# The efficacy and safety of electro-acupuncture for alleviating chemotherapy-induced peripheral neuropathy in colorectal cancer patients: study protocol for a pilot single-blinded, randomized sham-controlled trial

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**Study protocol**

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# Abstract

Background: Colorectal cancer is the most common cancer in Hong Kong. Oxaliplatin-based chemotherapy is a major first-line conventional therapy for advanced and metastatic colorectal cancer. However, oxaliplatin causes chemotherapy-induced peripheral neuropathy (CIPN). Acupuncture has long been used to alleviate limb numbness in Chinese Medicine Practice. This pilot study aims to examine the efficacy and safety of acupuncture for alleviating CIPN in colorectal cancer patients in Hong Kong. Methods/Design: This is a pilot single-blinded, randomized, sham-controlled trial. Eighty-four eligible patients, who are Hong Kong Chinese aged ≥18 years diagnosed with colorectal cancer and undergoing oxaliplatin-based chemotherapy, will be randomized in a ratio of 1:1 to electro-acupuncture group and sham-controlled group. During a 12-week treatment period, patients in electro-acupuncture group will undergo electro-acupuncture once a week from the first cycle of chemotherapy, patients in control group will receive sham-acupuncture, and the patients in both groups will be followed up for twelve weeks. The primary outcome measure is the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOC-Ntx) questionnaire. The secondary outcome measures include numerical rating scale (NRS) for numbness/pain, vibration and light touch sense test, quality of life questionnaire-C30 of European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) and Constitution of Chinese Medicine Questionnaire (CCMQ). Discussion: The study will compare electro-acupuncture with sham acupuncture to explore the feasibility for electro-acupuncture in improving symptoms caused by chemotherapy-induced peripheral neuropathy.


# Background

Colorectal cancer is the most common cancer in Hong Kong. In 2016, there were 5437 new cases and 2089 patients died due to colorectal cancer. Its crude death rate was 28.5 per 100,000[1]. in Hong Kong. Current conventional therapies include surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy. Surgery is the most common treatment for all stages of colorectal cancer and patients with advanced stage usually are given chemotherapy or radiotherapy to kill any possible remaining cancer cells. Oxaliplatin-based chemotherapy, regimens such as FOLFOX with or without (±) bevacizumab, CapeOX ± bevacizumab or FOLFOX ± panitumumab (KRAS wild type gene only), is one of the major treatments for advanced or metastatic colorectal cancer at first-line therapy[2]. However, 90% of patients with oxaliplatin developed acute chemotherapy-induced peripheral neuropathy (CIPN)[3] and it occurred in 68.3% patients within 2.5 ± 1.1 (mean ± standard deviation) chemotherapy cycles[4]. Symptoms include paresthesia and dysesthesia of the hands, feet and perioral area induced by cold stimuli[5]. About 30-50% of patients developed chronic CIPN after repetition of chemotherapy cycles[3] and its symptoms include paresthesia, numbness, sensory ataxia, functional deficits and pain. The mechanism of CIPN is complicated. Cytokine and chemokine binding are one of its possibilities. Chemotherapeutic agents enhance cytokines release (e.g. TNF-α, IL-1β) and binding of chemokines to their receptors located on neurons and glial cells, which contributes to increased sensation of pain[6]. Although symptoms induced by CINP are not vegetative, coasting effect is observed, meaning that the

symptoms continue to develop and progress for several months after the therapy, and a maximum duration of 8 years was documented[5]. Decrease in the levels of pro-inflammatory cytokines TNF-α, IL-1α, IL-1β induced by electro-acupuncture is thought to be related to its analgesic effect and thus its possibility to treat CINP.

In Traditional Chinese Medicine's theory, CIPN is similar to "Xue Bi"(□□), which means pain and numbness in the extremities[6]. Herbal medicine and acupuncture are common treatments for "Xue Bi". Systematic reviews of the CIPN found that the effectiveness of current treatments (included natural products and complementary therapies) were still unknown and only vitamin E is shown that may help alleviate CIPN[7,8]. The current studies of acupuncture for CIPN varied in different cancer and anti-cancer drugs such as taxanes for breast cancer[9], bortezomib and thalidomide for multiple myeloma[10], and a mix of neurotoxic anticancer drugs[11]. However, studies of acupuncture for oxaliplatin-induced peripheral neuropathy are rare and no randomized controlled trial was conducted[12]. Therefore, we design this pilot study using the method of single-blinded, randomized controlled clinical trial to explore the efficacy and safety of acupuncture on the relief of CIPN.

### Objective

The aim of this pilot study is to assess the efficacy and safety of electro-acupuncture compared to sham acupuncture on alleviating chemotherapy-induced peripheral neuropathy (CINP) in colorectal cancer patients.

# Methods/design

### Study design

This is a pilot single-blinded, randomized, sham-controlled trial on electro-acupuncture for alleviating symptoms of chemotherapy-induced peripheral neuropathy in patients with colorectal cancer. A total of 84 candidates will be recruited in this study. They will be assigned randomly into either the electro-acupuncture or sham-control group. Both groups will be given a total of 12 sessions of interventions, with 1 session per week. They will then be followed up regularly for up to 12 weeks after completion of intervention. The Functional Assessment of Cancer Therapy/Gynecology Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire will be used as the primary outcome measure. The questionnaire will be done before the start of the study as a baseline score. The score will be obtained on a weekly basis during the intervention and every three weeks during the follow-up period, up to 24 weeks.(Fig. 1) This study protocol has been approved by Hong Kong Baptist University Ethics Committee on the Use of Human Subjects for Teaching and Research (Approval no. HASC/17-18/C05) and Hospital Authority Kowloon West Custer Research Ethics Committee(KWC REC) (Approval no. KW/FR-18-041(121-01)) and

registered in clinicaltrials.gov (NCT03582423). The checklist for items in STRICTA 2010[13] is given in **Table 1.**

## Participants and setting

Patients with colorectal cancer are planning to receive oxaliplatin-based chemotherapy and do not have any pre-existing peripheral neuropathy will be recruited. The study is conducted in the Yan Chai Hospital cum Hong Kong Baptist University Chinese Medicine Clinic cum Training and Research Centre (Ha Kwai Chung).

## Inclusion criteria

Patients will be eligible for the study if they:

1. are aged ≥18 years old;
2. are newly diagnosed with stage to colorectal cancer;
3. plan to receive 8 cycles of adjuvant oxaliplatin-based chemotherapy;
4. have not received any acupuncture in the previous 3 months; and have a life expectancy ≥ six months

## Exclusion criteria

Patients will be excluded from the study if they:

1. are not able to comprehend and communicate;
2. fail to cooperate with the researcher;
3. are not able to read Chinese;
4. have prior peripheral neuropathy caused by other diseases including diabetes, stroke, cardiovascular diseases such as arrhythmia, heart failure, myocardial infarction, and patients with cardiac pacemakers;
5. have a bleeding tendency;
6. are pregnant or breast-feeding;
7. have impaired hepatic or renal function;
8. are using any pharmaceutical agents e.g. vitamin B6 and vitamin E, or herbal medication for CIPN treatment. All the above medication prescribed by physicians or Chinese medicine practitioners during the study will be recorded. Investigators will determine whether they need to be withdrawn from the study.

Candidates will be considered as dropout from the study if they:

1. withdraw his/her informed consent;

2. lost during follow-ups;
3. develop serious adverse event (SAE) or other safety/ efficacy issues in which suspension will be considered beneficial as suggested by investigators;
4. become pregnant;
5. stop taking the randomized treatment for any reason;

The date and reason for withdrawal should be noted in the case report form (CRF). All subjects who withdraw from the study should, if all possible, continue to conduct regularly follow up according to the schedule of measurement and be seen for a final evaluation (Termination Visit). Prematurely discontinued subjects will not be replaced.

## Recruitment

Subjects will be recruited through either of the following sources: (1) advertisements in newspapers, patients who are interest could contact research staff by phone; or (2) will be identified through clinic lists from the Princess Margaret Hospital (PMH) oncology outpatient department and Yan Chai Hospital cum Hong Kong Baptist University Chinese Medicine Clinic cum Training and Research Centre (Ha Kwai Chung). Potential participants will be approached initially by relevant clinical team and then screened by research staff. An informed consent will be taken from eligible patients.

## Interventions

### Electro-acupuncture treatment

Acupuncture intervention will be conducted for one session per week over 12 consecutive weeks. The most frequently used acupuncture points in CIPN are ba feng (EX-LE10), ba xie (EX-UE9), tai chung (LV3), he gu (LI4)[14]. Among them, the traditional effects of the points in hands and feet are regulating Qi and blood circulation and treating localized problems. With the clinical experience of our principal investigator and co-investigators, eight acupoints are chosen: he gu (LI4), nei guan (PC6), qu chi (LI12), ba xie (EX-UE9), zu san li (ST36), san yin jiao (SP6), tai chung (LV3) and ba feng (EX-LE10). The use of ba xie (EX-UE9) and ba feng (EX-LE10) will be optional if skin lesions of hands and feet occur due to Capecitabine (Xeloda). The details of acupoints and their functions are listed in **Table 2**. The acupuncture treatment will be conducted by a registered Chinese Medicine practitioner with more than 5 years of Chinese medicine college education plus at least 5 years of clinical experience. Disposable acupuncture needles (verum acupuncture needles Hwato 0.25×25mm matching the Streiterger sham needles) will be inserted at a depth of 10-25mm into the points. We will deliver electrical stimulation with continuous waves at 2 Hz, at an intensity of each patient's minimum sensation of stimulation through the electrical acupuncture stimulation instrument (KWD808I multi- purpose health device, Ying Di, Chang Zhou, China) to the points. The needles will be retained in position for 25 minutes.

### Sham acupuncture

For subjects assigned to the control group, Streitberger's non-invasive acupuncture needles (Gauge 8 × 1.2"/ 0.30 × 30mm) will be applied to serve as a sham control at the same acupoints with the same stimulation modality, except that the needles are only adhered to the skin by a small plastic ring instead of being inserted[15,16]and the stimulation will be a "pseudo stimulation", which will be given by connecting the needle to incorrect output socket of the electrical acupuncture stimulation instrument. The credibility and validity of this system has been well demonstrated[17,18].

## Outcome measures

The primary outcome is the validated Functional Assessment of Cancer Therapy/Gynecology Oncology Group/Neurotoxicity (FACT/GOC-Ntx) questionnaire[19,20]. The questionnaire includes 11 questions covering sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy. It results in a cumulative score ranging from 0 to 44, with the lower scores reflecting worse neuropathy symptoms. The secondary outcomes include (1) numerical rating scale (NRS) for numbness/pain score in hands and feet[20], which patients will be asked to rate their average neuropathy symptoms within one week, on an 0 to 10 scale (0 = no symptoms; 10 = worst possible symptoms), those <4 of 10 NRS will be considered as mild CIPN while ≥4 of 10 NRS will be considered as moderate to severe CIPN[21]; (2) the validated European Organization for Research and Treatment of Cancer (EORCTC) quality of life questionnaire QLQ-C30[22], which is a 30-items questionnaire assessing five functional scales (physical, role, cognitive, emotional and social), three symptoms scales (fatigue, pain, nausea and vomiting), and other symptoms and problem in cancer patients (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties); (3) the validated Constitution of Chinese Medicine Questionnaire (CCMQ)[23,24], which has 60 items measuring the 9 body constitution types: gentleness, Qi-deficiency, Yang-deficiency, Yin-deficiency, phlegm-wetness, wetness- heat, blood-stasis, Qi-depression, and special diathesis; (4) vibration sense test, which It is assessed using the graduated Rydel-Seiffer tuning fork (U.S. Neurologicals, Poulsbo, WA), with printed directions for use and its normative data[25]. Readings will be averaged and recorded as the vibration value. (5) light touch test, which is assessed with standard 10g monofilaments, contained within the Neuropen (Owen Mumford, Woodstock, UK). During testing, the fiber will be applied perpendicular to the plantar surface of the great toe and the palmar surface of the index finger until the fiber begins to bend and will be held in place for 1 second and removed. This will be repeated 3 times and the patient will be asked to report the ability to feel the fiber when it is applied[25]. The use of the above assessment questionnaires (FACT/GOC-Ntx, QLQ-C30 and CCMQ) will be required authorization from the authors. Besides at baseline (0 week), FACT/GOC-Ntx 11 items subscale, NRS, vibration sense test and light touch test will be assessed every week, EORTC QLQ-C30 will be assessed every 3 weeks, CCMQ will be assessed at the end of treatment (12$^{th}$ week). The post-trial access by phone or face to face interview will be performed at 15$^{th}$, 18$^{th}$, 21$^{st}$ and 24$^{th}$ week. The schedule of evaluations is presented in **Table 3**. Adverse events will be noted throughout the study, based on the participants reports and routine laboratory tests (complete blood counts, renal and liver functions) before every chemo-cycle. Subjects will undergo routine laboratory tests before every chemo-cycle for complete blood counts, renal and liver functions in hospitals where they received chemotherapy.

Laboratory reports will be collected and thus any adverse events will be reported and noticed. All clinical adverse events will be recorded according to terms of intensity (mild, moderate or severe), duration, outcome and relationship to the study.

## Randomization assignment

All subjects will be assigned to either the intervention or sham-control group randomly. Subjects in intervention group will receive electro-acupuncture treatment, whereas the subjects in the sham-control group will receive the sham treatment. A simple, non-sequential random numbers will be generated by a computer program prior to randomization. Randomization procedure will be carried out by the research unit of the School of Chinese Medicine, Hong Kong Baptist University. These randomization numbers will be contained in sealed, opaque and sequentially numbered envelopes and those envelops will be stored in a locker where key will be kept by the principal investigator (PI). Those envelops which corresponds to the group allocation will be provided to the acupuncturist by the PI after completion of the subject recruitment procedure. Both the clinical assessor and subjects are thus blinded to the group allocation. If there are medical concerns leading to an inevitable review of treatment assignment, the PI will be the responsible person for approval. The date, time and reason for treatment assignment disclosure should be noted in the CRF. Upon disclosure of treatment assignment, the concerned subject will be retained in the study. However, the number of cases in which randomization assignment is disclosed will be reported and, if necessary, sensitivity analyses may be performed removing these participants.

## Sample size calculation

The sample size calculation is based on the change of primary outcome. In this study, the difference in FACT/GOC-Ntx score between the intervention group and the sham-control group accounts for the calculation. As shown in a recent systematic review[12], there was only one study showing that acupuncture has significantly reduced the FACT GOC-Ntx score (MD = 5.40, SD = 3.91, 95% CI = 0.54-10.26)[26]. In this study, we assume the effect size between electro-acupuncture and sham acupuncture is 0.3. A minimum sample size of 62 should therefore be provided in order to achieve a significance level of $\alpha = 0.05$ with power (1-β) of 80%, [number of measurements is 3 and correlation among repeat measures is 0.5]with calculation by Gpower 3.1 (F tests, ANOVA, repeated measures, between factors). After taking 25% of dropout rate into consideration, the number of subjects for this study should raise to 84.

## Data processing and analysis

Descriptive data includes rate of recruitment, dropout and missing intervention will be analyzed and reported as count and percentage. All missing values, efficacy and safety analyses will be based on modified intention-to-treat (ITT) principle. Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 will be used for the statistical analysis. The statistical significance is defined as two-sided *P* value of $< 0.05$. Baseline characteristics will be reported as mean and SD for continuous variables and count and percentage for categorical variables. The differences in both the normally distributed and non-normally distributed variables between the intervention and the sham-control groups will be assessed

through Student's t test and Mann-Whitney U test respectively. The chi-squared test or Fisher's exact test will be used for calculating the categorical variables instead. Analysis of covariance (ANCOVA) will be used for the comparisons between the two groups every week, with treatment group as a factor in the model and baseline as the covariate. The difference between the baseline and endpoint score will be tested by using repeated measure analysis of variance (ANOVA). Paired t test and Wilcoxon signed-rank test will be used for analyzing the within-group data which are normally distributed and non-normally distributed respectively. Any deviation from this original statistical plan will be described and justified in the final report.

### Data management and confidentiality

Personal data will be handled by investigators. Hard copy data will be stored in a locker and electronic data will be stored in a specified computer with encryption. Key of locker and password of database will be kept by investigators only. Personal data will be kept for three years after the study. Hard copies will be discarded as confidential waste while the soft copy would be deleted and unrecoverable after completion of the study.

### Data monitoring and trial steering committee

Quarterly monitoring meeting will be held between PI, co-Is, the Hospital Authority Chinese Medicine Department (HACMD) and the School of Chinese Medicine, HKBU. The HACMD would monitor the Chinese Medicine Centre for Training and Research to ensure the quality of the trial and keep track of the study progress and compliance to the required standard and agreement.

## Discussion

This single-blinded, randomized controlled clinical trial aims to serve as a pilot study in evaluating the efficacy and safety of acupuncture on chemotherapy-induced peripheral neuropathy (CIPN) of colorectal cancer patients in Hong Kong. It will be the first of such study on Hong Kong population and will obtain relevant results for utilizing acupuncture in CIPN treatment especially for patients who are receiving chemotherapy. The outcome measures will include the quality of life and body constitution of Chinese medicine which will provide data to us on analysis of the treatment's potential benefit on the above items.

To date, similar studies are lacking in Hong Kong and this pilot study will provide a possible steppingstone for future large-scaled research such as a combined therapy on CIPN together with acupuncture and Chinese herbal medicine intervention. Further research on the side effects of chemotherapy and integrated medicine specifically targeting on different types of cancer patients can also be developed.

In this clinical trial, the selection of acupoints is standardized and utilized to every subject. Standardization of the acupoints provides easy and straightforward treatment implementation but the

limitation is that the selection of acupoints is not based on Syndromes Differentiation which traditional theories of Chinese acupuncture most concern about.

In conclusion, in this pilot study, a single-blinded, randomized controlled clinical trial will be conducted to evaluate the efficacy and safety of acupuncture on CIPN in Hong Kong. This pilot study will find out the possibility for CMPs to utilize acupuncture for CIPN and will also provide a platform to offer research training opportunities for junior CMPs.

### Trial status

This study protocol version number is 4 which dated on 26 February 2019. The participants are currently being recruited for the present study since October 2018. Thirty-three patients are under treatment and recruitment will be completed on December 2019.

## Abbreviations

Analysis of Covariance, ANCOVA; Analysis of Variance, ANOVA; chemotherapy-induced peripheral neuropathy, CIPN; Acupuncture; Chinese Medicine practitioners, CMPs; Intention-to-treat, ITT.

## Declarations

### Ethics approval and consent to participate

This study protocol has been approved by Hong Kong Baptist University Ethics Committee on the Use of Human Subjects for Teaching and Research (Approval no. HASC/17-18/C05) and Hospital Authority Kowloon West Custer Research Ethics Committee (Approval no. KW/FR-18-041(121-01)). Consent is obtained from every participant.

### Consent for publication

Written informed consent was obtained from the patient(s) for publication of this manuscript and accompanying images.

### Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

No competing financial interests exist.

### Funding

This research was financially supported by Hong Kong Hospital Authority Chinese Medicine Department Research Practical Training Programme. Hospital Authority Chinese Medicine Department provide training of research technique and monitor the progress of study.

### Authors' contribution

Kaiyin Chan drafted the manuscript. Linda Zhong and Chunkin Mak revised the manuscript. Kaiyin Chan, Linda Zhong, Zhao-Xiang Bian, Bacon Ng designed and supervised the study. Louisa Lui was responsible for the monitoring the safety of the patients and prescribing the laboratory tests. Kaling Yu, Kwongwai Lau, Manchi Lai, Waiwai Lau will do the data analysis and conduct the study. All authors have read and approved the final manuscript.

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# Table

Table 1 checklists for items in STRICTA 2010

| item | detail |
|---|---|
| · Acupuncture rationale | 1a) style of acupuncture<br><br>According to systematic reviews and clinical experiences of our principal investigator and co-investigators. Manual and electro-acupuncture based on traditional Chinese medicine theory |
| | 1b) reasoning for treatment provided, based on historical context, literature sources, and /or consensus methods, with references where appropriate |
| | 1c) extent to which treatment was varied:<br><br>Standard treatment is used. No variation of treatment among patients |
| · Details of needling | 2a) number of needle insertions per subject per session (mean and range where relevant):<br><br>28 needles |
| | 2b) names (or location if no standard name) of points used (uni/bilateral)<br><br>he gu □□(LI4), nei guan □□(PC6), qu chi □□(LI12), ba xie □□(EX-UE9), zu san li □□□(ST36), san yin jiao □□□(SP6), tai chung □□(LV3), ba feng □□(EX-LE10) |
| | 2c) depth of insertions, based on a specified unit of measurement or on a particular tissue level:<br><br>10-25mm |
| | 2d) response sought (e.g. de qi or muscle twitch response):<br><br>De qi |
| | 2e) needle stimulation (e.g. manual, electrical):<br><br>Manual and electrical – continuous waves at 2 Hz |
| | 2f) needle retention time:<br><br>25min |
| | 2g) needle type (diameter, length and manufacturer or material):<br><br>Disposable acupuncture needles<br><br>(verum acupuncture needles Hwato 0.25×25mm matching the Streiterger sham needles) |
| · Treatment regimen | 3a) number of treatment sessions: 12 sessions |
| | 3b) frequency and duration of treatment sessions:<br><br>Acupuncture will start after the day of 1st chemotherapy cycle.<br><br>1/week for 12 consecutive weeks even if the chemotherapy is stopped. |
| · Other components of treatment | 4a) details of other interventions administered to acupuncture group (e.g. moxibustion, cupping, herbs, exercise, lifestyle advice):<br><br>No other intervention |
| | 4b) setting and context of treatment, including instructions to practitioners, and information and explanations to patients:<br><br>Chinese Medicine Clinic cum Training and Research Centre |

| | |
|---|---|
| | Patients will be informed about acupuncture treatment in the study as follows: “in this study, acupoints for CINP will be used based on related reports and clinical experience of our investigators.” |
| · Practitioner background | 5) description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience):<br><br>Hong Kong registered Chinese medicine practitioners having at least 3 years of clinical experience and scholarship training in Chinese medicine oncology of Hong Kong Hospital Authority, who have undergone training and are able to provide identical acupuncture treatment in accordance with a predefined protocol. |
| · Control or comparator interventions | 6a) rationale for the control or comparator in the context of the research question, with source that justify this choice:<br><br>To assess the efficacy and safety of electro-acupuncture compared to sham acupuncture |
| | 6b) precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for items 1 to 3 above<br><br>-style of acupuncture<br><br>Sham acupuncture<br><br>-number of needle insertions per subjects per session:<br><br>28 sham needles at the same acupoints as the treatment group<br><br>-Depth of insertion:<br><br>Needles are only adhered to the skin<br><br>-needle retention time:<br><br>25 min<br><br>-needle type<br><br>Streitberger’s non-invasive acupuncture needles (Gauge 8 × 1.2”/ 0.30 × 30mm)<br><br>-number of treatment sessions:<br><br>12 sessions<br><br>-frequency and duration of treatment sessions:<br><br>1/week for 12 consecutive weeks |

this checklist, which should be read in conjunction with the explanations of the STRICTA items, is designed to replace CONSORT 2010’s item 5 when reporting an acupuncture trial

Table 2 acupoints of electro-acupuncture and their location

| acupoint | location |
|---|---|
| he gu (LI4) | In the middle of the 2nd metacarpal bone on the radial side |
| nei guan (PC6) | 2 cun*above the wrist crease between the tendons of palmaris longus and flexor carpi radialis |
| qu chi (LI11) | At the lateral end of the transverse cubital crease midway between LU5 and the lateral epicondyle of the humerus |
| ba xie (EX-UE9) | On the dorsum of the hand, at the webs between each finger, at the junction of red and white skin |
| tai chung (LV3) | On the dorsum of the foot in a depression distal to the junctions of the 1st and 2nd metatarsal bones |
| san yin jiao (SP6) | 3 cun directly above the tip of the medial malleolus on the posterior border of the tibia |
| zu san li (ST36) | 3 cun below ST35, one finger width lateral from the anterior border of the tibia |
| ba feng(EX-LE10) | On the dorsum of the foot between the web and metatarsophalangeal joint (4 points on each foot) |

*Cun is a standard measurement used to locate acupoints. It varies by patient and is equal to the width of the distal inter-phalangeal joint pf the thumb.

Table 3 schedule for outcome measurement

| period | B | T | | | | | | | | | | | | F | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chemo cycle | | 1st | | | 2nd | | | 3rd | | | 4th | | | 5th | 6th | 7th | 8th |
| week | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 15 | 18 | 21 | 24 |
| Informed consent | | | | | | | | | | | | | | | | | |
| FACT/GOC-Ntx | | | | | | | | | | | | | | | | | |
| NRS | | | | | | | | | | | | | | | | | |
| EORTC QLQ-C30 | | | | | | | | | | | | | | | | | |
| CCMQ | | | | | | | | | | | | | | | | | |
| Vibration sense test | | | | | | | | | | | | | | | | | |
| Light touch test | | | | | | | | | | | | | | | | | |
| Safety assessment | | | | | | | | | | | | | | | | | |

B: baseline, T: treatment phase, F: follow-up phase

# Figures

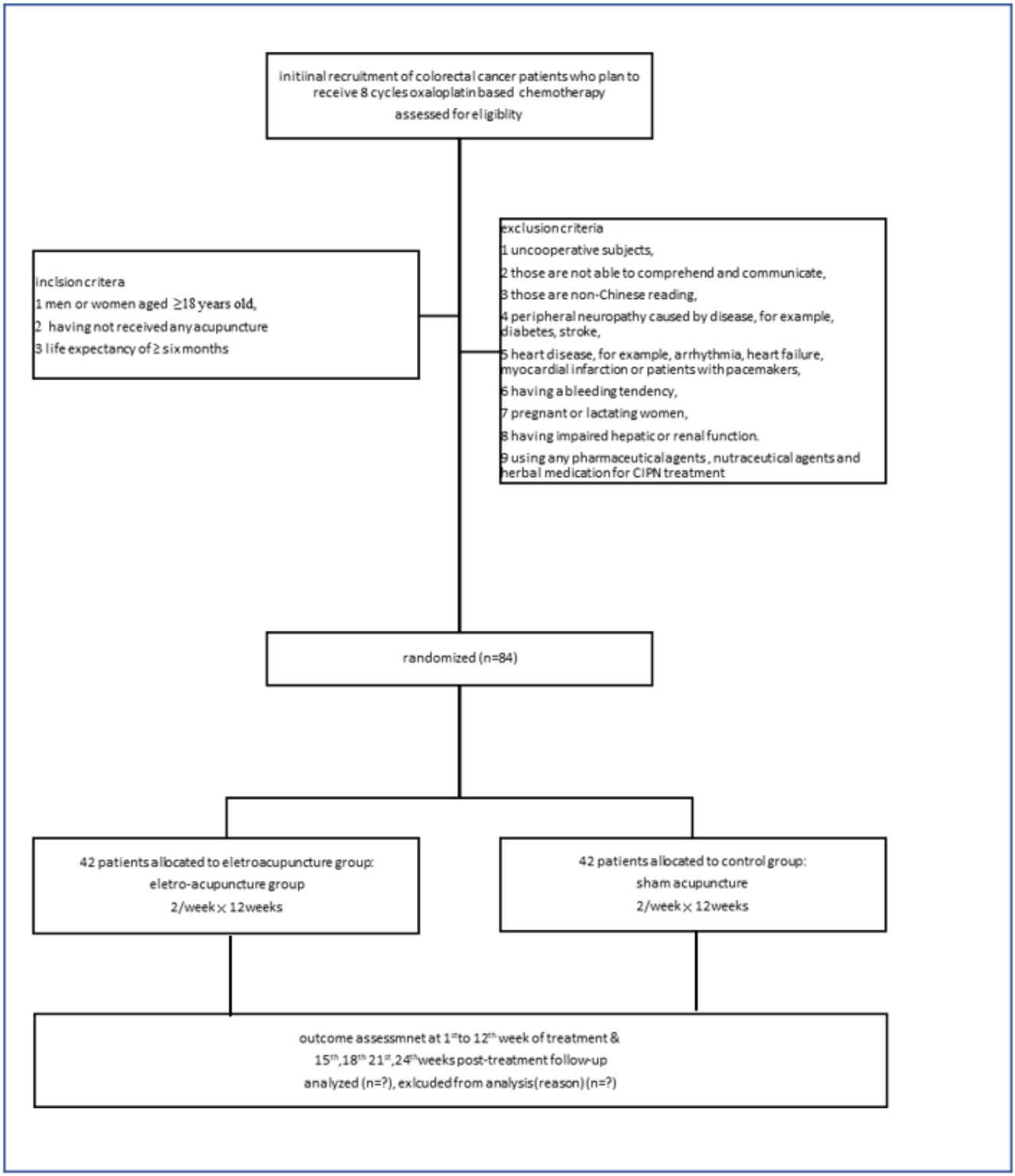


**Figure 1**

Participant flow diagram

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1checklistsforitemsinSTRICTA2010.pdf
- SignedContractYCHHKBU1363.pdf
- Appendix6informationsheetandconsentform.pdf
- Table2acupointsofeletroacupunctureandtheirlocation.pdf
- SPIRITChecklist.pdf
- Appendix4CCMQ.pdf
- Appendix2Numericalratingscale.pdf
- Appendix3QLQC30.pdf
- Appendix5Lighttouchtestandvibrationtest.pdf
- FR1804112101.pdf
- Appendix1FACTGOGNTX.pdf
- Table3scheduleforoutcomemeasurement.pdf