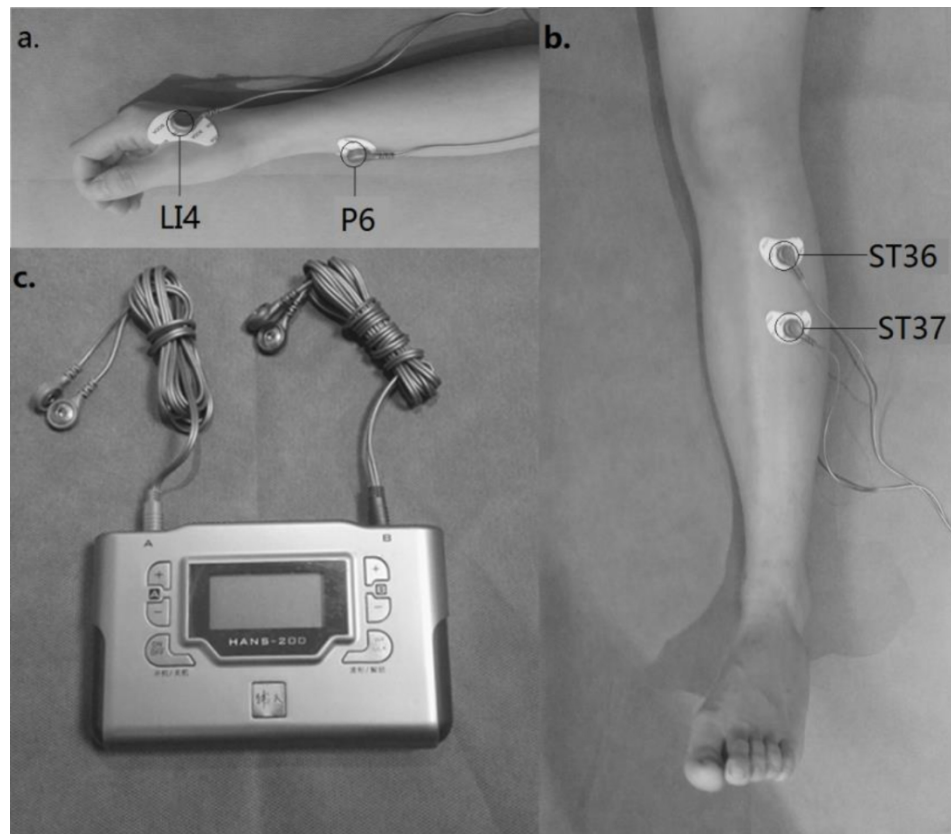


Figure 2. Acupoints selected in this trial. (a) shows Hegu (LI-4), Neiguan (P-6). (b) shows Zusanli (ST-36), Shangjuxu (ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)



SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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   | _____ 2 _____            |
| Protocol version                  | 3       | Date and version identifier  | _____ 2 _____            |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____ 11 _____           |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____ 1&11 _____         |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____ 11 _____           |
|                                   | 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 | _____ 11 _____           |
|                                   | 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)                         | _____ 9 _____            |

|    |   |     |   |               |
|----|---|-----|---|---------------|
| 1  | <b>Introduction</b>                                       |     |   |               |
| 2  |   |     |   |               |
| 3  | Background and  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant   | _____4&5_____ |
| 4  | rationale   |     | studies (published and unpublished) examining benefits and harms for each intervention                        |               |
| 5  |   |     |   |               |
| 6  |   | 6b  | Explanation for choice of comparators   | _____         |
| 7  |   |     |   |               |
| 8  | Objectives  | 7   | Specific objectives or hypotheses   | _____5_____   |
| 9  |   |     |   |               |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), | _____5_____   |
| 11 |   |     | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   |               |
| 12 |   |     |   |               |
| 13 |   |     |   |               |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |   |               |
| 15 |   |     |   |               |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will | _____6_____   |
| 17 |   |     | be collected. Reference to where list of study sites can be obtained  |               |
| 18 |   |     |   |               |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  | _____6_____   |
| 20 |   |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |               |
| 21 |   |     |   |               |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be | _____8&9_____ |
| 23 |   |     | administered  |               |
| 24 |   |     |   |               |
| 25 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  | _____         |
| 26 |   |     | change in response to harms, participant request, or improving/worsening disease)                             |               |
| 27 |   |     |   |               |
| 28 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        | _____         |
| 29 |   |     | (eg, drug tablet return, laboratory tests)  |               |
| 30 |   |     |   |               |
| 31 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 | _____         |
| 32 |   |     |   |               |
| 33 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       | _____7_____   |
| 34 |   |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, |               |
| 35 |   |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |               |
| 36 |   |     | efficacy and harm outcomes is strongly recommended  |               |
| 37 |   |     |   |               |
| 38 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   | _____7_____   |
| 39 |   |     | participants. A schematic diagram is highly recommended (see Figure)  |               |
| 40 |   |     |   |               |
| 41 |   |     |   |               |
| 42 |   |     |   |               |
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|   |             |    |   |             |
|---|-------------|----|---|-------------|
| 1 | 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 | _____8_____ |
| 2 |             |    |   |             |
| 3 |             |    |   |             |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | _____8_____ |
| 5 |             |    |   |             |

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

|    |                                  |     |  |             |
|----|----------------------------------|-----|--|-------------|
| 8  |                                  |     |  |             |
| 9  |                                  |     |  |             |
| 10 | 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_____ |
| 11 |                                  |     |  |             |
| 12 |                                  |     |  |             |
| 13 |                                  |     |  |             |
| 14 |                                  |     |  |             |
| 15 |                                  |     |  |             |
| 16 | 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_____ |
| 17 |                                  |     |  |             |
| 18 |                                  |     |  |             |
| 19 |                                  |     |  |             |
| 20 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | _____7_____ |
| 21 |                                  |     |  |             |
| 22 |                                  |     |  |             |
| 23 |                                  |     |  |             |
| 24 | Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | _____7_____ |
| 25 |                                  |     |  |             |
| 26 |                                  |     |  |             |
| 27 |                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | _____7_____ |
| 28 |                                  |     |  |             |
| 29 |                                  |     |  |             |
| 30 |                                  |     |  |             |

### 31 **Methods: Data collection, management, and analysis**

|    |                         |     |  |             |
|----|-------------------------|-----|--|-------------|
| 32 |                         |     |  |             |
| 33 | 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_____ |
| 34 |                         |     |  |             |
| 35 |                         |     |  |             |
| 36 |                         |     |  |             |
| 37 |                         |     |  |             |
| 38 |                         |     |  |             |
| 39 |                         | 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  | _____9_____ |
| 40 |                         |     |  |             |
| 41 |                         |     |  |             |
| 42 |                         |     |  |             |

|    |                                 |     |   |    |
|----|---------------------------------|-----|---|----|
| 1  | 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   | 9  |
| 2  |                                 |     |   |    |
| 3  |                                 |     |   |    |
| 4  |                                 |     |   |    |
| 5  | 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  | 8  |
| 6  |                                 |     |   |    |
| 7  |                                 |     |   |    |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8  |
| 9  |                                 |     |   |    |
| 10 |                                 | 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)   | 8  |
| 11 |                                 |     |   |    |
| 12 |                                 |     |   |    |
| 13 |                                 |     |   |    |
| 14 | <b>Methods: Monitoring</b>      |     |   |    |
| 15 |                                 |     |   |    |
| 16 | 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 | 9  |
| 17 |                                 |     |   |    |
| 18 |                                 |     |   |    |
| 19 |                                 |     |   |    |
| 20 |                                 |     |   |    |
| 21 |                                 |     |   |    |
| 22 |                                 | 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   | 9  |
| 23 |                                 |     |   |    |
| 24 |                                 |     |   |    |
| 25 | 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   | 9  |
| 26 |                                 |     |   |    |
| 27 |                                 |     |   |    |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 10 |
| 29 |                                 |     |   |    |
| 30 |                                 |     |   |    |
| 31 |                                 |     |   |    |
| 32 | <b>Ethics and dissemination</b> |     |   |    |
| 33 |                                 |     |   |    |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 2  |
| 35 |                                 |     |   |    |
| 36 |                                 |     |   |    |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | 10 |
| 38 |                                 |     |   |    |
| 39 |                                 |     |   |    |
| 40 |                                 |     |   |    |
| 41 |                                 |     |   |    |
| 42 |                                 |     |   |    |
| 43 |                                 |     |   |    |
| 44 |                                 |     |   |    |
| 45 |                                 |     |   |    |
| 46 |                                 |     |   |    |

|    |                               |     |   |              |
|----|-------------------------------|-----|---|--------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | _____6_____  |
| 2  |                               |     |   |              |
| 3  |                               |     |   |              |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | _____6_____  |
| 5  |                               |     |   |              |
| 6  |                               |     |   |              |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | _____9_____  |
| 8  |                               |     |   |              |
| 9  |                               |     |   |              |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | _____11_____ |
| 11 |                               |     |   |              |
| 12 |                               |     |   |              |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | _____9_____  |
| 14 |                               |     |   |              |
| 15 |                               |     |   |              |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | _____9_____  |
| 17 |                               |     |   |              |
| 18 |                               |     |   |              |
| 19 |                               |     |   |              |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____2_____  |
| 21 |                               |     |   |              |
| 22 |                               |     |   |              |
| 23 |                               |     |   |              |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | _____2_____  |
| 25 |                               |     |   |              |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | _____2_____  |
| 27 |                               |     |   |              |
| 28 |                               |     |   |              |
| 29 | <b>Appendices</b>             |     |   |              |
| 30 |                               |     |   |              |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | _____NA_____ |
| 32 |                               |     |   |              |
| 33 |                               |     |   |              |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | _____NA_____ |
| 35 |                               |     |   |              |
| 36 |                               |     |   |              |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

# BMJ Open

## Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2019-030694.R3   |
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4 1 **Pretreatment with transcutaneous electrical acupoint stimulation to prevent**  
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6 2 **postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for**  
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8 3 **a randomized controlled trial**  
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4 22 **Abstract**

5 23 **Introduction:** Postoperative ileus (POI), a common complication after surgery, severely affects  
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8 24 postoperative recovery. It is unclear whether pretreatment with transcutaneous electrical  
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10 25 acupoint stimulation (TEAS) can improve recovery from POI. This trial will evaluate the effects  
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12 26 of pretreatment with TEAS on POI.

13  
14 27 **Methods and analysis:** This will be a prospective, randomized, controlled trial. ASA I–III  
15  
16 28 level patients, aged 18–75 years and scheduled for laparoscopic colon surgery, will be included  
17  
18 29 in the study. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS  
19  
20 30 (STEAS) groups. The groups will undergo two sessions of TEAS/STEAS daily for three days  
21  
22 31 before surgery, with a final TEAS/STEAS treatment 30 minutes before anesthesia. The primary  
23  
24 32 endpoint of the study will be time to first defecation. Secondary endpoints will include time to  
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26 33 first flatus, time to tolerance of oral diet, GI-2 (composite outcome of time to first defecation  
27  
28 34 and time to tolerance of oral diet), time to independent walking , length of hospital stay,  
29  
30 35 postoperative pain VAS score on the first three days after surgery, analgesic requirements,  
31  
32 36 complications, and plasma concentrations of IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ . Multiple linear  
33  
34 37 regression will be used to identify independent predictors of outcome measures.

35  
36 38 **Ethics and dissemination:** This study has been approved by the Chinese Registered Clinical  
37  
38 39 Trial Ethics Review Committee (NO.ChiECRCT-20170084). The results of the trial will be  
39  
40 40 published in an international peer-reviewed journal.

41 41 **Trial registration:** This study has been registered with the Chinese Clinical Trial Registry (NO.  
42  
43 42 ChiCTR-INR-17013184).

44 43 **Trial status:** The study was in the recruitment phase at the time of manuscript submission.

45 44 **Abbreviations:** POI = postoperative ileus, TCM = traditional Chinese medicine, EA = electro-  
46  
47 45 acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index,  
48  
49 46 PACU = post anesthesia care unit, ERAS= enhanced recovery after surgery.

50  
51 47 **Key words:** transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI);  
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53 48 pretreatment.  
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4 49 Strengths and limitations of the study  
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- 7 51 ➤ This study aims to evaluate whether pretreatment with transcutaneous electrical  
8 52 acupoint stimulation (TEAS) can prevent postoperative ileus (POI).  
9 53 ➤ TEAS is a safe, noninvasive and easily accepted adjunctive intervention.  
10 54 ➤ This study will provide deeper insights into the mechanism by which TEAS  
11 55 pretreatment reduces the inflammatory response.  
12 56 ➤ This is a single-center study, which is a potential limitation.  
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For peer review only

## 57 **Introduction**

58 Postoperative ileus (POI) is a transient dysfunction of gastrointestinal propulsion that often  
59 occurs after abdominal surgery and may also occur following surgery at other sites<sup>1</sup>. The main  
60 symptoms of POI include abdominal pain and distention, nausea, vomiting, difficult defecation  
61 and intolerance to solid food. POI is usually temporary, but if prolonged, may lead to surgical  
62 incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection, intestinal  
63 ischemia, aspiration pneumonia and other serious complications<sup>2-4</sup>. A retrospective cohort study  
64 involving nearly 500 hospitals in the United States showed that POI is a key reason for  
65 prolonged hospitalization and increased medical costs for patients undergoing abdominal  
66 surgery<sup>1</sup>. The United States spends more than \$1.46 billion treating POI every year<sup>5</sup>. At present,  
67 the most common methods used to treat POI include: rational perioperative use of narcotic  
68 drugs and opioids, eating as soon as possible after surgery, avoidance of nasogastric tubes after  
69 the operation, early ambulation, postoperative epidural analgesia, restriction of fluid intake, the  
70 use of minimally invasive surgery (such as laparoscopic), drug therapy and the use of chewing  
71 gum. Despite the numerous treatment strategies, POI remains a difficult clinical challenge that  
72 compromises the rapid recovery of postoperative patients. It is, therefore, necessary to find  
73 more effective, convenient and economical treatment methods<sup>6-10</sup>.

74 The main mechanism underlying POI may be activation of macrophages in the external  
75 muscular layer during the surgical procedure<sup>11</sup>. Intestinal manipulation during surgery can  
76 activate macrophages in the outer muscle layer of the small intestine, leading to release of  
77 inflammatory factors (IL-6, IL-1 $\beta$ ) and the chemokine MIP-1 $\alpha$ , together with increased  
78 expression of the adhesion molecule ICAM-1 on endothelial cells and induction of neutrophils  
79 and monocytes in the circulation into the small intestine muscle layer. These cells, and activated  
80 macrophages, can release a large amount of inducible nitric oxide synthase (iNOS) and  
81 prostaglandin, which inhibit the movement and contraction of the gastrointestinal tract<sup>12,13</sup>.  
82 Transport of these inflammatory mediators in the blood stream causes activation of  
83 macrophages in the distal gastrointestinal tract, leading to postoperative ileus over the entire

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4 84 intestinal tract<sup>14</sup>. It has been confirmed by a large number of animal experiments that reducing  
5 85 the inflammatory response is an effective way to treat POI<sup>15-17</sup>.

6  
7 86 There is a long history in traditional Chinese medicine (TCM) of using acupuncture to treat  
8  
9 87 functional gastrointestinal diseases and, in recent years, there has been significant global  
10 88 interest in the beneficial effects of acupuncture on POI. The positive effect of  
11  
12 89 electroacupuncture (EA) on POI has been clearly demonstrated. Ng *et al.* used EA to treat POI  
13  
14 90 in patients undergoing laparoscopic colon surgery<sup>18</sup>. Defecation time and length of hospital stay  
15  
16 91 were significantly shortened in patients who received EA compared with those who did not  
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18 92 receive the treatment. In patients undergoing hepatic resection, You *et al.* found a significant  
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20 93 reduction in the incidence of POI in patients treated with a combination of acupuncture and  
21  
22 94 Chinese herbal medicine. The length of hospitalization was also significantly shortened in the  
23  
24 95 treated group ( $14.0 \pm 4.9$  d vs  $16.5 \pm 6.8$  d,  $P = 0.014$ )<sup>19</sup>.

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27 96 In previous studies, we proved that pretreatment with acupuncture could reduce excessive  
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29 97 activation of the innate immune system and inhibit the inflammatory response. This effect may  
30  
31 98 be achieved by activation of the vagal nervous system<sup>20,21</sup>. Other studies have shown that  
32  
33 99 transcutaneous electrical acupoint stimulation (TEAS) and EA have similar effects in the  
34  
35 100 treatment of pain and alleviating the inflammatory response<sup>22,23</sup>.

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38 101 Traditional Chinese medicine holds that the best treatment for disease is prevention. Based on  
39  
40 102 all of the above studies, we hypothesize that the use of TEAS as a preoperative treatment may  
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42 103 reduce the incidence of POI. There have, so far, not been any studies that address this question.  
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44 104 We have, therefore, designed a randomized, controlled trial to investigate whether pretreatment  
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46 105 with TEAS can reduce the incidence of POI in patients undergoing laparoscopic colon resection.  
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48 106 The study is also designed to verify that the anti-inflammatory effect is associated with the  
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50 107 immunomodulatory function of TEAS.

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## 53 54 109 **Methods and analysis**

### 55 56 110 ***Study objective***

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4 111 The primary objective is to assess the effect of TEAS on clinical recovery of bowel function  
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6 112 after laparoscopic colon surgery. The secondary objective is to verify that suppression of  
7  
8 113 overactivation of the innate immune system and reduction of the inflammatory response are the  
9  
10 114 mechanisms underlying the ability of pretreatment of percutaneous acupuncture to prevent POI.

11  
12 115 ***Study location***

13  
14 116 A prospective, single-center, double-blinded, randomized, controlled trial will be conducted at  
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16 117 Shuguang Hospital, which is affiliated to the Shanghai University of Traditional Chinese  
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18 118 Medicine, China.

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20 119 ***Study population***

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22 120 Participants will be recruited according to the inclusion and exclusion criteria.

23  
24 121 **Inclusion criteria**

- 25  
26 122 1. Male and female patients aged 18–75 years  
27  
28 123 2. Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such  
29  
30 124 as left colectomy, right colectomy, and anterior resection of the upper part of the rectum  
31  
32 125 and lower part of the sigmoid)  
33  
34 126 3. Body mass index (BMI) 18–31 kg/m<sup>2</sup>  
35  
36 127 4. ASA classification I–III  
37  
38 128 5. Patients provide signed informed consent (the consent form can be viewed in online  
39  
40 129 supplementary appendix 1.)

41  
42 130 **Exclusion criteria**

- 43  
44 131 1. Middle and lower rectal resection, total/proctocolectomy or the need for complex  
45  
46 132 endoscopic surgery  
47  
48 133 2. Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation  
49  
50 134 3. History of abdominal/pelvic operations or complications  
51  
52 135 4. Patients receiving epidural anesthesia or epidural analgesia  
53  
54 136 5. Patients with skin infections, surgical incision or scar at the point of application of  
55  
56 137 acupuncture  
57  
58 138 6. Patients have a history of limb surgery, spinal surgery or nerve injury  
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4 139 7. Patients who participated in other clinical trials, or received other acupuncture therapy, in  
5  
6 140 the previous four weeks  
7  
8 141 8. Patients with cardiac pacemakers  
9  
10 142 9. Patients have one of the following conditions before surgery: chronic pain, drug  
11  
12 143 addiction or alcohol dependence  
13  
14 144 10. Patients with preoperative combination of severe central nervous system disease and  
15  
16 145 severe mental illness

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18 146 **Endpoints**

19  
20 147 **Primary endpoint**

21  
22 148 First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.

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24 149 **Secondary endpoints**

25  
26 150 Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time  
27  
28 151 to first defecation and time to tolerance of oral diet), time to walk independently (h), length of  
29  
30 152 hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital  
31  
32 153 discharge include stability of vital signs with no fever, achievement of flatus or defecation,  
33  
34 154 ability to tolerate solid food without vomiting, control of postoperative pain, absence of other  
35  
36 155 postoperative complications and ability to function at home independently or with home care  
37  
38 156 provided. Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1,  
39  
40 157 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the  
41  
42 158 worst pain intensity). Postoperative requirements for analgesia will also be assessed.  
43  
44 159 Inflammatory mediators (IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ ) in blood will be measured before  
45  
46 160 TEAS/STEAS intervention and on days 1, 3 and 5 after the operation. Postoperative  
47  
48 161 complications will be recorded using the Clavien-Dindo classification for complication  
49  
50 162 assessment<sup>24</sup>. The follow-up period will be at least 6 months.

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52 163 We add GI-2 as a secondary outcome to the original protocol after recruitment of the study had  
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54 164 already begun. GI-2 is a time indicator, which will be calculated from two existing outcomes  
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56 165 (time to first defecation and time to tolerance of oral diet). There will be no harm to subjects,  
57  
58 166 no additional cost and no more work.

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5 168 ***Randomization and blinding***

7 169 Patients will be randomized to receive either TEAS or STEAS by stratified randomization  
8  
9 170 according to sex, in a 1:1 ratio (Figure 1). Using a computer-generated random sequence, a  
10  
11 171 sealed envelope will be opened to determine to which group the patient has been assigned. The  
12  
13 172 acupuncturist will be aware of the treatment group. Patients as well as the outcome investigator  
14  
15 173 (nurse anesthetist) , will be blinded to the treatment allocation.  
16

17  
18 174 ***Current sample size justification***

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20 175 According to Wang Jian and Song Jiangang's preliminary study of transcutaneous electrical  
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22 176 acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing  
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24 177 laparoscopic colon surgery in Shuguang Hospital, the mean time to first defecation following  
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26 178 laparoscopic colon surgery was  $62 \pm 19$  h ( $M \pm SD$ ). Working on the assumption that a clinically  
27  
28 179 meaningful difference in mean time to first defecation between the TEAS and STEAS groups  
29  
30 180 is 1 day or 24 h, 66 patients would be needed in each group to reach a power of 80% and a 5%  
31  
32 181 Type I error rate. If the drop-out rate is 10%, a total sample size of 146 patients for the two  
33  
34 182 groups is needed for this study.  
35

36 183 ***Statistical analysis***

37  
38 184 Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance  
39  
40 185 of oral diet, time to walking independently, length of hospital stay) will be reported using the  
41  
42 186 mean and standard deviation ( $M \pm SD$ ) for normally distributed data or median (range) for  
43  
44 187 skewed data. Data for categorical variables will be expressed as a number (percentage).  
45  
46 188 Intergroup differences will be assessed using the Student's t-test or Mann-Whitney U test.  
47  
48 189 Intergroup differences in inflammatory mediators (at time points of pre-TEAS/STEAS  
49  
50 190 treatment, and on post-operative days 1, 3, and 5) were assessed by two-way repeated measures  
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52 191 analysis of variance with Bonferroni post hoc test. The significance level will be set at 5%. All  
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54 192 data will be analyzed using SPSS 17.0 software or other appropriate statistical software  
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56 193 packages.  
57

58 194 ***Pretreatment***

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4 195 Patients randomized to the TEAS and STEAS groups will undergo two treatment sessions daily  
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6 196 for three consecutive days before surgery. The patients will then be treated for a final time 30  
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8 197 minutes before anesthesia.

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10 198 For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and  
11  
12 199 Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes  
13  
14 200 (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists  
15  
16 201 carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint  
17  
18 202 nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China),  
19  
20 203 at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight  
21  
22 204 twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness,  
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24 205 distention and heaviness. The STEAS group will receive a strong, but comfortable current for  
25  
26 206 30 s, and the current will then gradually vanish over the next 15 s<sup>25</sup>. The participants of both  
27  
28 207 groups will be told that they are receiving current stimulation. Each session of acupoints  
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30 208 treatment will last for 30 min. During the application of TEAS, patients will be required not to  
31  
32 209 change the current settings themselves. A prompt beep at the end of TEAS will indicate the end  
33  
34 210 of treatment.

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36 211 All surgery will be carried out under general anesthesia, using standardized anesthetic  
37  
38 212 procedures. Patients will be fasted for 12 h before surgery. Right upper extremity venous access  
39  
40 213 will be established before the patients entering the operating theater. Ringer's lactate solution  
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42 214 (8 mL/kg) will be administered by intravenous infusion for compensatory expansion before  
43  
44 215 induction of anesthesia. Patients will then receive midazolam (0.04 mg/kg), fentanyl (3 µg/kg),  
45  
46 216 vecuronium bromide (0.1 mg/kg) and propofol (1.5–2.0 mg/kg) intravenously for induction of  
47  
48 217 anesthesia. Anesthesia will be maintained using a CP-600 anesthesia delivery system (Slgo  
49  
50 218 Medical Technology Co., Ltd., Beijing, China). The dose of propofol will be adjusted to  
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52 219 maintain the bispectral index (BIS) in the range 40–60. After surgery, all patients will remain  
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54 220 in the post anesthesia care unit and then return to the ward for recovery until discharge.  
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4 221 The perioperative management of all patients will be standardized. Early ambulation will be  
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6 222 encouraged and oral feeding will be resumed as early as possible. All patients will be followed-  
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8 223 up for at least 6 months after discharge from the hospital.

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10 224 ***Adverse events***

11 225 All adverse reactions will be closely monitored through spontaneous reports by patients or  
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13 226 direct observation by clinicians, or by asking the patients about adverse events using open  
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15 227 questions. All adverse reactions will be recorded and appropriate treatment will be provided if  
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17 228 necessary. Serious adverse events will be reported to the ethics committee.

19  
20 229 ***Data collection and management***

21  
22 230 Demographic variables and clinical data will be collected from all patients. During the study,  
23  
24 231 blood pressure, heart rate and oxygen saturation will also be monitored. Any adverse events  
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26 232 will be recorded. Data will be collected throughout the study and will be securely managed  
27  
28 233 under conditions of confidentiality. Data collection will be performed by a nurse anesthetist.  
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30 234 The participants will be referred to by their participant number rather than by their name  
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32 235 throughout the study, unless otherwise specified. All relevant documents and files will be  
33  
34 236 archived for 5 years. The data will be accessible only by investigators who sign the confidential  
35  
36 237 disclosure agreement and by institutional or governmental auditors during the study. Data  
37  
38 238 without patient identifiers will be publicly accessible after the study. Data collection and  
39  
40 239 management will be monitored by the Institutional Ethics Committee for Clinical Research of  
41  
42 240 Shuguang Hospital.

43  
44 241 ***Patient and public involvement***

45  
46 242 This study is currently in the recruitment phase. Patients and/or public were not involved in  
47  
48 243 study design or conduct of the study. The participants will be able to access the study results  
49  
50 244 through social media.

51  
52 245 ***Discussion***

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54 246 POI continues to represent an important cause of morbidity following colon surgery. The  
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56 247 prevention of POI is thus of great importance in reducing perioperative complications and  
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58 248 reducing hospitalization costs. Although it has been shown that EA can shorten the duration of  
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4 249 POI<sup>18</sup>, the effectiveness of TEAS, which is a similar technique, in preventing POI has not been  
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6 250 investigated. It is, therefore, important to assess the effectiveness of TEAS in preventing POI  
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8 251 through a clinical study.

9  
10 252 This study has several strengths. Firstly, the intervention strategy of the protocol will be  
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12 253 pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic  
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14 254 effect. For example, pretreatment with TEAS has been shown to improve pain treatment<sup>26,27</sup>  
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16 255 and to improve resuscitation after anesthesia, with reduction of postoperative nausea and  
17  
18 256 vomiting<sup>28</sup>. It is, however, unclear whether preoperative TEAS can prevent POI. Studies  
19  
20 257 suggest that early preoperative intervention may be more beneficial in regulating physiological  
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22 258 functions and preventing POI<sup>29</sup>. In an extension to these findings, the present study will help to  
23  
24 259 determine whether TEAS pretreatment could improve POI.

25  
26 260 Secondly, the effectiveness of TEAS will be evaluated by assessing clinical function and by  
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28 261 serological examination. In this randomized controlled trial of patients undergoing laparoscopic  
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30 262 colorectal surgery, our aim is to assess the effects of preoperative TEAS on POI using relevant  
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32 263 clinical parameters associated with bowel function. These include time to first defecation, time  
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34 264 to first flatus, time to tolerance of oral diet and GI-2. Importantly, we will also measure serum  
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36 265 concentrations of inflammatory mediators associated with POI, such as IFN- $\beta$ , IFN- $\gamma$ , IL-6 and  
37  
38 266 IL-1 $\beta$ . Our findings may, thus, provide deeper insights into the mechanisms by which TEAS  
39  
40 267 improves POI.

41  
42 268 There are also limitations to this protocol. Various clinical indicators have been used in studies  
43  
44 269 for the diagnosis of POI, but there is no consensus on which clinical parameter is the best for  
45  
46 270 assessment of gastrointestinal (GI) transit<sup>9,30,31</sup>. Two indicators that are widely used to assess  
47  
48 271 bowel movement will be used in this study. Time to first defecation will be the primary outcome  
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50 272 and time to first flatus will be one of the secondary outcomes. There is a possibility that we  
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52 273 may observe conflicting results (i.e., significant improvement in time to flatus, but not  
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54 274 defecation). Because flatus can vary considerably between patients, clinical trials support the  
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56 275 time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to  
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58 276 first tolerance of solid food and time to first bowel movement) as supplementary

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4 277 secondary outcomes to measure the recovery time of GI function and these will be used in this  
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6 278 study<sup>32,33</sup>. Other limitations of these indicators are that they require objective measurement of  
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8 279 motility and are time consuming to measure<sup>34,35</sup>. Recently, this situation has been improved by  
9  
10 280 the use of in vivo monitoring techniques to assess the function of gastrointestinal movements.  
11  
12 281 Innovative devices, such as Sitz markers, have been used to evaluate postoperative recovery of  
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14 282 small bowel movement by counting the number of Sitz markers that did not pass through the  
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16 283 ileocecal valve, but remained in the small intestine using radiography<sup>36</sup>. The SmartPill is a  
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18 284 swallowable device that record parameters within the GI tract. Indicators, such as pH,  
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20 285 temperature and intracavitary pressure, can be collected to analyze gastrointestinal transit times  
21  
22 286 in vivo<sup>37</sup>. These devices acquire objective parameters to evaluate bowel movement and could  
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24 287 save time. Research into the satisfaction of both doctors and patients with these device needs  
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26 288 to be carried out. Furthermore, this study is a single-center trial and, because the therapeutic  
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28 289 effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-  
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30 290 center and large sample studies in the future.  
31  
32 291 Notwithstanding its limitations, this study can clearly indicate the overall effects of TEAS on  
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34 292 postoperative recovery. We hypothesize that pretreatment with TEAS could improve recovery  
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36 293 of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides  
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38 294 positive results, it will be possible to recommend this pretreatment strategy for patients  
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40 295 undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of  
41  
42 296 consideration.

#### 43 44 297 ***Acknowledgements***

45  
46 298 We thank Dr. Stanley Tao from Shanghai Ruihui Biotech for his valuable assistance in the  
47  
48 299 statistical design of this study.

#### 49 50 300 ***Funding***

51  
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53  
54 302 China (No. 81703898, 81603702, 81603700 and 81774108) and the commercial sponsorship  
55  
56 303 of SINCH Pharmaceuticals Tech. Co., Ltd.

#### 57 58 304 ***Availability of data and materials***

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4 305 The dataset to be generated during the study will be available from the corresponding author  
5  
6 306 on reasonable request via email.

7  
8 307 ***Author contributions***

9  
10 308 Jian Wang conceived the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated  
11  
12 309 in its design and coordination. Wen-ting Chen, Yue Yong, Wei Song and Jun Guo collected  
13  
14 310 references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistical  
15  
16 311 analyses. Rui Feng will follow-up with patients and record data. Jian Wang, Li-hua Fan and  
17  
18 312 Jian-gang Song drafted the manuscript. All authors have read and approved the final manuscript.

19  
20 313 ***Competing interests***

21  
22 314 None declared.  
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#### 465 **Figure Legend**

466 Figure 1. Flow chart of the study protocol

467 Figure 2. Acupoints selected in this trial (a) Hegu (IL-4) and Neiguan (P-6); (b) Zusanli (ST-

468 36) and Shangjuxu (ST-37); (c) Han's acupoint nerve stimulator

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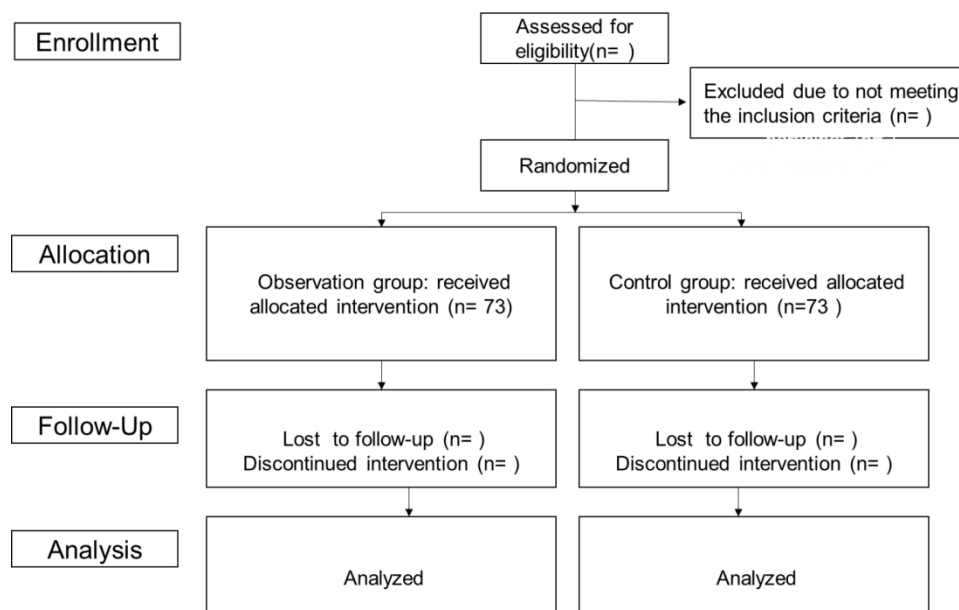


Figure 1. Flow chart of the study

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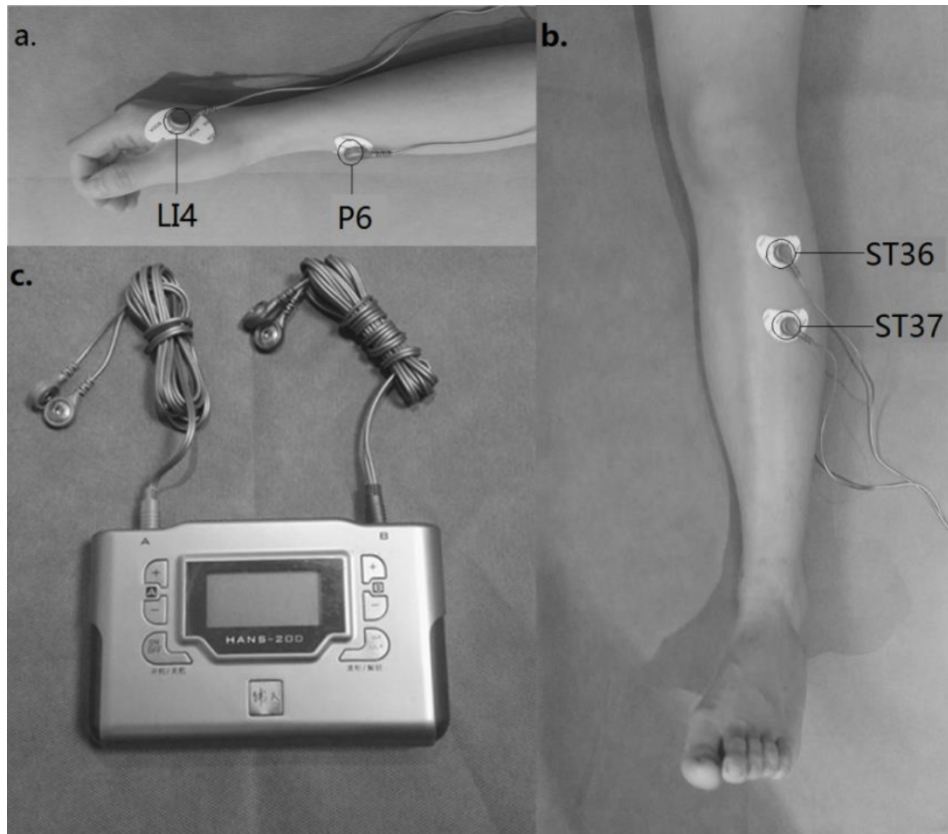


Figure 2. Acupoints selected in this trial. (a) shows Hegu (LI-4), Neiguan (P-6). (b) shows Zusanli (ST-36), Shangjuxu (ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)

## Informed consent • informed consent page

Dear Mr/Miss,

We will invite you to participate in a study, this study is supported by the project of the National Natural Science Foundation of China (No. 81703898, 81603702, 81603700 and 81774108) and the commercial sponsorship of SINCH Pharmaceuticals Tech. Co., Ltd. This study protocol has been reviewed by the Chinese Registered Clinical Trial Ethics Review Committee (NO.ChiECRCT-20170084) and approved for clinical study.

Before you decide whether or not to participate in this study, please read the following as carefully as possible. It will help you understand the study and why it was conducted, the procedures and duration of the study, and the benefits, risks and discomfort that may result from your participation in the study. If you wish, you can also discuss it with your relatives or friends, or ask your doctor for an explanation to help you make a decision.

### **I. Research background and purpose**

#### ***1.1 Disease burden and treatment status***

Postoperative ileus (POI) refers to the stagnation of gastrointestinal propulsion caused by surgical operation after abdominal surgery, which is mainly manifested as abdominal pain, abdominal distension, nausea and vomiting, cessation of exhaust and defecation, and intolerance of solid food.

Postoperative intestinal paralysis is usually temporary, but if the duration of intestinal paralysis is prolonged, it may lead to serious complications such as surgical incision dehiscence, intestinal anastomotic fistula, abdominal infection, intestinal ischemia, and aspiration pneumonia.

A retrospective cohort study of nearly 500 U.S. hospitals showed that postoperative ileus was an important cause of longer hospital stays and higher medical costs for patients undergoing abdominal surgery. The United States spends more than \$1.46 billion annually on treatment for POI. At present, measures used in treating POI mainly include: perioperative rational use of narcotic drugs and opioids, eat early after surgery, avoid to use nasogastric tube after operation, early ambulation, postoperative epidural analgesia, restrict fluid intake, the minimally invasive surgery (such as laparoscopic), drug therapy, chewing gum, etc. However, although there are many treatment measures, they are affected by many factors (such as complicated operation, whether the patient accepts, cost-benefit ratio, surgical conditions, etc.), and the mechanism of POI is complex and far from clear, so the clinical treatment effect is still not ideal.

POI is still a clinical problem that seriously affects patients' postoperative recovery.

Therefore, it is necessary to find more effective, convenient and economical treatment methods.

### ***1.2 purpose of this study***

The purpose of this study is to assess the effect of TEAS on clinical recovery of bowel function after laparoscopic colon surgery and explore the mechanism of TEAS treatment on POI.

## **II. What will be required to participate in the study?**

***1. Before you are enrolled in the study, the doctor will inquire and record your medical history, and perform physical examination, blood routine, urine routine, stool routine, liver function, kidney function and other physical and chemical examinations, as well as 12-lead electrocardiogram.***

You are eligible for inclusion. You may participate in the study voluntarily and sign the informed consent.

If you do not wish to participate in the study, we will treat you as you wish.

***2. If you are willing to participate in the study, you will follow the following steps:***

- **Sign the informed consent**

- **TEAS treatment**

We will provide you with TEAS treatment in 3 consecutive days before surgery, twice a day, each time for 30 minutes, giving another acupoint electrical stimulation treatment for 30 minutes before anesthesia.

- **Clinical test indicators:**

You will need to cooperate to provide the following information, which will be recorded by the researcher

- First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.
- Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to walk independently (h)
- Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1, 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the worst pain intensity).
- Inflammatory mediators (IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-1 $\beta$ ) in blood will be measured before TEAS/STEAS intervention and on days 1, 3 and 5 after the

1  
2  
3 operation.

- 4 ■ Postoperative complications will be recorded, and the follow-up period will be at  
5 least 6 months.  
6  
7

### 8 **3. Clinical safety evaluation:** 9

10 Patients were assessed for clinical safety by spontaneous reporting, direct observation  
11 by clinicians, or by non-inductive questioning about adverse events.  
12  
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#### 14 ● **Quality control during operation and anesthesia:** 15

16 All surgery will be carried out under general anesthesia, using standardized anesthetic  
17 procedures. After surgery, all patients will remain in the post anesthesia care unit and  
18 then return to the ward for recovery until discharge. The perioperative management of  
19 all patients will be standardized.  
20  
21  
22

- #### 23 ● **Postoperative complications will be recorded, and the follow-up period will 24 be at least 6 months.** 25 26

27 Other matters requiring your cooperation

28 You must come to the hospital according to the follow-up time agreed by the doctor  
29 and you (generally medical records, personal treatment diary card, etc.).  
30

31 Your follow-up is important because your doctor will determine whether the treatment  
32 you receive is truly effective and will guide you in a timely manner.  
33  
34

### 35 **III. Potential benefits of participating in the study** 36

37 Although there is evidence that transcutaneous electrical acupoint stimulation has a  
38 satisfactory effect, it is not guaranteed to be effective for you.

39 The percutaneous electrical stimulation of acupoints used in this study is not the only  
40 method for the treatment of postoperative intestinal paralysis.  
41

42 If it does not work for you, ask your doctor about alternative treatments that may be  
43 available.  
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46

### 47 **IV. Possible adverse reactions, risks, discomfort and inconvenience** 48

49 The transcutaneous electrical acupoint stimulation used in this study has the  
50 advantages of safety, noninvasiveness and small impact on cardiovascular system. No  
51 serious adverse reactions have occurred during the treatment.  
52

53 If you experience any discomfort, illness aggravating or any unexpected  
54 circumstances during the study, whether related to the study or not, you should inform  
55 your doctor in time. He/she will make a judgment on this and give appropriate  
56 medical treatment.  
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59 During the study, you need to come to the hospital on time for follow-up visits and  
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3 some examinations, which may take up some of your time and may also cause trouble  
4 or inconvenience to you.  
5

## 6 7 **V. Related expenses** 8

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10 The drugs and related tests used in this study are free of charge. If you have any injury  
11 related to this study, the research group will pay your medical expenses. In case of  
12 serious adverse events, the research team will pay compensation according to relevant  
13 national regulations. For other diseases that you combine at the same time, the  
14 treatment and examination required will not be free of charge  
15  
16

## 17 **VI. Confidentiality of personal information** 18

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20 Your medical records (study records /CRF, lab notes, etc.) will be kept intact in the  
21 hospital you visit.  
22

23 Your doctor will record the results of tests and other tests on your medical record.  
24 Researchers, ethics committees and drug regulators will be allowed to access your  
25 medical records.  
26

27 Any public report on the results of this study will not disclose your personal identity.  
28 We will make every effort to protect the privacy of your personal medical data to the  
29 extent permitted by law.  
30

31 In accordance with medical research ethics, in addition to personal privacy  
32 information, test data will be available for public inquiry and sharing, which will be  
33 limited to web-based electronic databases, ensuring that no personal privacy  
34 information will be disclosed.  
35  
36

## 37 **VII. How to get more information?** 38

39  
40 You may raise any questions about this study at any time and get the corresponding  
41 answers.  
42

43 If there is any important new information during the study that may affect your  
44 willingness to continue to participate in the study, your doctor will inform you in time.  
45

## 46 **VIII. You may voluntarily participate in the study or withdraw from the study** 47

48  
49 Participation in the study is entirely up to you.

50 You may refuse to participate in the study or withdraw from the study at any time  
51 during the study, which will not affect the relationship between you and the doctor,  
52 nor will it affect your medical treatment or the loss of other benefits.  
53

54 In your best interests, the doctor or researcher may discontinue your participation in  
55 this study at any time during the study.  
56

57 If you withdraw from the study for any reason, you may be asked about the use of the  
58 test drug.  
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60 You may also be required to have a laboratory and physical examination if your

1  
2  
3 doctor deems it necessary.  
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6 **IX. What should I do now?**  
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8 Participation in this study is up to you (and your family).  
9

10 Before you make a decision to participate in the study, please ask your doctor as many  
11 questions as possible. Thank you for reading the material. If you decide to participate  
12 in this study, please tell your doctor that he/she will arrange all matters related to the  
13 study for you. Please keep this information.  
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For peer review only

### Informed consent

**Clinical study title:** Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

**Project unit:** Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

**Project partner:** \_\_\_\_\_

**Project assignment no.:** \_\_\_\_\_

#### Agree with the statement

I have read the above introduction to this study and have the opportunity to discuss and raise questions with my doctor about this study.

All my questions were answered satisfactorily.

I know the possible risks and benefits of participating in this study.

I understand that participation in the study is voluntary and I confirm that I have had sufficient time to consider this and understand that:

- I can consult my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights and interests will not be affected.

I also know that if I drop out of the study, especially if I drop out of the study due to drugs, if I tell the doctor about my condition change and complete the corresponding physical examination and physical and chemical examination, it will be very beneficial to the whole study.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him the truth afterwards.

I agree with the ethics committee of the drug regulatory agency or the sponsor's representative to access my research materials.

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

In the end, I decided to agree to participate in this study, and promised to follow the doctor's advice as much as possible.

Patient signature: \_\_\_\_\_ DATE: \_\_\_\_\_(YYYY-MM-DD)

Contact number: \_\_\_\_\_

I confirm that I have explained to the patient the details of this trial, including its rights and possible benefits and risks, and have given it a copy of the signed informed consent.

Signature of doctor: \_\_\_\_\_ DATE: \_\_\_\_\_(YYYY-MM-DD)

Contact number: \_\_\_\_\_



SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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   | _____ 2 _____            |
| Protocol version                  | 3       | Date and version identifier  | _____ 2 _____            |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____ 11 _____           |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____ 1&11 _____         |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____ 11 _____           |
|                                   | 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 | _____ 11 _____           |
|                                   | 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)                         | _____ 9 _____            |

|    |   |     |   |               |
|----|---|-----|---|---------------|
| 1  | <b>Introduction</b>                                       |     |   |               |
| 2  |   |     |   |               |
| 3  | Background and  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant   | _____4&5_____ |
| 4  | rationale   |     | studies (published and unpublished) examining benefits and harms for each intervention                        |               |
| 5  |   |     |   |               |
| 6  |   | 6b  | Explanation for choice of comparators   | _____         |
| 7  |   |     |   |               |
| 8  | Objectives  | 7   | Specific objectives or hypotheses   | _____5_____   |
| 9  |   |     |   |               |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), | _____5_____   |
| 11 |   |     | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   |               |
| 12 |   |     |   |               |
| 13 |   |     |   |               |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |   |               |
| 15 |   |     |   |               |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will | _____6_____   |
| 17 |   |     | be collected. Reference to where list of study sites can be obtained  |               |
| 18 |   |     |   |               |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  | _____6_____   |
| 20 |   |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |               |
| 21 |   |     |   |               |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be | _____8&9_____ |
| 23 |   |     | administered  |               |
| 24 |   |     |   |               |
| 25 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  | _____         |
| 26 |   |     | change in response to harms, participant request, or improving/worsening disease)                             |               |
| 27 |   |     |   |               |
| 28 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        | _____         |
| 29 |   |     | (eg, drug tablet return, laboratory tests)  |               |
| 30 |   |     |   |               |
| 31 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 | _____         |
| 32 |   |     |   |               |
| 33 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       | _____7_____   |
| 34 |   |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, |               |
| 35 |   |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |               |
| 36 |   |     | efficacy and harm outcomes is strongly recommended  |               |
| 37 |   |     |   |               |
| 38 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   | _____7_____   |
| 39 |   |     | participants. A schematic diagram is highly recommended (see Figure)  |               |
| 40 |   |     |   |               |
| 41 |   |     |   |               |
| 42 |   |     |   |               |
| 43 |   |     |   |               |
| 44 |   |     |   |               |
| 45 |   |     |   |               |
| 46 |   |     |   |               |

|   |             |    |   |             |
|---|-------------|----|---|-------------|
| 1 | 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 | _____8_____ |
| 2 |             |    |   |             |
| 3 |             |    |   |             |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | _____8_____ |
| 5 |             |    |   |             |

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

|    |                    |     |  |             |
|----|--------------------|-----|--|-------------|
| 8  |                    |     |  |             |
| 9  |                    |     |  |             |
| 10 | Sequence           | 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_____ |
| 11 | generation         |     |  |             |
| 12 |                    |     |  |             |
| 13 |                    |     |  |             |
| 14 |                    |     |  |             |
| 15 |                    |     |  |             |
| 16 | Allocation         | 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_____ |
| 17 | concealment        |     |  |             |
| 18 | mechanism          |     |  |             |
| 19 |                    |     |  |             |
| 20 | Implementation     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | _____7_____ |
| 21 |                    |     |  |             |
| 22 |                    |     |  |             |
| 23 |                    |     |  |             |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | _____7_____ |
| 25 |                    |     |  |             |
| 26 |                    |     |  |             |
| 27 |                    | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | _____7_____ |
| 28 |                    |     |  |             |
| 29 |                    |     |  |             |
| 30 |                    |     |  |             |

### 31 **Methods: Data collection, management, and analysis**

|    |                 |     |  |             |
|----|-----------------|-----|--|-------------|
| 32 |                 |     |  |             |
| 33 | Data collection | 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_____ |
| 34 | methods         |     |  |             |
| 35 |                 |     |  |             |
| 36 |                 |     |  |             |
| 37 |                 |     |  |             |
| 38 |                 |     |  |             |
| 39 |                 | 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  | _____9_____ |
| 40 |                 |     |  |             |
| 41 |                 |     |  |             |
| 42 |                 |     |  |             |

|    |                                 |     |   |    |
|----|---------------------------------|-----|---|----|
| 1  | 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   | 9  |
| 2  |                                 |     |   |    |
| 3  |                                 |     |   |    |
| 4  |                                 |     |   |    |
| 5  | 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  | 8  |
| 6  |                                 |     |   |    |
| 7  |                                 |     |   |    |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8  |
| 9  |                                 |     |   |    |
| 10 |                                 | 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)   | 8  |
| 11 |                                 |     |   |    |
| 12 |                                 |     |   |    |
| 13 |                                 |     |   |    |
| 14 | <b>Methods: Monitoring</b>      |     |   |    |
| 15 |                                 |     |   |    |
| 16 | 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 | 9  |
| 17 |                                 |     |   |    |
| 18 |                                 |     |   |    |
| 19 |                                 |     |   |    |
| 20 |                                 |     |   |    |
| 21 |                                 |     |   |    |
| 22 |                                 | 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   | 9  |
| 23 |                                 |     |   |    |
| 24 |                                 |     |   |    |
| 25 | 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   | 9  |
| 26 |                                 |     |   |    |
| 27 |                                 |     |   |    |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 10 |
| 29 |                                 |     |   |    |
| 30 |                                 |     |   |    |
| 31 |                                 |     |   |    |
| 32 | <b>Ethics and dissemination</b> |     |   |    |
| 33 |                                 |     |   |    |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 2  |
| 35 |                                 |     |   |    |
| 36 |                                 |     |   |    |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | 10 |
| 38 |                                 |     |   |    |
| 39 |                                 |     |   |    |
| 40 |                                 |     |   |    |
| 41 |                                 |     |   |    |
| 42 |                                 |     |   |    |

|    |                               |     |   |              |
|----|-------------------------------|-----|---|--------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | _____6_____  |
| 2  |                               |     |   |              |
| 3  |                               |     |   |              |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | _____6_____  |
| 5  |                               |     |   |              |
| 6  |                               |     |   |              |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | _____9_____  |
| 8  |                               |     |   |              |
| 9  |                               |     |   |              |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | _____11_____ |
| 11 |                               |     |   |              |
| 12 |                               |     |   |              |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | _____9_____  |
| 14 |                               |     |   |              |
| 15 |                               |     |   |              |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | _____9_____  |
| 17 |                               |     |   |              |
| 18 |                               |     |   |              |
| 19 |                               |     |   |              |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____2_____  |
| 21 |                               |     |   |              |
| 22 |                               |     |   |              |
| 23 |                               |     |   |              |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | _____2_____  |
| 25 |                               |     |   |              |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | _____2_____  |
| 27 |                               |     |   |              |
| 28 |                               |     |   |              |
| 29 | <b>Appendices</b>             |     |   |              |
| 30 |                               |     |   |              |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | _____NA_____ |
| 32 |                               |     |   |              |
| 33 |                               |     |   |              |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | _____NA_____ |
| 35 |                               |     |   |              |
| 36 |                               |     |   |              |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.