


# BMJ Open 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.<sup>1 2</sup> The most common symptoms of sensory neuropathy include numbness and tingling, which occur more often than 'shooting/burning' neuropathic pain.<sup>3 4</sup> CIPN reduces treatment tolerability and is a common cause of dose modification, leading to reduction or premature cessation of chemotherapy treatment.<sup>5</sup> In addition, CIPN can also produce long-term functional deficits and reduced quality of life.<sup>6</sup> Although some patients experience improvement of CIPN symptoms once chemotherapy is completed,<sup>7 8</sup> approximately 30% of patients experience persistent CIPN ≥6 months postchemotherapy resulting in long-term disability.<sup>8</sup> 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.<sup>9</sup>

### Rationale

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

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.<sup>13</sup> EA has a demonstrated safety profile,<sup>14–16</sup> with no potential for drug interaction with chemotherapy and limited risk for treatment side effects in oncology patients.<sup>17 18</sup> The intervention involves insertion of acupuncture needles at specific points, with electrical impulses administered at a specific frequency and intensity via the needles.<sup>19</sup>

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<sup>20</sup> and more generalised pain.<sup>21</sup> 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.<sup>22</sup> Furthermore, as well as its potential antihyperalgesic effect, EA has been shown to mediate an anti-inflammatory action through the hypothalamus–pituitary–adrenal axis,<sup>13</sup> potentially exerting direct effects<sup>23</sup> on the nearby nerves and surrounding neural tissues.<sup>24</sup>

There have been a number of clinical studies and systematic reviews of the efficacy of acupuncture in people with CIPN.<sup>14 25–29</sup> Most studies assessed the efficacy of EA or acupuncture for CIPN in a postchemotherapy setting<sup>16 30–34</sup> 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.<sup>30</sup> 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.<sup>35</sup>

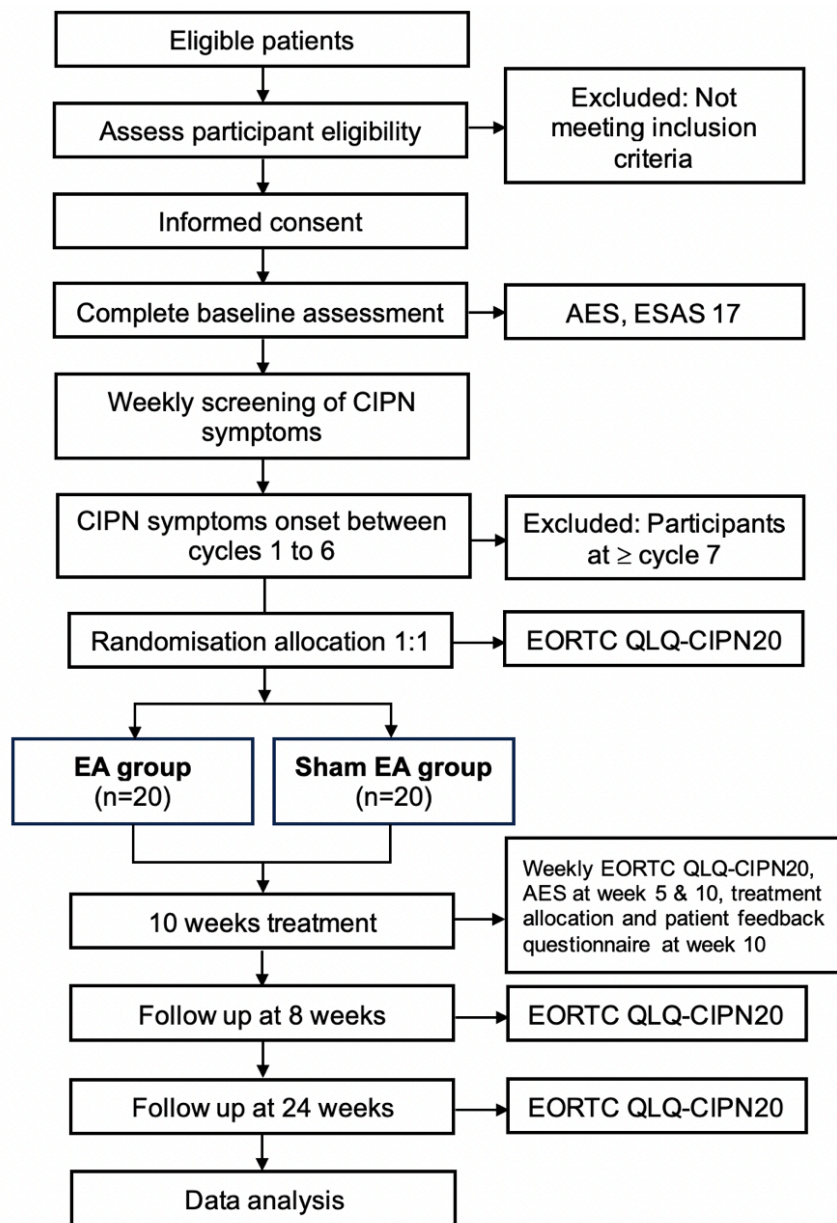
More recently, there have been a subset of studies looking at acupuncture use during chemotherapy to treat established CIPN.<sup>15 36</sup> In the single-arm phase IIA study, Bao *et al* investigated the use of acupuncture at onset of CIPN in women with breast cancer.<sup>15</sup> Findings of the study 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.<sup>36</sup> 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.<sup>19</sup> 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<sup>37 38</sup> 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.<sup>2 7 39</sup> 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.<sup>8</sup> 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 Lifecare 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.<sup>40</sup>

### Inclusion criteria

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

- ▶ Age  $\geq 18$  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  $\geq 1$  and  $\leq 6$  doses of paclitaxel chemotherapy.<sup>11</sup>
- ▶ Patients scoring  $\geq 1$  on the Edmonton Symptom Assessment Scale 17 (ESAS 17)<sup>41</sup> 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).<sup>42</sup>
- ▶ Adequate haematological function: neutrophil count  $>1.0 \times 10^9/L$ , platelet count  $>50 \times 10^9/L$ .

### 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  $\geq 7$  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 ( $t_1 - t_{10}$ )	$t_{10}+8w$ ( $\pm 2$ weeks)	$t_{10}+24w$ ( $\pm 2$ 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<sup>42</sup> 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.<sup>43 44</sup> 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.<sup>41</sup> 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.<sup>45</sup> This is important as patients’ expectations can be a major contributor to change in symptoms<sup>46</sup> 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.<sup>45</sup>

### 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,<sup>47 48</sup> ‘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*<sup>49</sup> 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  $\leq 6$  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*<sup>50</sup> and *A Manual of Acupuncture*<sup>51</sup> 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.<sup>52</sup>

### 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 (2Hz) 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.<sup>53</sup> 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.<sup>13</sup> The practitioner will also wipe the needle sites as the needles are removed with either a clean gauze or tissue, to ensure blinding.<sup>54</sup> 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,  $\geq 18$  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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