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Electroacupuncture use for treatment of taxane-induced peripheral neuropathy in patients with breast cancer: protocol for a pilot, randomised, blinded, sham-controlled trial (EA for CIPN)

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ABSTRACT

Introduction Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting side effect of neurotoxic chemotherapy. Acute symptoms of CIPN during treatment can lead to dose reduction and cessation. Trials using electroacupuncture (EA) to treat established CIPN postchemotherapy have shown some efficacy. The current trial aims to assess the feasibility and preliminary efficacy of using EA to treat CIPN during chemotherapy.

Methods and analysis The current study is a single-centre, 1:1 randomised, sham-controlled pilot study set in a tertiary cancer hospital in Sydney, Australia, and will recruit 40 adult patients with early breast cancer undergoing adjuvant or neoadjuvant paclitaxel chemotherapy. Patients who develop CIPN within the first 6 weeks of chemotherapy will receive either true EA or sham-EA once a week for 10 weeks. The coprimary endpoints are recruitment and adherence rate, successful blinding of patients and compliance with the follow-up period. Secondary endpoints are mean change of CIPN symptoms from randomisation to end of treatment, sustained change in CIPN symptoms at 8-week and 24-week follow-up postchemotherapy, proportion of subjects attaining completion of 12 weeks of chemotherapy without dose reduction or cessation, change in acupuncture expectancy response pretreatment, during treatment and posttreatment. The primary assessment tool for the secondary endpoints will be a validated patient-reported outcome measure (European Organisation for Research and Treatment of Cancer Quality of Life Chemotherapy-Induced Peripheral Neuropathy) captured weekly from randomisation to week 12 of chemotherapy.

Ethics and dissemination The study protocol (2021/ETH12123) has been approved by the institutional Human Research Ethics Committee at St Vincent's Hospital Sydney and Chris O'Brien Lifehouse. Informed consent will be obtained prior to starting study-related procedures. The results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number ACTRN12622000081718.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised and sham controlled with patient and assessor blinding, successful blinding of patients to be assessed.
⇒ Gold standard sham device will be used for the control group.
⇒ Six months follow-up to identify long-term effects of electroacupuncture.
⇒ As a pilot study, the current trial has a small sample size.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent dose-limiting side effect of neurotoxic chemotherapeutic agents including taxanes, platinum-based agents and vinca alkaloids. CIPN commonly produces sensory disturbances including paresthesia and dysesthesia in hands and feet, with a 'glove-and-stocking' distribution, less commonly affecting motor dysfunction in the areas of balance and gait.[1 2] The most common symptoms of sensory neuropathy include numbness and tingling, which occur more often than 'shooting/burning' neuropathic pain.[3 4] CIPN reduces treatment tolerability and is a common cause of dose modification, leading to reduction or premature cessation of chemotherapy treatment.[5] In addition, CIPN can also produce long-term functional deficits and reduced quality of life.[6] Although some patients experience improvement of CIPN symptoms once chemotherapy is completed,[7 8] approximately 30% of patients experience persistent CIPN ≥6 months postchemotherapy resulting in long-term disability.[8] In particular, a common survivorship issue identified in breast cancer patients receiving curative intent (neo)

adjuvant chemotherapy is long-term mild to severe sensory neuropathy that can be present for more than 5 years following the completion of chemotherapy.[9]

Rationale

The current proposed potential mechanisms associated with taxane-related CIPN include altered excitability of peripheral neurons[10] and immune system modulation/neuroinflammation,[11] as well as microtubule damage, axonal mitochondrial abnormalities and direct axonal toxicity at distal terminals.[2 11] Although there have been increasing research efforts to profile CIPN, there remains a gap in knowledge around optimal management.[12] The current standard of care relies on dose reduction or cessation, which are inadequate at addressing CIPN and increase the risk of mortality.[7]

With a lack of effective treatment options, there has been an increasing focus on non-pharmacological strategies. Electroacupuncture (EA) is a traditional Chinese medicine therapy used within integrative oncology as a non-pharmacological treatment option for oncology patients.[13] EA has a demonstrated safety profile,[14–16] with no potential for drug interaction with chemotherapy and limited risk for treatment side effects in oncology patients.[17 18] The intervention involves insertion of acupuncture needles at specific points, with electrical impulses administered at a specific frequency and intensity via the needles.[19]

The specific mechanism for EA is largely unknown; however, there is an increasing use in cancer care to manage various cancer pain syndromes, including CIPN, aromatase inhibitor-related arthralgia[20] and more generalised pain.[21] There are a range of documented effects on nerve function, and in animal models, EA has been shown to activate a range of nerve fibre types, including those involved in skin and muscle innervation.[22] Furthermore, as well as its potential antihyperalgesic effect, EA has been shown to mediate an anti-inflammatory action through the hypothalamus–pituitary–adrenal axis,[13] potentially exerting direct effects[23] on the nearby nerves and surrounding neural tissues.[24]

There have been a number of clinical studies and systematic reviews of the efficacy of acupuncture in people with CIPN.[14 25–29] Most studies assessed the efficacy of EA or acupuncture for CIPN in a postchemotherapy setting[16 30–34] where patients have well-established and persistent CIPN, usually 3 months or more after completion of chemotherapy. Notably, in the pilot randomised controlled trial (RCT) of women with CIPN postadjuvant taxane therapy for breast cancer, a significant reduction in CIPN sensory symptoms was seen after 8 weeks of EA.[30] Similar results were seen in a larger pragmatic trial conducted by Molassiotis *et al* where the assessor-blinded RCT showed a significant reduction of pain intensity and pain interference scores on the Brief Pain Inventory at the end of intervention and a significant improvement ($p<0.05$) of Total Neuropathy Score-Clinical Version.[35]

More recently, there have been a subset of studies looking at acupuncture use during chemotherapy to treat established CIPN.[15 36] In the single-arm phase IIA study, Bao *et al* investigated the use of acupuncture at onset of CIPN in women with breast cancer.[15] Findings of the study showed that 26 out of the 27 patients completed 12 cycles of paclitaxel treatment without developing grade III CIPN on the NCI-CTCAE clinical grading scale. These preliminary findings suggest that EA or acupuncture may be beneficial as an early intervention to improve the prognosis of CIPN. A similar outcome was seen in a larger RCT with 168 patients undergoing taxane therapy for breast or gynaecological cancers.[36] The trial showed significant improvement of sensory-based symptoms after 6 weeks of two-times-per-week acupuncture. However, the study did not provide treatment blinding with a sham group; instead, it incorporated a comparison arm that combined acupuncture with other touch and mind-body therapies.

Only one study investigated EA used during chemotherapy for its potential neuroprotective effects in paclitaxel-treated patients.[19] In the study by Greenlee *et al*, the use of EA did not show a protective effect to prevent CIPN and the EA group demonstrated worsening of pain symptoms compared with the sham group. However, while the study was a sham-controlled RCT, the findings of the study were restricted by a small sample size. Other studies have been limited by retrospective study design and lack of a control group[37 38] to show efficacy in prevention of CIPN.

Overall, there is consensus that more robust clinical trials are needed to investigate the efficacy of acupuncture in this setting. There are also substantial differences between studies in terms of inclusion and exclusion criteria, CIPN assessment tools, endpoints and duration of study. The current study aims to trial EA as an early intervention for the onset of CIPN during chemotherapy. The current pilot study addresses a key research concern in cancer care and survivorship as supported by numerous local and global collaborative efforts.[2 7 39] The current proposed study is aimed at addressing this gap by conducting an RCT pilot study of EA to assess its feasibility and acceptability in a comprehensive cancer care setting. A key feature of the study design is weekly screening for CIPN during chemotherapy, to allow early detection and timely EA intervention of CIPN while symptoms are low grade, with the aim to prevent worsening of symptoms.[8] Identification of an effective intervention to treat CIPN during paclitaxel chemotherapy would significantly reduce patient treatment burden and promote quality of life in patients exposed to neurotoxic chemotherapies.

METHODS AND ANALYSIS

The EA for CIPN trial is an Australian-based blinded, sham-controlled RCT. The primary aim is to determine the feasibility and acceptability of EA use in treating the onset of CIPN during paclitaxel chemotherapy in a randomised controlled setting. The secondary aim is to determine if

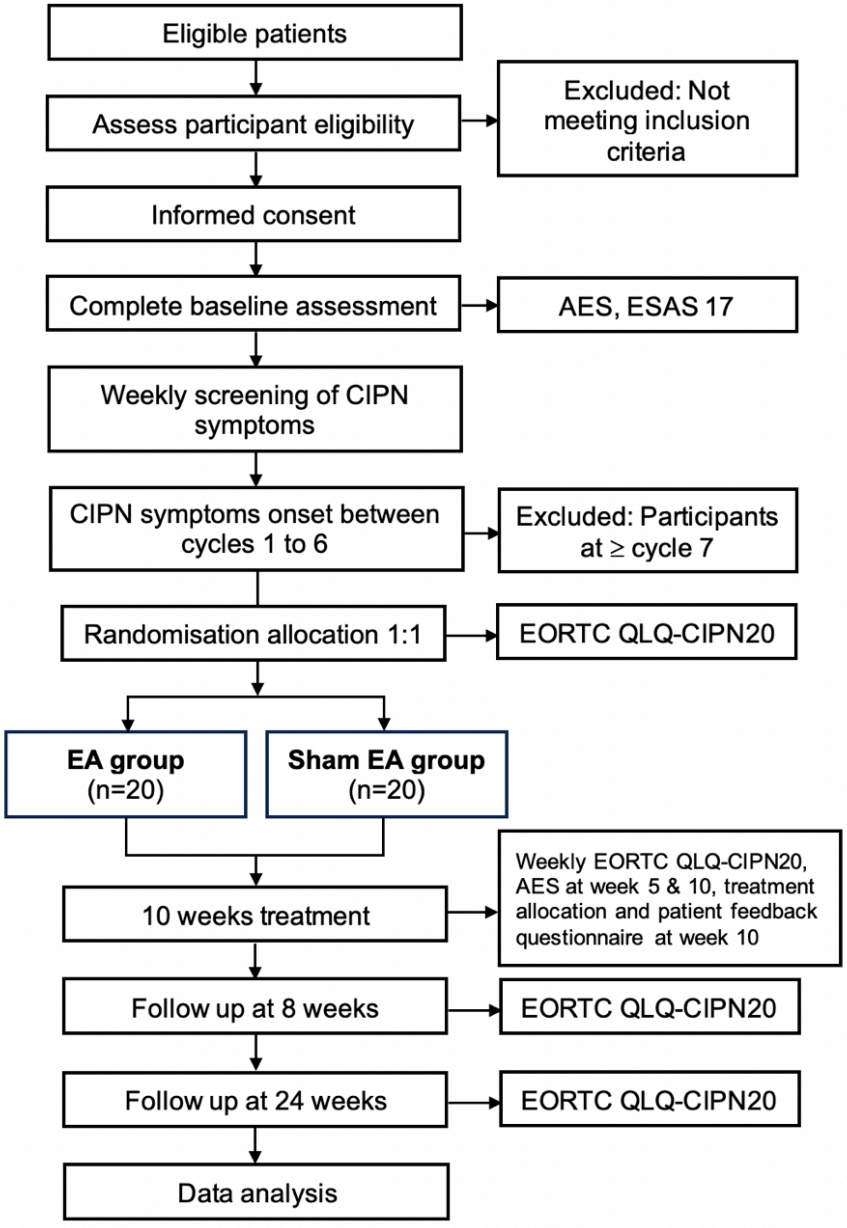

Figure 1 Study schema of EA for CIPN trial design. AES, Acupuncture Expectancy Scale; CIPN, chemotherapy-induced peripheral neuropathy; EA, Electroacupuncture, ESAS 17, Edmonton Symptom Assessment Scale 17, EORTC QLQ-CIPN20, European Organisation for Research and Treatment of Cancer Quality of Life Chemotherapy-Induced Peripheral Neuropathy 20.

EA shows preliminary effectiveness in reducing the extent of deterioration of CIPN from symptom onset during paclitaxel with sustained benefit postchemotherapy.

Trial design

The protocol is a pilot phase II, participant and assessor blinded, randomised, sham-controlled, two-armed, parallel-group study with a sample size of 40 patients, 20 patients in each arm (figure 1). The pilot trial will be conducted at a single site, Chris O'Brien Lifehouse cancer hospital in Sydney, Australia. The reporting of this trial protocol has been in line with the Standards for Reporting Interventions in Clinical Trials of Acupuncture.[40]

Inclusion criteria

Patients who fulfil the following characteristics will be considered eligible for enrolment:

- Age ≥18 years.
- Stages I–III breast cancer.
- Scheduled to receive weekly adjuvant or neoadjuvant paclitaxel chemotherapy.

To be randomised to a treatment group, patients must qualify the following characteristics:

- Received ≥1 and ≤6 doses of paclitaxel chemotherapy.[11]
- Patients scoring ≥1 on the Edmonton Symptom Assessment Scale 17 (ESAS 17)[41] for the 'numbness and tingling' item.

- New onset of symptoms consistent with CIPN reported by a validated tool for screening CIPN symptoms.
- Completed European Organisation for Research and Treatment of Cancer Quality of Life Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20).[42]
- Adequate haematological function: neutrophil count >1.0×10^9/L, platelet count >50×10^9/L.

Exclusion criteria

Patients with the following characteristics will be excluded from the study enrolment:

- Prior use of acupuncture for CIPN on more than one occasion within 6 months prior to commencement of the study.
- Peripheral neuropathy due to a pre-existing condition prior to chemotherapy (eg, including alcoholism, diabetes, congenital neuropathy, toxic neuropathy, nerve compression or injury, neuroma).
- Presentation of autonomic-related CIPN symptoms.

Randomisation, allocation concealment and participant and assessor blinding

Eligible patients will be assigned to either EA or sham-EA group with a 1:1 allocation rate as per computer-generated randomisation scheduled using random permuted block sizes. The study participants will be blinded to group allocation until the end of the study, after the final assessments (8-week and 24-week follow-up) have been completed. The acupuncturist applying the treatment will be partially blinded; they will only know what treatment to provide once they receive an opaque, sealed envelope indicating either active or sham treatment at the time of intervention. Complete blinding for acupuncture treatment is not possible. The outcome assessor and data analyst are blinded as they will only receive data once it has been deidentified and coded. The data are collected electronically via an automated weekly text message that delivers a URL for the patient to select and complete. These data are held in our data management system.

Study objectives

The primary objective of this study is to assess feasibility and acceptability of EA use for treatment of CIPN during 12 weeks of paclitaxel chemotherapy in a randomised controlled setting. Feasibility and acceptability will be determined by recruitment rate, the number of participants recruited per month; adherence rate, the proportion of participants who complete ≥7 out of 10 study interventions; successful blinding of patients, the proportion of participants who correctly identify the intervention received (ie, EA or sham-EA at final (10th) treatment, and compliance with follow-up, the proportion of participants that are followed up at 8-week and 24-week postchemotherapy (figure 1).

The secondary objectives are to compare among participants randomised to EA or sham-EA (table 1).

Preliminary efficacy

Table 1 Schedule of enrolment, treatments and assessments

	Enrolment and baseline	CIPN Screening	Randomisation	Intervention period	Follow-up period week 8	Follow-up period week 24
Time point	**–t_1**	**Weekly at infusion (0)**	**After CIPN symptom onset (0)**	**Weekly for 10 weeks (t_1 – t_{10})**	**t_{10}+8 w (± 2 weeks)**	**t_{10}+24 w (± 2 weeks)**
Enrolment:						
Eligibility screen	X					
Informed consent	X					
Allocation			X			
Interventions:						
Electroacupuncture				X		
Sham-electroacupuncture				X		
Assessments:						
ESAS 17	X	X				
EORTC QLQ-CIPN20			X	X	X	X
Patient feedback form				X (t_{10})		
AES	X			X (t_5 + t_{10})		
Concomitant CIPN treatments			X	X	X	X

AES, Acupuncture Expectancy Scale; CIPN, chemotherapy-induced peripheral neuropathy; EA, electroacupuncture; EORTC QLQ-CIPN20, European Organisation for Research and Treatment of Cancer Quality of Life Chemotherapy-Induced Peripheral Neuropathy 20; ESAS 17, Edmonton Symptom Assessment Scale 17; X, required.

- Change in CIPN symptoms (from randomisation to end of 12 weeks of paclitaxel chemotherapy) as measured by summary scores of EORTC QLQ-CIPN20.
- Sustained change in CIPN symptoms at 8 weeks and 24 weeks follow-up as measured by summary scores of EORTC QLQ CIPN20.
- Number of CIPN-related dose modifications or delays by final scheduled paclitaxel chemotherapy.
- Change in acupuncture response expectancy (Acupuncture Expectancy Scale (AES)) from before 1st, at 5th (midpoint) and 10th (end) intervention session.

EA-related adverse events (AEs)

- Proportion of participants with unexpected EA-related AEs at any point during the intervention.

Outcome measures

Clinical characteristics

Comorbidity, body mass index (BMI), level of exercise and history of smoking and alcohol consumption will be ascertained from the participant and medical records. Any concomitant CIPN treatment provided to patients during the trial intervention period will be permitted and recorded.

European Organisation for Research and Treatment of Cancer Quality of Life Chemotherapy-Induced Peripheral Neuropathy 20

The EORTC QLQ-CIPN20 is a validated patient-reported outcome measure (PROM) to measure peripheral neuropathy[42] and will serve as the main CIPN assessment tool for the current study. It is a 20-item questionnaire that assesses sensory, motor and autonomic CIPN and it is scored using a 4-point Likert-type scale ranging from 1 to 4. The total score ranges from 20 to 80 and is converted to a 0–100 scale, where higher scores indicate worse CIPN.[43 44] Participants will be asked to complete the EORTC QLQ-CIPN20 once weekly, from randomisation until week 12 of paclitaxel (refer figure 1).

Edmonton Symptom Assessment Scale 17

The ESAS 17 is a validated and widely used PROM in the acute cancer and supportive and palliative care setting to measure the severity of symptom burden.[41] The measure consists of an 11-point Numeric Rating Scale, scores ranging from 0 to 10 for each item, where higher scores represent worse symptom intensity. For the current study, the ESAS may be used as a screening tool for CIPN symptoms during paclitaxel treatment for 'numbness and tingling' item score.

Acupuncture Expectancy Scale

The AES is a four-item questionnaire that has been validated and used to measure the potential role of expectancy in acupuncture treatments.[45] This is important as patients' expectations can be a major contributor to change in symptoms[46] and, therefore, should be accounted for. The questionnaire asks for the subjects' expectation of the effect the acupuncture treatment will have on their symptom/illness after the entire course of acupuncture therapy. The subjects are then expected to rate 1–5 on a 5-point Likert scale, with a possible score between 4 and 20, where higher scores indicate greater expectancy.[45]

Patient feedback form (treatment allocation question and acceptability of intervention)

To assess the effective blinding of participants of true or sham EA, the participants will be asked to identify which treatment they believe they were given,[47 48] 'based on your experience, which study treatment do you believe that you were provided with: (a) EA, (b) sham-EA and (c) don't know.' The participants will also be given a short implementation outcome measure 'acceptability of intervention measure', as developed by Weiner *et al*[49] to determine the acceptability of intervention.

Investigational intervention

The study intervention consists of EA or sham-EA which will be administered once a week over 10 weeks, with a total of 10 treatments for each participant (t_1–t_{10}) (table 1). Participants will be randomised into an intervention arm at CIPN symptom onset and have received ≤6 doses of paclitaxel chemotherapy; participants beyond this time point will be ineligible for randomisation (figure 1). A participant will not be excluded from the study if any EA or sham-EA treatment sessions are missed throughout the ten weeks of the intervention period; the absences will be considered an outcome of non-adherence. The intervention will be carried out 24–48 hours prior to the participants' scheduled paclitaxel infusion. The interventions will be administered onsite at Chris O'Brien Lifehouse in an outpatient clinical setting by a registered acupuncturist with over 5 years' experience, who is trained according to the clinical protocol set out by PI Choi. Any unexpected AEs related to the intervention will be recorded throughout the study and any concomitant CIPN treatments the participant received during the intervention will be recorded weekly.

The participants will receive EA or sham-EA at the following locations: upper limb acupoints: LI4, TE6, Baxie (M-UE-22) and lower limb acupoints: ST36, LR3, Bafeng (M-LE-8). The acupuncture needles will be inserted into acupoints as per the locations identified in the Systematic Classics of Acupuncture and Moxibustion Acupuncture[50] and A Manual of Acupuncture[51] with no manual stimulation or elicitation of de qi. The needles will be in situ for 15 min, with the duration of each appointment lasting 45 min. For the duration of the treatment, the patients will also be blindfolded to add another level of blinding.[52]

Electroacupuncture

The needles in the webs of the toes and fingers will be inserted to the depth of between 5 and 10 mm at Baxie and Bafeng acupoints and 10–13 mm at the remaining acupoints. Single-use disposable stainless steel Dongbang needles (0.20×15 mm) will be used. Leads from the EA machine (ITO, 143609 Acuneeds Australia—stimulator,

electrical, acupuncture) will be placed on the points Baxie and Bafeng. The electrostimulation will be delivered at a low frequency (2 Hz) on a dispersed continuous setting with moderate intensity. Once the treatment has been administered, the needles will be removed and disposed into a sharps-bin.

Sham-EA

The frequency and duration of the intervention will be the same as the active EA group. The participants will receive sham-EA at the same acupoints as the active group. The sham-acupuncture will be a non-penetrative method where a specialised device called a 'Streitberger needle' will be used to elicit a similar sensation only on the surface of the skin.[53] Leads from the EA device will be attached to the sham device at prescribed acupoints with no electrostimulation administered. To allow the treatment to appear realistic, the machine will be turned on and the machine will sound a beeping noise while switched on; however, the leads will be connected to a terminal without stimulation. The sham-EA will be applied over true acupoints without manual or electrical stimulation, as this was shown to be an adequate sham-control intervention.[13] The practitioner will also wipe the needle sites as the needles are removed with either a clean gauze or tissue, to ensure blinding.[54] Unblinding of participants will only occur if there is a concern for participants' safety and the issue has been investigated and assessed by the trial management committee.

Recruitment and consent

Patient screening and enrolment will take place at Chris O'Brien Lifehouse and will be overseen and performed by the principal investigator. To achieve targeted trial sample size of n=40, the sample size for the recruitment and weekly screening period is estimated at n=90, if only approximately 50% of the enrolled patients develop CIPN. Potential participants will be identified and prescreened by clinicians (medical and day therapy nursing staff) based on patients' age (ie, ≥18 years old), cancer diagnosis (ie, stages I–III breast cancer), treatment plan (ie, adjuvant or neoadjuvant) and no pre-existing peripheral neuropathy. Recruitment and screening of participants will be during doxorubicin and cyclophosphamide treatment (four cycles), prior to start of paclitaxel to allow baseline measures. A screening log will document all eligible patients screened. Patients' informed consent will be collected electronically prior to study enrolment (refer online supplemental material 1 for participant information sheet and consent form).

Data acquisition

Patients will complete assessments electronically using Qualtrics, a secure data management programme. Trial data will be recorded on electronic case report forms also using Qualtrics. Once patients have been randomised, there will be weekly assessments of patients at their allocated EA or sham-EA treatments of whether any concomitant CIPN treatments have been provided outside of the study and if there were any AEs related to the study intervention.

Statistical considerations

Sample size estimation

As this is a phase II pilot study, the sample size calculation was based on the detection of an effect size of 0.8 ('large effect size') in any of the continuous measures. The results obtained from this study will inform targeted sample size calculations in a future prospective trial. Using a two-sample t-test and assuming equal numbers in EA and sham-EA groups, and equal variances in the groups, a total of 40 participants (20 per treatment arm) will provide 80% power at a two-sided significance level of 5%, allowing 20% drop-out rate, to detect a 'large' change in a continuous outcome measure.

Statistical analysis

- The statistical analysis will be performed by a qualified biostatistician who will be blinded to the group allocation. Subjects will be analysed according to the intention-to-treat principle.
- Demographic characteristics and baseline scores: Continuous variables will be summarised as mean (SD), and also as medians (quartiles), because of the small sample size; counts with percentages will be presented for categorical variables.
- The primary endpoints will be summarised as counts (percentages) by treatment group.
- The main CIPN assessment will be the change in EORTC QLQ-CIPN20 score from baseline to end of treatment (t_{10}). The mean change in each treatment group will be summarised as mean (SD) and compared using a nonparametric test (Mann-Whitney).
- Secondary outcomes will be summarised as mean (SD) by treatment group at each time point of interest. Generalised estimating equations will be used to assess the effect of treatment over time, from baseline to end of intervention, and 8-week and 24-week follow-ups. Covariables of interest will include age, gender and BMI.
- Results will be presented with 95% CIs and p value. No interim analysis will be carried out for this study.
- The primary analysis will be on a complete case basis. If there are missing data values, multiple imputation will be used to provide a sensitivity analysis.

Patient and public involvement

The current study was presented at multiple concept workshops during the development phase, where the Chris O'Brien Lifehouse consumer advisory panel was involved. Patient advocates had the opportunity to provide feedback openly in these settings. General feedback regarding the burden of intervention and respondent fatigue of participants were considerations that were incorporated in the study design to minimise their impact. Overall study results will be made available to the general

public via the institutional website in consultation with the Chris O'Brien Lifehouse consumer advisory panel. Participants of the study may also choose to be contacted with the outcomes of the study.

ETHICS AND DISSEMINATION

The study protocol (2021/ETH12123) has been approved by the institutional Human Research Ethics Committee (HREC) at St Vincent's Hospital Sydney and Chris O'Brien Lifehouse. The study protocol has also been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000081718) in accordance with WHO International Standards for Clinical Trial Registration.

The study will be conducted according to the Note for Guidance on Good Clinical Practice and the Consolidated Standards of Reporting Trials (CONSORT) statement. Informed consent will be obtained in accordance with the Declaration of Helsinki, and local standard operating procedures/regulation prior to starting any study-related procedures including screening.

Study findings will be submitted for publication in a peer-reviewed journal as well as presented at national and international conference presentations, annual institutional reports and media. The participants and general public will have access to a consumer-friendly version of the study findings. The results of the project will be presented as group data, individual data will not be available.

Trial oversight and monitoring

The EA for CIPN trial is a single-site trial and the study sponsor is Chris O'Brien Lifehouse. The Chris O'Brien Lifehouse will be responsible for coordination, monitoring, site audits, management, data acquisition and statistical analysis. A trial management committee meets regularly (at least every 6 months) to monitor AEs, recruitment and interventions. All data (including personal data) obtained will be treated as confidential. The personal data will be stored at each study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorised study staff have access. Audits of the data collected will take place quarterly or if there is a breach in set collection and storage protocols or if there is suspected error by any of the study investigators involved. Any protocol amendments must be approved by the institutional HREC prior to implementation.

Data on AEs expected with taxane chemotherapy will not be collected in this study; however, any unexpected AEs or serious AEs (SAEs) will be recorded and any urgent safety matters will be escalated and reported to the Research Governance Office at Chris O'Brien Lifehouse and HREC within 24 hours of identification. For all AE or SAE reported, investigators will determine relatedness of an event to study intervention based on a temporal relationship to the study intervention, as well as whether the event is unexpected or unexplained given the participant's clinical course, previous medical conditions and concomitant medications. Study intervention-related AE or SAE data collected will be reported with the findings of the study.

Trial status

Patient enrolment for this pilot study commenced in May 2022 at the Chris O'Brien Lifehouse in NSW, Australia. To date, 47 patients have been enrolled, with the anticipated pilot study enrolment completion by December 2023.

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Chris O'Brien Lifehouse

Title	Pilot randomised sham-controlled trial of electroacupuncture for taxane-induced peripheral neuropathy in breast cancer patients during treatment.
Short Title	Electroacupuncture for taxane-induced peripheral neuropathy
Protocol Number	2.0
Project Sponsor	Chris O'Brien Lifehouse Surfebruary Cancer Research Fund.
Coordinating Principal Investigator/ Principal Investigator	Dr Victoria Choi
Location	Chris O'Brien Lifehouse

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you may be at risk of developing chemotherapy-induced peripheral neuropathy (CIPN) during your chemotherapy treatments. The research project is testing a new treatment for CIPN using a new treatment called electroacupuncture.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Single-use acupuncture needles and electromachines are approved in Australia to treat to perform electroacupuncture.

The purpose of this research is to test the use of electroacupuncture to treat early symptoms of chemotherapy-induced peripheral neuropathy during chemotherapy (CIPN). Up to 68% people receiving chemotherapy may develop CIPN within the first month of treatment and currently there are limited treatment options for CIPN. Electroacupuncture is a safe and non-pharmacological treatment that can potentially help treat CIPN symptoms.

This research has been initiated by the Principal Investigator, Dr Victoria choi and it is supported by Chris O'Brien Lifehouse Surfebruary Cancer Research Fund

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). You will have a one in two chance of receiving the investigational treatment.
This is a blind study which means that in a blind study you do not know which of the treatments you are receiving. However, your study practitioner will know which treatment you are receiving.

The study will include a placebo treatment, a placebo is a medication with no active ingredients or a procedure without any medical benefit, it looks like the real thing but is not.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. All intervention and testings required as part of the research project will be provided to you free of charge.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project. Here are the main steps to the study:

I. Informed consent and eligibility screening

Agreeing to participate in the study
When you have read this information, you will have the opportunity to discuss further any questions you may have about the study with a designated study team member, and they will answer any questions you may have.

Any procedures required by the trial will only take place after you have signed the consent form.

Screening for eligibility and enrolment

i. Pre-screening

To qualify for the study, you must meet the follow criteria:

- You are older than 18 years old
- You have been diagnosed with stage I-III breast cancer
- You are scheduled to receive weekly adjuvant or neoadjuvant paclitaxel treatments
- You have no pre-existing peripheral neuropathy

Pre-screening takes place to evaluate general suitability of the study for you, this may stake place prior to you consenting to the study.

ii. Screening

Screening will take place once you have consented to participating in the study, to ensure that the study is suitable for you. The study team will take a detailed history of your health and drawn some information from your medical records. The procedures involved at this stage will include:

Procedure	*Details*
Demographic data	The study team will record your date of birth, gender, race, ethnicity, previous acupuncture experience
Clinical data	The study team will also record any comorbidities, body mass index, smoking history, alcohol history
Symptom questionnaire	Part of the screening process will involve you completing a questionnaire called the Edmonton Symptom Assessment Scale 17 (ESAS 17), to assess if you have any pre-existing peripheral neuropathy. The questionnaire consists of 17 questions, and it will require you to score your symptoms out of 10.

iii. Enrolment

Once you have met the pre-screening and screening eligibility criteria and have provided informed consent, you will be enrolled into the study.

II. Weekly symptom screening (screening and randomisation)

Weekly screening of CIPN

Once you have consented and have been enrolled in the study, you will progress to the symptoms screening part of the study. Weekly screening will take place once you have started you taxane (i.e., paclitaxel) chemotherapy treatment. Prior to or at your chemotherapy infusion appointment at Day Therapy, you will be asked to complete a short questionnaire to score your chemotherapy-induced peripheral neuropathy (CIPN) related symptoms. The weekly screening will take place from first 1st chemotherapy to your 6th, if you develop any CIPN, you will then progress to the intervention phase of the study. If no CIPN is present by your 6th chemotherapy you will not be allocated to an intervention.

Randomisation

If you develop CIPN between the 1st and 6th chemotherapy infusions, you will be asked to complete a longer questionnaire called the European Organization for Research and Treatment of Cancer Qualify of Life Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20). The questionnaire consists of 20 questions regarding peripheral neuropathy. Once this questionnaire is completed you will be randomly assigned to one of two groups to receive either electroacupuncture or sham-electroacupuncture.

III. Treatment procedures

The treatments consist of either electroacupuncture or sham-electroacupuncture, what treatment you receive will depend on what group you are randomly allocated to. You will receive 10 weekly treatments a day or two before your scheduled chemotherapy infusion. The treatment involves receiving acupuncture around your hands, forearms, feet, and lower legs. Once the acupuncture needles have been placed, the electrodes from the electromachine will be attached to the needles to provide stimulation. This procedure is painless and typically does not cause

any discomfort, however, if you feel pain or unbearable discomfort you should notify your practitioner immediately. Each appointment will take approximately 45 minutes, the treatment itself will take 15-20 minutes.

Before every treatment you will be asked to complete the EORTC QLQ-CIPN20 questionnaire, to provide weekly measurement of your peripheral neuropathy symptoms.

IV. Follow-up

8 weeks post-chemotherapy
Once you have finished your chemotherapy treatments, we will follow up with you 8 weeks later to ask you to complete the EORTC QLQ-CIPN20 questionnaire. No treatments related to the study will be provided at this appointment. This appointment may be in person or over the phone.

24 weeks post-chemotherapy
We would like to follow up with you again at 24 weeks after finishing chemotherapy. At this appointment, we would like to ask you to complete the EORTC QLQ-CIPN20 questionnaire.

Following up with you at these timepoints helps us understand how the study treatments you received are potentially benefiting you after finishing chemotherapy.

4 What do I have to do?

If you choose to take part in the study, there are no restrictions around lifestyle or medication. You are allowed to receive standard care and regular medications. You will not be able to participate if:

- You are under 18 years old
- You have a cancer diagnosis other than breast cancer
- You are scheduled to receive chemotherapy that does not include taxane-based chemotherapy
- You have used acupuncture for chemotherapy-induced peripheral neuropathy on more than one occasion within 6 months before the start of this current study
- You have peripheral neuropathy due to a pre-existing condition prior to chemotherapy (including but not limited to e.g., alcoholism, diabetic, congenital neuropathy, toxic neuropathy, nerve compression or injury neuroma)
- You have autonomic related chemotherapy-induced peripheral neuropathy

5 Other relevant information about the research project

This study is a single site study, where the entirety of this study will be conducted at Chris O'Brien Lifehouse (Camperdown). The study is aiming to recruit 90 participants at Chris O'Brien Lifehouse, to be part of the screening process and a total number of 40 people will take part in the intervention part of the study.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Chris O'Brien Lifehouse.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include anti-pain medications, exercise, massage, and reflexology. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include improvement of potential chemotherapy-induced peripheral neuropathy symptoms. The findings from the study will also help inform further research in this area, as well as guide clinical practice.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study practitioner. Your study practitioner will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study practitioner immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study practitioner may need to stop your treatment. Your study practitioner will discuss the best way of managing any side effects with you.

Potential common side effects of electroacupuncture:

- Minor pain during acupuncture insertion (common*);
- Some tenderness or mild discomfort during needle retention (common*);
- Bruising and tenderness at the place of needle insertion (common*);
- Mild dizziness or fainting after the first treatment (rare**);
- Stuck or bent needle (very rare***);
- Headache or drowsiness after treatment (very rare***).

*Common = greater than 1 in every 100 people may experience the side effect
**Rare = greater than 1 in every 10,000 people may experience the side effect
***Very rare = less than 1 in every 10,000 may experience the side effect

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

Whilst you are participating in this research project, you will be able to continue any medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

12 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the Principal Investigator and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results.

13 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing
- Decisions made by local regulatory/health authorities.

14 What happens when the research project ends?

Once the treatment from the study has ended, you may wish to continue the treatment. Acupuncture is widely available and can be accessed at the Livingroom at Chris O'Brien Lifehouse, however, the service will be at a cost to you as it is an outpatient private service.

At the end of the study, you have the option to be contacted by the study staff regarding the result of the study. If you wish, the study staff can email or call you regarding the outcome of the study. The study outcomes will also be made available for the general public via the Chris O'Brien Lifehouse website.

Part 2 How is the research project being conducted?

15 What will happen to information about me?

By signing the consent form you consent to the Principal Investigator and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Any identified data collected for the duration of the study will be stored either in a locked cabinet

and/or on a secure network, where access will be limited to the Principal Investigator and relevant research staff. This data will be kept for 5 years in a locked cabinet and/or secure network from time of study completion and access will be limited to the Principal Investigator.

Your information will only be used for the purpose of this research project, and it will only be disclosed with your permission, except as required by law. Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Chris O'Brien Lifehouse Surfebruary research fund, the institution relevant to this Participant Information Sheet, Chris O'Brien Lifehouse, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

In accordance with relevant Australian and/or NSW privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in Section 16 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

16 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

17 Who is organising and funding the research?

This research project is being conducted by Dr Victoria Choi, which is sponsored by Chris O'Brien Lifehouse.

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of St. Vincent's Hospital Sydney.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the Principal Investigator or any of the following people:

Clinical contact person

Name	Dr Victoria Choi
Position	Principal Investigator
Telephone	0466 807 734
Email	Victoria.choi@lh.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Dr Victoria Choi
Position	Principal Investigator
Telephone	0466 807 734
Email	Victoria.choi@lh.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details
This study has been reviewed by the St Vincent's Hospital Sydney Human Research Ethics Committee. If there are any concerns or complaints about the conduct of this study you can contact the Research Office, 97-105 Boundary Street, Darlinghurst NSW 2010, website: https://www.svhs.org.au/research-education/research-office/contact-us

Local HREC Office contact (Single Site -Research Governance Officer)

Name	St Vincent's Hospital HREC
Position	Research Office Manager
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

Choi V, *et al*. *BMJ Open* 2024; 14:e076391. doi: 10.1136/bmjopen-2023-076391

PARTICIPANT CONSENT FORM

Title	Pilot randomised sham-controlled trial of electroacupuncture for taxane-induced peripheral neuropathy in breast cancer patients during treatment.
Short Title	Electroacupuncture for taxane-induced peripheral neuropathy
Protocol Number	1.0
Project Sponsor	Chris O'Brien Lifehouse Surfebruary Cancer Research Fund.
Coordinating Principal Investigator/ Principal Investigator	Dr Victoria Choi
Location	Chris O'Brien Lifehouse

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand. I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Chris O'Brien Lifehouse concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Principal Investigator/Senior Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Principal Investigator/ Senior Researcher† (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.† A senior member of the research team must provide the explanation of and information concerning the research project.

WITHDRAWAL OF PARTICIPATION FORM

Title	Pilot randomised sham-controlled trial of electroacupuncture for taxane-induced peripheral neuropathy in breast cancer patients during treatment.
Short Title	Electroacupuncture for taxane-induced peripheral neuropathy
Protocol Number	1.0
Project Sponsor	Chris O'Brien Lifehouse Surfebruary Cancer Research Fund.
Coordinating Principal Investigator/ Principal Investigator	Dr Victoria Choi
Location	Chris O'Brien Lifehouse

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Chris O'Brien Lifehouse.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Principal Investigator/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.