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

Effects of electroacupuncture on opioid-induced constipation in patients with cancer: a multicenter randomized controlled trial

Clinical Sites:

1. Guang'an men Hospital Affiliated to China Academy of Chinese Medical Sciences
2. Guizhou University of Traditional Chinese Medicine
3. The Affiliated Hospital of Nanjing University of Chinese Medicine
4. Hunan University of Chinese Medicine
5. Wangjing Hospital Affiliated to China Academy of Chinese Medical Sciences
6. Yantai Hospital of Traditional Chinese Medicine
7. Zhejiang Hospital

Data Management and Statistical Centers:

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Data：

Original protocol date: September 30, 2018
Amendment date: November 29, 2019

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2. Study Design

2.1 Study Overview

The objective of study is to assess the efficacy of electro-acupuncture (EA) for opioid-induced constipation(OIC) in adult patients with cancer pain.

2.2 Background

In advanced diseases, 70-80% of patients experience moderate to severe pain[1]. As the cornerstone of treatment for moderate to severe cancer pain, opiate analgesics, such as morphine and oxycodone, are recommended by WHO Cancer Pain Relief Guidelines [2-3]. The use of systemic opioids is recommended by some studies for cancer patients

experiencing moderate to severe pain, regardless of the underlying causes[4]. Opioids stimulate receptors both in the central nervous system (CNS) and the peripheral nervous system, reducing pain and improving quality of life for patients [5]. The drug can, however, be associated with serious adverse events (AEs) with a rate ranging from 1.8% to 13.6%[6-7], the most common of which is opioid-induced constipation (OIC). OIC represents a change in baseline bowel habits or defecation patterns that occurs following the administration or modification of opioid therapy [8-10]. Approximately 41% of non-cancer patients and 94% of cancer patients who use opioids for pain have this condition [11-12]. Symptoms of OIC are usually persistent and difficult to tolerate [9], which adversely affects patients' quality of life[8, 13-15] and results in reductions in dose or discontinuation of opioid analgesics [16]. OIC is the result of multiple factors contributing to it [17]: Opioids may activate μ-receptors throughout the gastrointestinal tract and cause changes to gut motility, decreases in gut secretion, and an increase in sphincter tone, which can lead to constipation [18]. Various pharmacological and nonpharmacological interventions are used to manage OIC, such as laxatives and increased fluid intake [8-9, 19]. However, these interventions are limited in effectiveness, and they do not address the pathophysiological mechanisms of OIC [8-9]. Several peripherally acting μ-opioid receptor antagonists (PAMORAs), such as naloxegol and methylnaltrexone, have recently been shown to be effective in treating OIC patients who do not respond to simple medications [20]. However, longer-term efficacy and safety of PAMORAs are unclear, and they haven't been approved in China yet. Clinical trials are still underway to test these drugs. Additionally, PAMORAs are often associated with AEs such as abdominal pain and flatulence[21]. As a result, it is still necessary to explore new treatment approaches for OIC.

In traditional Chinese medicine, acupuncture has been used to treat gastrointestinal disease, including constipation, for thousands of years. According to two systematic reviews, acupuncture can improve spontaneous bowel movements (SBMs) in functional constipation [22-23]. Additionally, the results of our study indicated that electroacupuncture (EA) could increase complete spontaneous bowel movements (CSBMs) and SBMs, with a long-term effect that continues for 24 weeks after treatment ceased among patients with chronic, severe functional constipation [24-25]. Through stimulation of the somatic and peripheral nervous systems, acupuncture can facilitate the gut motility and improve

gastrointestinal function [26]. The effectiveness of acupuncture for OIC is currently lacking evidence. The purpose of this study is to compare the efficacy and safety of EA with sham acupuncture (SA) in the treatment of OIC in cancer patients.

2.3 Study Hypothesis

We hypothesize that EA is better than SA in treating OIC in adult patients with cancer pain.

2.4 Methodology

2.4.1 Trial Design

This is a multicenter, prospective, sham-controlled, parallel-group, subject- and assessor-blinded, randomized trial at 7 centers in China. Cancer patients must meet the Rome IV[10] diagnostic criteria for OIC.

2.4.1.1 Randomization

Web-based central randomization will be performed by the Linkermed Pharm Technology Co. Ltd (Beijing, China). Participants will be randomly allocated, in a 1:1 ratio, to either the EA or the SA group using permuted block-randomization. Acupuncturists in each center will be responsible for getting random numbers. Via inputting the screening information of the participant in the central randomization system through the web, they will get the random number and group allocation.

2.4.1.2 Blinding

In this study, participants, outcome evaluators, and data analysts will be blinded to the group assignments. The acupuncturists who perform the treatment will not be blinded due to the nature of the acupuncture treatment. Participant blinding will be achieved via a minimal needling at non-acupoints. Bilateral sham points will be attached with the same EA apparatus using a continuous wave of 10Hz and a current intensity of 0.1–0.2mA for 30 minutes after a brief activation period of 30 seconds.

For blinding assessment, all participants will be requested to answer the following question: “Is EA the acupuncture modality that you have received?”within five minutes after any treatment at week 8.

2.4.1.3 Sample Size

On the basis of unpublished data, a 14% response rate was assumed for the sham acupuncture group in this study. We estimated that a sample size of 100 participants would provide 90% power to detect a between-group difference of 31.4% at the two-sided significance level of 0.05 and 20% loss to follow-up.

2.4.2 Subjects

Participants with cancer will be publicly recruited from inpatient and outpatient departments through posters and networks from 6 centers in China.

2.4.2.1 Inclusion Criteria

(1) Cancer patients must meet the Rome IV[10] diagnostic criteria for OIC. Participants have at least 2 of the following new or worsening symptoms of constipation following initiation, alteration, or increase in opioid treatment: fewer than three SBMs per week, straining (>25% of defecations), sensation of incomplete evacuation (>25% of defecations), lumpy or hard stools (>25% of defecations), and/or sensation of anorectal obstruction/blockage (>25% of defecations). For patients with a history of chronic functional constipation, he/she must have worsening symptoms of constipation when the opioid therapy is initiated, changed, or the dose is increased;(2)Patients recruited in this trial must have a history of OIC symptoms for at least 1 week;(3) Patients must be ≥18 years of age and ≤85 years of age; (4) Patient's cancer condition must be stable with a life expectancy that is more than six months; (5)Patients must have an Eastern Cooperative Oncology Group (ECOG)[27]performance status of 0-3; (6)Patients must have been receiving a stably maintained opioid regimen, consisting of a total daily dose of 30 mg to 1000 mg oral morphine equivalents for at least 2 weeks prior to screening for cancer pain. Furthermore, it must be anticipated that the opioid will be maintained for at least 10 weeks;(7)The SBM frequency of the patients must be 2 times a week when laxatives are not being taken;(8)Patients must be capable of oral intake of drugs, food and beverages; (9)Provision of written informed consent before inclusion.

2.4.2.2 Exclusive Criteria

Participants will be excluded from this trial if they have any of the following conditions:

(1) Patients diagnosed with clinically significant abnormal defecation due to functional

disorders or structural abnormalities of the gastrointestinal tract and other tissues related to gastrointestinal tract (not including OIC): inflammatory bowel disease, rectal prolapse, gastrointestinal obstruction, peritoneal metastasis, or peritoneal tumor at the time of enrollment; (2)Patients with a history of gastrointestinal tract operation, abdominal operation, or abdominal adhesion within one month prior to screening; history of intestinal obstruction within three months prior to screening; (3)Diagnosis of active diverticular disease; or severe hemorrhoid; or anal fissure; or artificial rectum or anus; (4) Patients with an intraperitoneal catheter or those that use a feeding tube to maintain vital signs; (5)Diagnosis of pelvic disorder, which are considered to have obvious effects on the intestinal transport of feces (such as uterine prolapse ≥degree 2, uterine fibroids [located in the posterior of the uterus with a diameter ≥ 5 cm] affecting bowel movement); (6)Patients that are being treated with a new cancer chemotherapy, which had never been administered in the past, within 14 days of the screening or are scheduled to receive such therapy during the study; (7)Patients that received radiotherapy within 28 days of the screening or are scheduled to receive such therapy during the study; (8)Patients that underwent a surgery or intervention that is considered to have an obvious effect on the gastrointestinal functions within 28 days of the screening or are scheduled to receive surgery or intervention which is considered to have obvious effects on the gastrointestinal functions during the study, or scheduled to receive surgery or intervention which will be anticipated to prevent the patients from completing the trial; (9)Patients with uncontrolled hyperthyroidism, severe hypertension, heart disease, systematic infection or blood coagulation disorders (hypercoagulation status or hemorrhagic tendency); (10)Patients that consumed >4 additional opioid doses per day, for breakthrough pain, for more than 3 days during the baseline period, or if their maintenance opioid dosing regimen was modified during this period; (11)Patients with severe cancerous pain (e.g., typical average daily pain intensity rating of 7 to 10 on a numerical rating scales (NRS; 0 [no pain] to 10 [the worst pain possible]) after the utility of routine dose and frequency of opioids) refractory to opioid therapy;(12) Patients with a history of opioid discontinuation due to severe adverse events or patients that are suspected to discontinue opioid use due to the potential risk of adverse events; (13)Patients that received an opioid receptor antagonist or agonist within one month of the screening, or those who are scheduled to receive such

therapy during the study; (14) Patients with a history of nerve neurolysis;(15) Patients with severe cognitive impairment, aphasia, or psychiatric disorders; abdominal aortic aneurysm; hepatomegaly; or splenomegaly;(16) Patients that have received acupuncture within three months of the screening; (17)Other patients who are considered ineligible for the study by the investigator on the basis of concomitant therapy and medical findings.

2.4.2.3 Subject Withdrawals

There will be at least one oncologist or gastroenterologist in each center. They will assess the severe adverse events (SAEs) and then determine whether the participant to continue or terminate the trial. Subjects may leave the study at their own discretion, or the investigator may determine whether it is in the best interest of subjects to withdraw from the trial due to worsening of symptoms, or the occurrence of a serious adverse event.

2.4.2.4 Subject Recruitment, Screen and Grouping Assignment

Participants with cancer will be publicly recruited from inpatient and outpatient departments through posters and networks. Research assistants of each site will preliminarily screen the participants by recording their disease condition, history of the disease and treatment, and the demographic data. An oncologist or gastroenterologist of each site will take charge of the diagnosis and the differential diagnosis of the OIC. Potential participants will fill out a 1-week patient diary to record bowel movements, the stool consistency, degree of difficulty in defecation, the rescue medicine drugs and duration of usage, and the intensity of cancerous pain, etc. Eligible participants then will be randomized to EA or SA group. Acupuncturists are in charge of the participants' group assignment, and the EA or SA treatments. They are also responsible for the assessment of safety during treatment. During the trial, the professional evaluators of each site will instruct the participants how to fill in patients' self- assessment related to the trial and their patient diaries and the evaluators will record the data on the case report form (CRF) through the whole trial period. The subject flow was shown in Figure 1.

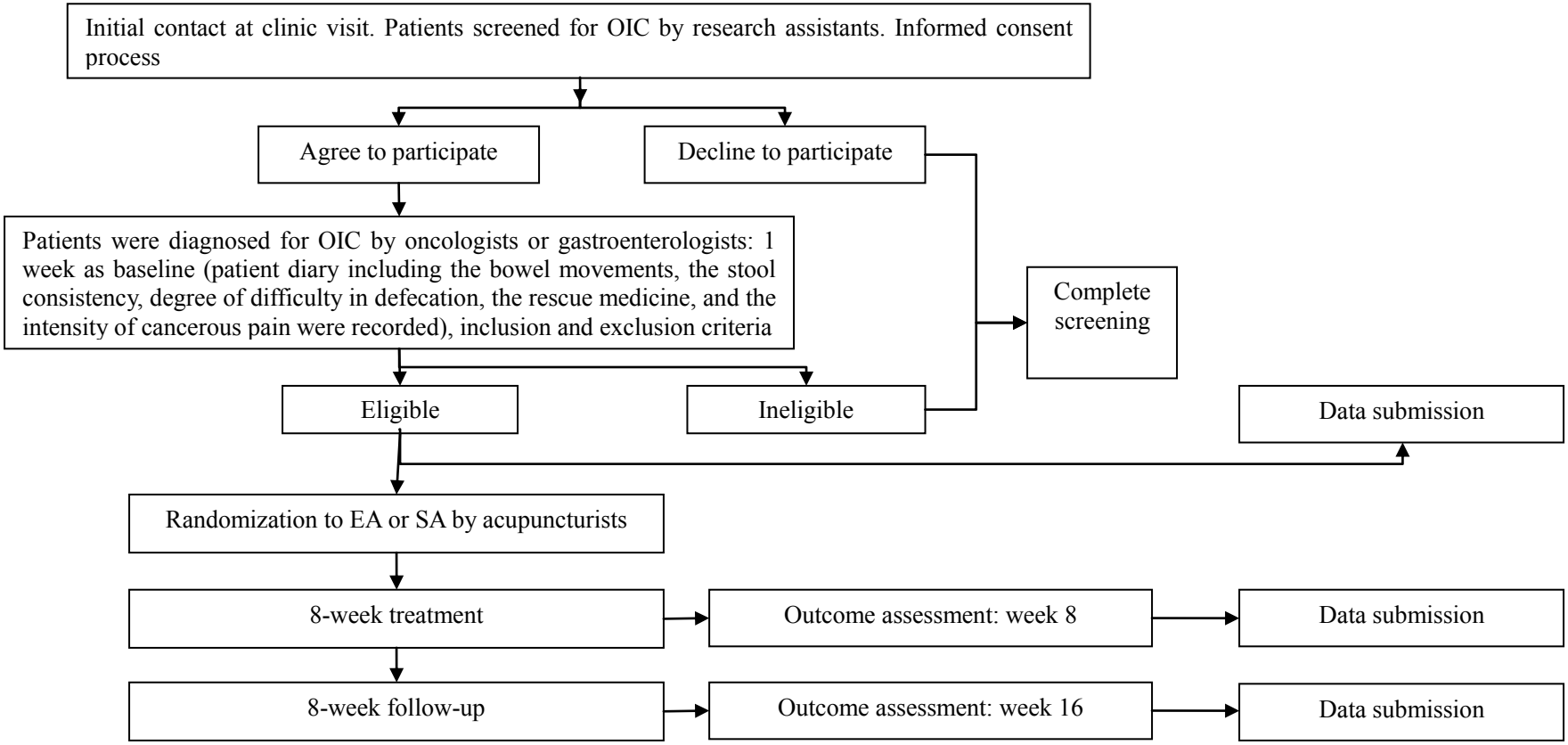


Figure 1. Subject flow

2.4.3 Trial flow chart

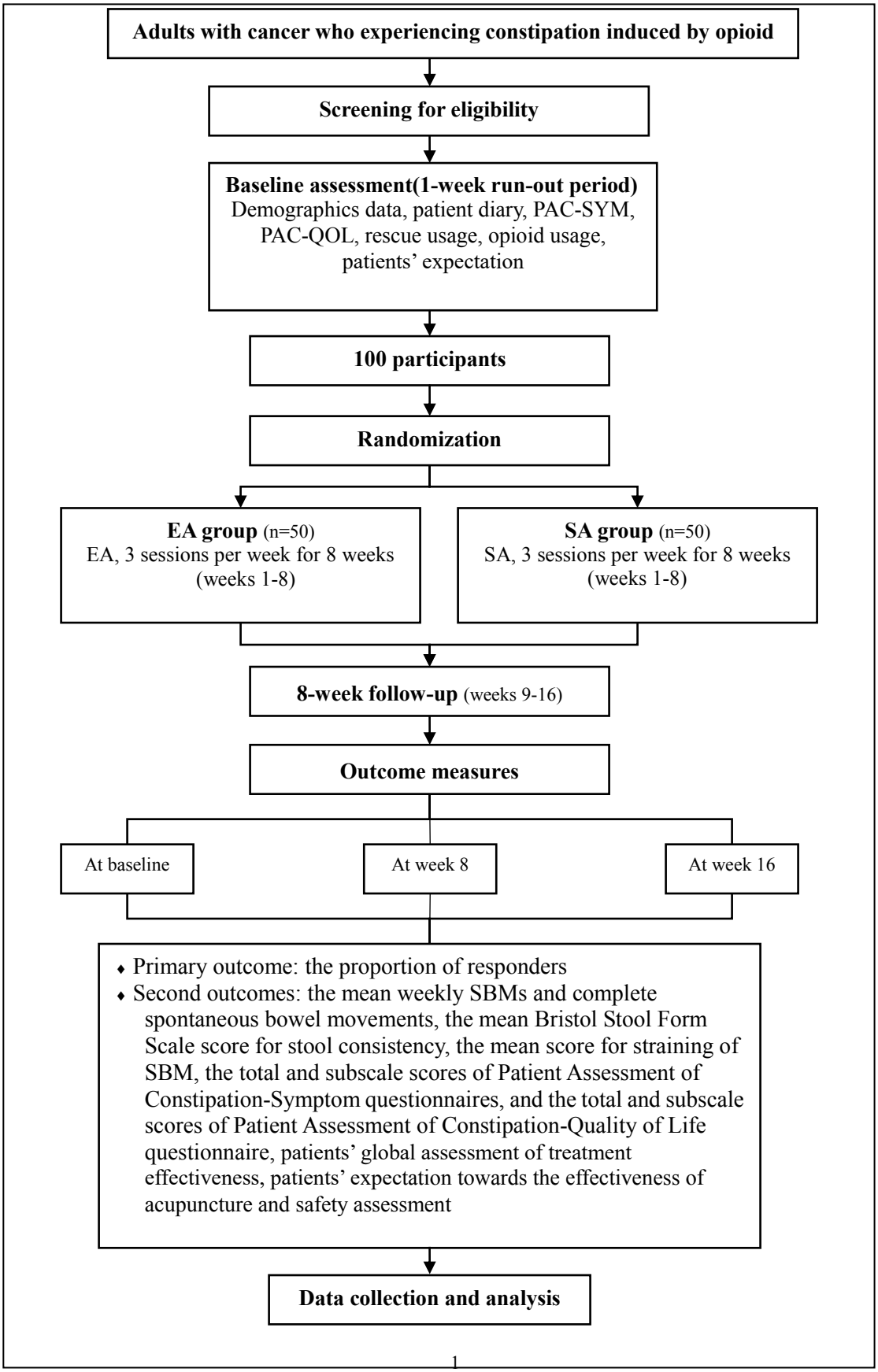
The trial flow chart was shown in Figure 2.

Enrollment	Study Period			
	Baseline	**Allocation**	**Treatment**	**Follow-up**
	Weeks -1	Week 0	Weeks 1 to 8	Weeks 13 to 16
Eligibility criteria	×			
Demography characteristics	×			
Disease history of cancer	×			
Disease history of OIC and constipation	×			
Eligibility screen	×			
Informed consent	×			
Allocation		×		
Interventions				
Electroacupuncture			×	
Sham electroacupuncture			×	
Assessments				
SBMs	×		×	×
CSBMs	×		×	×

Mean Bristol Stool Form Scale score for stool consistency of SBM	×		×	×
Mean score for straining of SBM	×		×	×
PAC-SYM total score and subscale scores	×		×	×
PAC-QOL total score and subscale scores	×		×	×
Patients' global assessment of treatment efficacy			×	×
Rescue medicine usage	×		×	×(weeks 9 -16)
Opioid usage	×		×	× (weeks 9-16)
Patients' expectation of the acupuncture efficacy	×			
Blinding assessment			×	
Cancer pain			×	×
Adverse events	×		×	× (weeks 9-16)
Safety assessment	×		×	× (weeks 9-16)

Abbreviations: OIC, Opioid-induced constipation; SBMs, spontaneous bowel movements; CSBMs, complete spontaneous bowel movements; PAC-SYM, Patient Assessment of Constipation-Symptom questionnaires; PAC-QOL, Patient Assessment of Constipation-Quality of Life questionnaires.

Figure 3. The schedule of enrollment, interventions, and assessments



2.4.4 Outcomes Measurement

2.4.4.1 Primary Outcome

The primary outcome will be the the proportion of responders, defined as a patient that has ≥3 SBMs/wk and ≥ increase of 1 SBM from baseline simultaneously for at least 6 out of 8 weeks of the treatment period. SBM refers to a bowel movement that occurred without medication or assistance within the previous 24 hours. When a bowel movement occurs within 24 hours of the use of an optional assisted method (rescue medication or other bowel-treatment regimens) for defecation, it is not regarded as an SBM.

Every participant will be required to keep a diary 13 weeks: baseline (run-out period before randomization), 8 weeks of treatment, and 4 weeks of follow-up. Diary entries include the frequency of bowel movements, the consistency of the stool, the difficulty in defecating, the rescue medicine drugs applied and their duration, and the intensity of the cancer pain. During the treatment period, the diary will be collected weekly, and during the follow-up period, it will be collected at the end of week 16. The outcome evaluators will examine the diary content and determine the SBM and frequency accordingly.

2.4.4.2 Secondary Outcomes

(1) Changes in the mean weekly SBMs from the baseline during weeks 1-8 and weeks 13-16. The mean weekly SBMs equals the total frequency of SBMs divided by the numbers of week(s) recorded. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

(2) The proportion of patients with ≥3 mean weekly SBMs during weeks 1-8 and weeks 13-16. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

(3) The proportion of patients with an increase of ≥1 mean weekly SBM from the baseline during weeks 1-8 and weeks 13-16. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

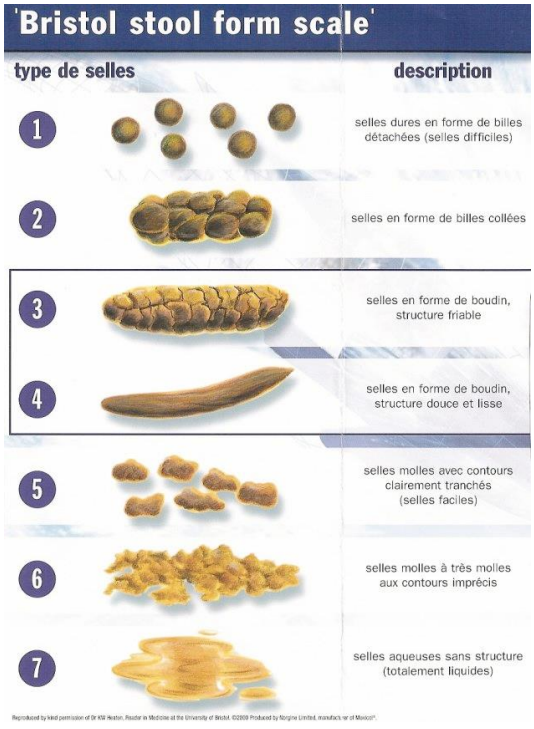
(4) A change in the mean weekly CSBMs from the baseline during weeks 1-8 and weeks 13-16. A CSBM is defined as an SBM with the feeling of complete evacuation. The mean weekly CSBMs equals the total frequency of CSBMs divided by number of week(s)

recorded. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

(5) The proportion of patients with ≥3 mean weekly CSBMs during weeks 1-8 and weeks 13-16. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

(6) The proportion of patients with an increase of ≥1 mean weekly CSBM from the baseline during weeks 1-8 and weeks 13-16. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

(7) A change in the mean Bristol Stool Form Scale score for stool consistency of SBMs from the baseline during weeks 1-8 and weeks 13-16. For stool consistency, each patient will be asked to record their stool consistency according to the Bristol Stool Form Scale[28] on the following seven points scale (scored from 1 to 7 for stool types 1 to 7, respectively). Assessment time frame: at baseline, over weeks 1-8 and 13-16.



- Type 1: Separate hard lumps, like nuts (hard to pass)
- Type 2: Sausage-shaped, but lumpy
- Type 3: Like a sausage but with cracks on its surface
- Type 4: Like a sausage or snake, smooth and soft
- Type 5: Soft blobs with clear cut edges (passed easily)
- Type 6: Fluffy pieces with ragged edges, a mushy stool
- Type 7: Watery, no solid pieces. Entirely liquid

(8) A change in the mean score for the straining of SBMs from the baseline during weeks 1-8 and weeks 13-16. For assessment of the straining of SBMs, each patient will be asked to rate his/her score of straining, using the following five-point scale[29]: not at all difficult (0), a little bit difficult (1), moderately difficult (2), quite a bit difficult (3), extremely difficult (4). Assessment time frame: baseline, over weeks 1-8 and 13-16.

(9) A change in the total and subscale score of the Patient Assessment of

Constipation-Symptom (PAC-SYM) questionnaire from the baseline at weeks 8 and 16. The PAC-SYM is a questionnaire used to evaluate the severity of chronic constipation in the past 2 weeks. It consists of 12 items, which are subdivided into abdominal (4 items), rectal (3 items), and stool (5 items) scales.34 36 The score of each item ranges from 0 to 4, with 0 = symptom absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. Lower scores indicate a lower symptom burden. Each subscale score will be calculated as the mean of the completed items for that subscale. The total score will be calculated as the mean of all completed items. In this trial, the Chinese version of PAC-SYM, which has been validated to have a satisfactory psychometric property[30], will be used. Assessment time frame: at baseline, at weeks 8 and 16.

(10) A change in the total and subscale scores of the Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaires from the baseline at weeks 8 and 16. The PAC-QOL is a 28-item self-reported questionnaire to assess the burden of constipation on patients' everyday functioning and well-being in the 2 weeks (14 days) prior to assessment[31]. This questionnaire is divided into four subscales: physical discomfort (items 1-4), psychosocial discomfort (items 5-12), worries/concerns (items 13-23), and satisfaction (items 24 to 28). Each of the item scores ranges from 0 (not at all) to 4 (extreme), with lower scores indicating a better quality of life. For each visit, individual subscale scores will be calculated as the mean of the completed items for that subscale. The total score will be calculated as the mean of all of the completed items. We will use the Chinese version of this test[32] in our trial, which has been demonstrated to be a reliable and valid tool. Assessment time frame: at baseline, at weeks 8 and 16.

(11) Patients' global assessment of treatment efficacy. Each patient will be asked to rate his/her efficacy of treatment using the following 7-point self-reporting scale: markedly worse (1), moderately worse (2), slightly worse (3), no change (4), slightly improved (5), moderately improved (6), markedly improved (7). Scales with seven response categories are easy to use and have shown a high reliability and validity[33]. This questionnaire will be completed at week 8 and week 16. Assessment time frame: baseline, at weeks 8 and 16.

(12) The proportion of patients using rescue medicine and the mean frequency of rescue medicine use per week during weeks 1-8 and weeks 9-16. Assessment time frame: at baseline, over weeks 1-8 and 13-16.

Other Pre-specified Outcome Measures

(13) The proportion of patients discontinuing the opioid, and those with a ≥30% weekly mean increase or decrease in the dose of opioid from baseline during weeks 1-8 and weeks 9-16. Assessment time frame: at baseline, at weeks 8 and 16.

(14) The proportion of patients with a change from baseline in anti-tumor therapy that could impair the defecation during weeks 1-8 and weeks 9-16. Assessment time frame: at baseline, at weeks 8 and 16.

(15) Patients' belief in the efficacy of acupuncture. Participants will be asked to answer the following questions at baseline: "Do you think acupuncture will be effective in treating the disease in general?" and "Do you think acupuncture will be effective in improving the OIC?" For each question, patients will choose one of the following answers: "unclear/whatever", "Yes", or "No". Assessment time frame: at baseline.

(16) Blinding assessment. The blinding is regarded as successful when a patient guesses he/she has received a conventional EA. Before treatment, we told patients that they had a 50% chance of receiving conventional electroacupuncture (EA) with a deeper insertion versus minimal electroacupuncture (SA) a superficial penetration. Conventional electroacupuncture and minimal electroacupuncture have a possible similar efficacy. Both treatments used a relatively small electric intensity, and they may or may not feel the stimulation during treatment. Patients were treated separately to avoid communication. To assess the success of blinding, within 5 minutes after treatment at week 8, patients were asked to guess whether they received conventional EA. Assessment time frame: at week 8.

3. Safety Assessment

All adverse events (AEs) will be recorded throughout the whole trial in Adverse Event Form (AEF) by patients themselves and outcome assessors. In our trial, the serious AEs will be defined as events that cause death, exacerbation of the preexisting condition, interruption of treatment, prolongation of existing hospitalization, permanent disability or damage, or required medical intervention to prevent one of the above outcomes. AEs will

be categorized as treatment related or non-treatment related based on its potential association with acupuncture needling procedure by acupuncturists and related specialists within 24 hours. The treatment related AEs defined as follows: dizziness, fainting, localized hematoma, localized minor infection, or some discomforts after acupuncture. Safety assessments also include an 11-point NRS (0 indicates no pain, and 10 indicates the severest pain) to evaluate the intensity of cancer pain. The mean and largest intensity of cancer pain during the preceding week will be evaluated at baseline, as well as weeks 2, 4, 6, 8 and 16.

4. Interventions

The intervention scheme of this trial is based on our previous trials regarding acupuncture for functional constipation[24, 25]. Acupuncturists who had an acupuncture license and at least 2 years of clinical experience in acupuncture will perform the treatment. We will use disposable acupuncture needles (of the following sizes: 0.30 ×40, 0.30 ×50 and 0.30 × 75 mm) and SDZ-V EA apparatus (all Hwato Brand, Suzhou Medical Appliance Factory, Suzhou, China) in this trial. The duration of the trial for each participant will be 17 weeks: 1- week baseline assessment (run-out period), 8- week treatment and 8- week follow- up.

4.1 EA

Bilateral Tianshu (ST25), Fujie (SP14), Shangjuxu (ST37) will be used in the EA group. The location of the acupoints will be based on Nomenclature and location of acupuncture points[34] drafted in 2006 by the National Standard of the People's Republic of China (GB/T 12346–2006). The local skin will be routinely sterilized while the patient is in a supine position. For ST25 and SP14, 0.30×50 mm or 0.30×75 mm needles will be gently vertically inserted to the muscle layer of the abdominal wall, where patients will feel sharp pain and acupuncturists will feel resistance from the needle tip. For ST37, 0.30×40 mm needles will be vertically inserted approximately 15 mm deep, followed by three-time manipulation of even lifting and twisting method to elicit the sensation of deqi. Paired alligator clips of the EA apparatus will then be attached to the needle holders of the bilateral ST25, SP14, and ST37. The stimulation will be retained for 30 minutes, with

a continuous wave of 10 Hz and current intensity of 0.5 to 4 mA. All needles will be removed after 30 minutes and pressure will be applied using a dry sterilized cotton ball to avoid bleeding. Patients will be followed up for another 8 weeks after the treatment stopped.

4.2 SA

The patients in the SA group will receive minimal needling at non-acupoints as bilateral sham ST25, SP14, and ST37. The sham ST25 and SP14 are located 2 cm horizontally outward of the points stimulaed in the EA group. The sham ST37 point is located outward of ST37 in the middle of the stomach and gallbladder channel. After sterilization of the skin, 0.30×40 mm needles will be directly inserted about 2 -3 mm until they can stand up when attached by the alligator clips. No manipulation will be used and no deqi sensation will be elicited at any of the sham points. The bilateral sham ST25, SP14, and ST37 points will be attached by the same EA apparatus with a continuous wave of 10 Hz and current intensity of 0.1 to 0.2 mA for 30 minutes with only the initial 30 seconds on.

Patients in both groups will receive 24 treatment sessions over an 8-week period (3 sessions each week, ideally every other day). Each session will last for 30 minutes. Patients will be treated separately to prevent between-patient communication. Patients will be followed up for another 8 weeks after the treatment stopped.

4.3 Rescue medication

During the trial, other medication or intervention for OIC will be discouraged. However, if a patient has no bowel movement for 72 consecutive hours and cannot tolerate it, only bisacodyl (5 to 10 mg; up to 20 mg per day) or a 110ml glycerol enema will be permitted as a rescue medication. Details of drug use (time and frequency) will be recorded.

5. Informed consent

Informed Consent: Study Introduction

Dear participants：

Opioid analgesics, such as morphine and oxycodone, are recommended as the cornerstone for the management of moderate to severe cancer pain by WHO Cancer Pain Relief Guidelines. Opioid-induced constipation (OIC) is the most prevalent serious adverse events (AEs). It is reported in 94% of cancer patients who take opioids for pain. OIC is defined as a change in baseline bowel habits or defecatory patterns following the initial administration or modification of opioid therapy.

Unlike many other opioid-related AEs, the symptoms of OIC tend to be persistent and difficult to tolerate, which can adversely reduce patients' quality of life. The mechanism of OIC involves multiple contributing factors: exogenous opioids can activate μ-receptors throughout the gastrointestinal tract and lead to a change in gut motility, a decrease in gut secretion and an increase in sphincter tone, which will result in OIC. The management of OIC is multifaceted, involving a combination of pharmacological and non-pharmacological interventions, such as laxatives and increased fluid and fiber intake. However, the efficacy of these interventions is limited and these approaches do not address all of the underlying pathophysiological mechanisms of OIC. Recently, peripherally acting μ-opioid receptor antagonists (PAMORAs), such as naloxegol and methylnaltrexone, have been shown to be effective in treating OIC patients who response poorly to simple laxatives. However, these drugs are still under test in clinical trials with unclear long-term efficacy and safety; they have not been approved for use in China. In addition, the use of PAMORAs is often accompanied by AEs of abdominal pain and flatulence. At present, traditional Chinese medicine, glycerin enema and other methods are also can be used to treat OIC.

If you have been experiencing cancer-related pain and were haunted by the symptom of OIC. We invite you to participate in the study. This study was supported and funded by the 2019 National Administration of Traditional Chinese Medicine "Project of building evidence-based practice capacity for TCM--Project BEBPC-TCM" (NO. 2019XZZX-ZJ). The objective of this study is to assess the efficacy and safety of EA compared to sham acupuncture (SA) in the treatment of OIC in patients with cancer. Participating in this study can relieve symptoms of OIC while also contributing to the development of medicine, especially for acupuncture and moxibustion of Traditional Chinese medicine.

Patients with the following conditions should not participate in this study: If you cannot participate in the study, we will provide free scale testing and related consultation.

(1) Patients diagnosed with clinically significant abnormal defecation due tostructural abnormalities of the gastrointestinal tract and other tissues related to gastrointestinal tract (not including OIC): inflammatory bowel disease, rectal prolapse, gastrointestinal obstruction, peritoneal metastasis, or peritoneal tumor at the time of enrollment;
(2) Patients with a history of gastrointestinal tract operation, abdominal operation, or abdominal adhesion within one month prior to screening; history of intestinal obstruction within three months prior to screening;
(3) Diagnosis of active diverticular disease; or severe hemorrhoid; or anal fissure; or artificial rectum or anus;
(4) Patients with an intraperitoneal catheter or those that use a feeding tube to maintain vital signs;
(5) Diagnosis of pelvic disorder, which are considered to have obvious effects on the intestinal transport of feces (such as uterine prolapse ⩾degree 2, uterine fibroids [located in the posterior of the uterus with a diameter ⩾ 5 cm] affecting bowel movement);
(6) Patients that are being treated with a new cancer chemotherapy, which had never been administered in the past, within 14 days of the screening or are scheduled to receive such therapy during the study;
(7) Patients that received radiotherapy within 28 days of the screening or are scheduled to receive such therapy during the study;
(8) Patients that underwent a surgery or intervention that is considered to have an obvious effect on the gastrointestinal functions within 28 days of the screening or are scheduled to receive surgery or intervention which is considered to have obvious effects on the gastrointestinal functions during the study, or scheduled to receive surgery or intervention which will be anticipated to prevent the patients from completing the trial;
(9) Patients with uncontrolled hyperthyroidism, severe hypertension, heart disease, systematic infection or blood coagulation disorders (hypercoagulation status or hemorrhagic tendency);

(10) Patients that consumed >4 additional opioid doses per day, for breakthrough pain, for more than 3 days during the baseline period, or if their maintenance opioid dosing regimen was modified during this period;

(11) Patients with severe cancerous pain (e.g., typical average daily pain intensity rating of 7 to 10 on a numerical rating scales (NRS; 0 [no pain] to 10 [the worst pain possible]) after the utility of routine dose and frequency of opioids) refractory to opioid therapy;

(12) Patients with a history of opioid discontinuation due to severe adverse events or patients that are suspected to discontinue opioid use due to the potential risk of adverse events;

(13) Patients that received an opioid receptor antagonist within one month of the screening, or those who are scheduled to receive such therapy during the study;

(14) Patients with a history of nerve neurolysis;

(15) Patients with severe cognitive impairment, aphasia, or psychiatric disorders; abdominal aortic aneurysm; hepatomegaly(liver span > 14cm at the mid-clavicular line by ultrasound examination); or splenomegaly(spleen length [cranial to caudal] > 13cm by ultrasound examination);

(16) Patients that have received acupuncture within three months of the screening;

(17) Other patients who are considered ineligible for the study by the investigator on the basis of concomitant therapy and medical findings.

We plan to enroll a total of 100 participants with 50 in each group in this trial. If the patients can participate in this study, doctors will randomly assign them to conventional electroacupuncture(EA) group or minimal electroacupuncture group. Each patient will have a 50% chance to be in the EA group or minimal electroacupuncture group. Patients in both groups will receive 24 treatment sessions over an 8-week period (3 sessions each week, ideally every other day). Patients will be followed up for another 8 weeks after the treatment stopped. During the study period, subjects are required to cooperate with doctors to complete relevant scales and carry out necessary auxiliary examinations, as well as to adherence to the schedule for treatment, examination, and follow-up visit. Additionally, you are also responsible for reporting any changes in your physical and mental status to your doctor during the study process regardless of whether you think these changes are related to the study or not. During the trial, other

medication or intervention for OIC will be discouraged. However, if a patient has no bowel movement for 72 consecutive hours, only bisacodyl (5 to 10 mg; up to 20 mg per day) or a 110ml glycerol enema will be permitted as a rescue medication. Details of drug use (time and frequency) will be recorded. The doctors will make every effort to prevent and treat any side effects brought on by this study. During acupuncture treatment, you may feel soreness, numbness, heavy, distension sensation, etc., which are normal reactions to acupuncture. Acupuncture treatment may have some adverse effects (e.g., dizziness, fainting, localized hematoma, localized minor infection), but it is rare and mild. We promise that in case of adverse events, we will do our best to provide treatment in accordance with the routine diagnosis and treatment according to professional judgment, and will follow the condition until it stabilizes or until the event is otherwise explained. The hospital will bear all the costs. Free treatment, consultation and scale measurement will be provided throughout the trial (including the follow-up period). You and your legal representative will be promptly notified of any information that may affect the subject's participation in the study. Whether to participate in this study will be entirely determined by the patients themselves, and the subjects' privacy will be kept strictly confidential within the scope of the law. Only the institutes responsible for the study, clinical research institutes, and ethics committees may have access to your medical records to verify clinical trial procedures and data. Your name will not appear in any publications or reports related to this study. Subjects have the right to withdraw from the study at any time during the study without any discrimination or retaliation, and without affecting any medical services. For your best interests(such as unbearable acupuncture pain or severe AEs), researchers may terminate your participation at any time during the study. Personal data of participants in the study are kept confidential. If you need more information, feel free to talk to your doctor. Subjects are entitled to ask our physicians at any time and to contact the ETHICS committee office if they have complaints.

Patient statement

I have been informed of the research purpose, content and method of this research, and I have fully understood the nature, significance, and possible risks and benefits of this research. I have the right to participate in this study voluntarily or not.My personal

information will be kept confidential.I grant access to the study data to the DRUG regulatory agency or the ethics committee.

I have fully understood the above and made the decision on my own after full consideration: I volunteered to be a subject in the study "Effects of electroacupuncture on opioid-induced constipation in patients with cancer: a multicenter randomized controlled trial". I am willing to accept research requests and cooperate with researchers.I am willing to actively cooperate with relevant examinations and fulfill the rights and obligations of subjects to ensure the final completion of this study.

Signature of patient Year month day

Telephone:

Researcher declaration:

I have carefully explained to the subjects the situation of this study and the benefits and risks of participating in this study.His signature is valid.Medical problems, language or education do not preclude an understanding of the above.

Signature of researcher Year month day

Telephone:

:

6. Quality Control

All staff members will undergo training prior to the trial. Monitors will check the case report forms and the acupuncture operation regularly. To improve adherence to intervention protocols, the majority of patients will come from the inpatient setting. The outcomes will be evaluated by independent assessors who are unaware of the group allocation. The data will be input by a clinical research coordinator according to the contents of CRF using the Electronic Data Capture System (EDC), which will be monitored by Clinical Research Associate. Detailed documentation of drop-outs and withdrawals, including the reasons, will be obtained throughout the trial. All of the

investigators will always maintain a strict privacy policy to protect confidentiality before, during and after the trial.

7. Data Management

7.1 The Raw Data Management and Archiving

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

7.2 Data Entry and Storage

7.2.1 Database Building and Testing, Data Entry Interface

The eCRF will be noted through CDISC SDTM standard, and the data entry interface will be generated through the Oracle Clinical software. The data entry interface should be in accordance with the paper-version CRF as far as possible. The inputted data will be stored in the Oracle database.

After preliminarily setting up the database, the entry clerks will input some analog data according to the CRF to test the database. The testing contains: (1) the agreement of the data entry interface and the paper-version CRF; (2) the agreement of the exported data from the database and the analog data; (3) the agreement of the structure of the exported database and the paper-version CRF. After the testing, data administrators should revise the database and make a testing report. Then they electrically signed on the approval page of the database to indicate that the testing is completed. The electrical files of the analog CRF, Noted CRF, screenshot of the data entry interface, database testing report, and the approval page of the database should be saved. If the database updates during the trial, the electrical files mentioned above are also need to be updated.

7.2.2 Data Entry and Inspection

The research assistants take charge of the data entry for our trial. Before the entry, all the research assistants will accept the related training according to the data entry handbook. Researchers will inspect the database, and then sign electrically to let the data go in to effect.

7.3 Data Verification and Problems Solving

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

7.4 Medical Coding

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

7.5 Data Report

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

Data report will be performed monthly since the first entry of the eCRF.

7.6 Data Auditing

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

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

7.7 Database Locking

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

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

8. Statistical Consideration

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

8.1 Statistical Analysis

The primary study hypothesis is that EA is more effective than SA in the treatment of OIC in patients with cancer. The primary outcome is the proportion of responders, defined as a patient that has ≥ 3 SBMs/wk and ≥ increase of 1 SBM from baseline simultaneously for at least 6 out of 8 weeks of the treatment period. The primary analysis will be intention-to-treat, which is defined as all randomized participants.

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

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

8.2 Statistical Analysis Plan (SAP)

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

9 Ethical principle

For every study site, only when the trial protocol is approved by the IRB, the enrollment of participant will begin, but all should be after May 1, 2019.

10 Funding

This study was supported and funded by the 2019 National Administration of Traditional Chinese Medicine "Project of building evidence-based practice capacity for TCM--Project BEBPC-TCM" (NO. 2019XZZX-ZJ) by China Academy of Chinese Medical Sciences.

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12 Major update of the published protocol

Important Changes Made to Study Design After Trial Commencement

No.	Item	Original version	Final version	Reason(s) for making change(s)
1	Exclusion criteria	(1)Patients diagnosed with clinically significant abnormal defecation due to functional disorders or structural abnormalities of the gastrointestinal tract and other tissues related to gastrointestinal tract (not including OIC)	Patients diagnosed with clinically significant abnormal defecation due to structural abnormalities of the gastrointestinal tract and other tissues related to gastrointestinal tract (not including OIC)	To reconsider the appropriate exclusion for more enrollment
2	Exclusion criteria	(13)Patients that received an opioid receptor antagonist or agonist within one month of the screening, or those who are scheduled to receive such therapy during the study	Patients that received an opioid receptor antagonist one month before the screening, or those who are scheduled to receive such therapy during the study	To reconsider the appropriate exclusion for more enrollment