



A randomised, pragmatic clinical trial of ACUpuncture plus standard care versus standard care alone FOR Chemotherapy Induced peripheral Neuropathy (ACUFOCIN)

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ABSTRACT

Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose limiting toxicity posing a major clinical challenge for managing patients receiving specific chemotherapy regimens (e.g., Taxanes). There is a growing body of literature suggesting acupuncture can improve CIPN symptoms. The purpose of the ACUFOCIN trial was to collect preliminary data on the safety, feasibility, acceptability and initial effectiveness of acupuncture as a treatment for CIPN, comparing use of acupuncture plus standard care (Acupuncture) against standard care alone (Control).

Method: At a tertiary cancer centre, a pragmatic, randomised, parallel group design study was used to investigate the effectiveness of a 10-week course of acupuncture. Participants experiencing CIPN of \geq Grade II, recording a 'Most Troublesome' CIPN symptom score of ≥ 3 using the "Measure Yourself Medical Outcome Profile" (MYMOP 2), were randomised to 'Acupuncture' or 'Control' arms. Clinicians were blinded to allocated groups, however as it was not possible to blind participants, it cannot be guaranteed they did not disclose study allocation within their clinic assessments. The primary outcome measure was the number of patients reporting a ≥ 2 -point improvement (success) in their MYMOP2 score at week 10. 100 participants (120 to allow for attrition) were required for a hypothesised improvement in success proportions from 30% to 55% using a primary analysis model with logistic regression adjusted for stratification factors and baseline MYMOP2 scores. Feasibility and acceptability of study design was addressed through percentage return of primary outcome, retention rate and a nested qualitative study.

Results: Primary MYMOP2 outcome data at week 10 was available for 108/120 randomised participants; this is greater than the 100 participants required to adequately power the study. There were 36/53 (68%) successes in 'Acupuncture' compared to 18/55 (33%) in 'Control'. Beneficial effects were seen in the secondary outcome data, including clinicians' grading of neuropathy, EORTC, QLQ-CIPN20, QLQ-C30 summary scores and patient reported pain scores. There were no serious adverse events reported within the study and only 16 acupuncture associated events, none of which required intervention.

Conclusion: A 10-week course of acupuncture resulted in measurable improvement in participants symptoms of CIPN. The results warrant further investigation.

1. Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a common,

dose-limiting and debilitating side-effect for patients receiving systemic anti-cancer therapy drugs including taxanes, (especially paclitaxel), platinum-based drugs (e.g., oxaliplatin) thalidomide and bortezomib

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(Molassiotis et al., 2019a). Symptoms include pain, paraesthesia and loss of proprioception, all having a detrimental effect on patients' quality of life by affecting gait, mobility and by limiting the ability to perform activities of daily living such as buttoning a shirt or tying a shoelace. Persistent CIPN is associated with poor physical function, falls, and greater disability in cancer survivors (Kolb et al., 2016; Winters-Stone et al., 2017). Management of persistent CIPN during chemotherapy is dose reduction or discontinuation of chemotherapy. Commonly used medication for CIPN is not consistently effective (Li et al., 2019; Desforges et al., 2022) and except for duloxetine for painful CIPN after chemotherapy, there are no standard treatments (Loprinzi et al., 2020). Investigation of interventions that would allow patients to continue chemotherapy at appropriate doses, as well as alleviate CIPN symptoms during and after the course of chemotherapy is therefore of clinical importance (Brami et al., 2016).

Acupuncture, a non-pharmacological intervention, has attracted attention as a treatment for the complex symptoms associated with neuropathy including pain. The exact mechanism of acupuncture analgesia remains unclear. Experimental data from functional magnetic resonance imaging (fMRI) studies have confirmed that areas of the limbic system, such as the nucleus raphe magnus, locus ceruleus and periaqueductal gray, become deactivated during acupuncture stimulation whilst regions within sensorimotor structures become activated (Cai et al., 2018). This may be why acupuncture can reduce perception of pain and increase sensation in the case of 'numbness' – two key problematic manifestations of peripheral neuropathy. Reviews of the literature have proposed that acupuncture reduces central sensitization or hyper-reactivity, through mechanisms such as segmental inhibition and the release of endogenous opioids (Lai et al., 2019; Seo et al., 2020). Research points to the involvement of a variety of endogenous ligands as biochemical mediators in the acupuncture response to not only opioids (e.g., β -endorphin), but neurotransmitters (e.g., GABA, glutamate), neuropeptides (e.g., oxytocin) and neurotrophins (e.g., nerve growth factor) (Armstrong et al., 2020; Li et al., 2013), suggesting acupuncture may cause the release of biochemical mediators that work directly on the nervous system. In addition, local effects of acupuncture include reduction in levels of inflammatory mediators such as substance P (Lai et al., 2019). CIPN acupuncture protocols consistently include local needling of feet and hands, particularly between the toes and fingers. It has been suggested that this stimulation elicits a local 'flare reaction' with activation of neurotransmitters and opioid production, possibly responsible for improved sensation, increased blood flow, improved oxygenation of tissue, relief of pain and potential local nerve regeneration (Franconi et al., 2013; Irvani et al., 2020). The findings from these research studies suggest acupuncture impacts multiple pathways both central and peripheral, which provides a possible theoretical framework to explain how and why acupuncture might work to manage the complex symptom profile seen in CIPN.

A service evaluation at the study site ($n = 18$), utilising an established acupuncture protocol of weekly sessions for 10-weeks, reported improvements in CIPN symptoms for 14 participants whose symptoms were refractory to standard management practice (Donald et al., 2011). Additional benefits included reduction in use of analgesia and improved sleep. The current trial was designed to build on the clinical experience of the in-house CIPN acupuncture protocol. This protocol has been further validated more recently as similar acupuncture protocols for CIPN, with treatments delivered once or twice a week for between 8 weeks and 16 weeks, have been used in other clinical studies (Molassiotis et al., 2019b; Jeong et al., 2018). The current ACUFOCIN trial was set up to investigate the safety, efficacy and feasibility of a 10-week course of acupuncture, added to standard of care, for the management of patients' most troublesome symptoms relating to CIPN measured by a self-reported outcome scale. The research question for the work was as follows: "Does the addition of acupuncture to standard treatment reduce the level of CIPN experienced by patients during or following treatment with neurotoxic chemotherapy?"

2. Methods

2.1. Design

ACUFOCIN (Trial No. [NCT02275403](https://clinicaltrials.gov/ct2/show/study/NCT02275403) on [Clinicaltrials.gov](https://clinicaltrials.gov/)) was designed as a parallel group, open label, pragmatic randomised control trial (RCT). The study was set over two sites, which form part of a large tertiary cancer centre in Northwest England. Ethical approval was received from the National Research Ethics Service Committee North West. Greater Manchester East on 19th February 2015 (Reference: 14/NW/1492). Written consent was obtained from all participants.

The primary objective of the study was to investigate the efficacy of a 10-week course of acupuncture in the management of patients most troublesome symptoms relating to CIPN as measured by subjective improvement in most troublesome symptom of CIPN as measured by the Patient Reported Outcome Measure (PROM): Measure Yourself Medical Outcome Profile (MYMOP2). The secondary objectives were to record clinicians' functional assessments of CIPN, including any improvement of CIPN to grade \leq I, graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) v4.03. To additionally document concomitant CIPN medication usage, patient reported pain related scores, quality of life assessments using the European Organisation for Research & Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and CIPN20 module, acupuncture treatment compliance and uptake of the offer of acupuncture at the end of the study period.

The primary outcome on which the study was powered, was a two point or better improvement in MYMOP 2 score for the self-declared most troublesome CIPN symptom (the definition of "success"). With 1:1 allocation, a 10% one-tail significance level and 90% power if the true 'success' proportions were 0.30 and 0.55 respectively 100 participants were required. To allow for attrition the recruitment target was 120. Given the relaxed type I error, rejection of the null hypothesis was to be taken as evidence meriting testing the intervention in a fully powered phase III trial. Feasibility and acceptability of the current study design was addressed through monitoring participant completion and retention. There were post-hoc minimum thresholds agreed for acceptability of $\geq 80\%$ acupuncture delivery and $\geq 80\%$ retention (i.e. return of the primary outcome). This was in addition to a nested qualitative study, the results of which will be published in a separate paper.

Recruitment ran between April 2015 and November 2018. Participants remained on the study for 10 weeks, with those allocated to the Acupuncture arm attending the hospital for acupuncture every week, with a follow-up one week after the final acupuncture session to document adverse events. The aim of this study was to verify data from clinical practice, therefore no long-term follow up was included.

Initially, participants with breast cancer and multiple myeloma only were eligible for randomisation, if their neuropathy was of grade II or above (CTCAE v4.03). The protocol was amended to include gastrointestinal and gynaecological cancer diagnoses, thereby incorporating participants who would have been exposed to the three classes of drugs with the highest rates of neurotoxicity: platinum-based drugs (e.g. ovarian, colorectal), taxanes (e.g. breast, ovarian) and thalidomide (multiple myeloma) (Banach et al., 2017). It is recognised that is will introduce a higher degree of heterogeneity onto the chemotherapy regimens, which may affect the pattern of CIPN and treatment outcomes. However, the focus of this initial (pragmatic) study was to explore whether acupuncture could offer a treatment of CIPN regardless of how it presents. Inclusion of participants on and post treatment was permitted, to explore effectiveness of acupuncture of both 'acute' and 'chronic' CIPN.

Participants randomised to the Acupuncture intervention arm (A) received 10 weekly sessions of acupuncture from a trained acupuncturist in addition to medication to manage symptoms of CIPN in accordance with local clinical policy (gabapentin/pregabalin, and/or amitriptyline). Participants randomised to the Control arm (C) received only medication to manage symptoms of CIPN in accordance with local clinical

policy.

2.2. Participants

The main inclusion criteria were patients ≥ 18 years with breast cancer, multiple myeloma, gastrointestinal cancer, or gynaecological cancer who are receiving or who have received neurotoxic chemotherapy treatment and had CIPN of \geq Grade II (CTCAE v4.03). "Measure Yourself Medical Outcome Profile" (MYMOP2) score of their most troubling CIPN symptom ≥ 3 . Capacity to and having given written informed consent, able to comply with, scheduled visits and study procedures, including the self-report QoL (Quality of Life) questionnaires and patient diaries.

Patients who had received acupuncture within the previous 6 months and/or had a bleeding disorder/thrombocytopenia $< 30 \times 10^9/L$ and/or had a needle phobia were excluded. There were no specific exclusion criteria for other causes of neuropathy as randomisation would be expected to balance this phenomenon. Additionally, the majority of such patients would be excluded from treatment with potentially neurotoxic systemic anti-cancer therapy.

2.3. Interventions

Eligible participants, who gave informed consent, were randomised in a 1:1 ratio to either Acupuncture or Control arms. A stratified permuted block (size 6–10) allocation scheme was implemented by the study statistician using a bespoke computer system which had username/password control and a full audit trail. Researchers telephoned a central number whereupon trained Manchester Clinical Trial Unit (CTU) staff recorded the participant's details in the system and the allocated trial ID and arm were only revealed after commitment of these details ensuring "allocation concealment" from both researchers and CTU staff. The system also sent an automatic confirmatory e-mail to site. The following two factors were controlled for in the algorithm:

1. Cancer diagnosis (breast cancer vs. multiple myeloma vs. gastrointestinal cancer vs. gynaecological cancer)
2. Treatment intention for participants (one of the below):
 - Currently on chemotherapy or any other cancer treatment (to end during the 10-week study or beyond)
 - Chemotherapy suspended due to neuropathy or continued but the neurotoxic agent omitted (but could restart in the 10-week study period)
 - Due to start their next line of chemotherapy during the 10-week study period
 - Finished treatment for their cancer and no further treatment is planned to start within the 10-week study period

Participants in the Control group were only required to have contact with the research team face to face or by telephone (as requested by the participants), for the compulsory assessment visits at baseline: 6 and 10 weeks. Whilst not a documented aim of the study, participants were assessed at week 6 as an interim time point, to provide explorative data on whether benefits of acupuncture were measurable after 6 sessions.

All participants were provided with contact details for the research team and, if they were onsite for review by their clinical team and/or had concerns, the team were available to them.

2.3.1. Intervention - acupuncture

The intervention was documented based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations for reporting acupuncture trials (MacPherson et al., 2015). The acupuncture protocol, including standardised points identified for CIPN, was developed by the seven acupuncturists providing the clinical service, through a collaborative review of practice at the study site, and was based on literature available at the time. This was validated

through a service evaluation focused on acupuncture for CIPN (Donald et al., 2011) and is described below.

Participants received a standardised 40-min, weekly acupuncture session. If a participant was experiencing both lower and upper limb CIPN, a maximum of 26 core points would be needed as follows: Eight bilateral core points (LV3, SP6, ST36, EXLE (Ba Feng) and BL60 for lower limb CIPN, as utilised by Zhang and Ye (2010) and Schroeder et al., (2012). Five bilateral core points EXUE (Ba Xie) and LI4 for upper limb CIPN as previously employed by Bao et al., (2012) who used LI4 as the distal and analgesic point. In cases of lymphoedema, with one or more limb affected, core points could be as low as 16. All additional points and rationale for use were documented (see Table 1). The needles used in this study were for single use. For the core points of EXLE, EXUE, LV3, LI4, BL60 only small needles (0.20 \times 13mm) were used. For SP6, and ST36 larger needles (0.25 mm \times 25 mm) were used.

Conversation between therapist and participant was limited to facilitation of treatment only. Although appropriate care was shown to the participant, any conversation about the effects of acupuncture was kept to the minimum and in response to questions the participants' raised.

With regard to safety, side effects and risks associated with medical acupuncture using sterile needles at peripheral body sites are rare. Although the risk of side effects is minimal the known risks for acupuncture are:

- Localised bruising
- Localised bleeding
- Localised infection
- Localised pain
- Fainting/dizziness

Guidelines were provided for the management of three potential side effects specific to acupuncture:

- "De-Qi:" the eliciting of the 'de qi' sensation through needle manipulation (e.g. flicking) is routine clinical practice, with the sensation often described as a dull ache/heaviness associated with needling into deep tissues below the acupoint. This is known to be a positive response, however, it was judged to be unreliable as a compulsory part of the protocol, as patients with CIPN have altered sensation as evidenced for peripheral points, such as Ba Feng and Ba Xie (Zhou and Benharash 2014). Participants were advised of the possibility of their experiencing it, but nothing will be done to prevent it.
- *Bleeding:* given that acupuncture needles break the skin there is the possibility of minor haemorrhage. The risk is very low as acupuncture needles are extremely fine and the points used, situated away from blood vessels of significant size. However, the risk of bleeding

Table 1
Acupuncture points used.

	Points	Location/comments
CIPN Feet	LV 3	On the dorsum of the foot between the 1st and 2nd metatarsals
	SP6	Above the tip of the medial malleolus and posterior to the medial boarder of the tibia
	ST36	Below the knee in the anterior boarder of the tibia
	EXLE (x4)	In the webs between the bases of the toes
	BL60	Posterior to the tip of the lateral malleolus, midway between this and the Achilles tendon
CIPN Hands	EXUE (BAXI) (x4)	In the webs between the bases of fingers
	LI4	On the dorsum of the hand between the first and second metacarpal bones
Extras	GV20, Yin Tang, K3, K6 and K7	Additional points used as appropriate to address associated symptoms (e.g., anxiety, insomnia, hormonal and genito-urinary dysfunction)

was further reduced by ensuring platelet levels to be at or above 30 × 10⁹/L prior to each treatment. This involved the acupuncturist reviewing the participant's most recent standard of care bloods. If the patient experienced any bleeding, this was managed by applying gentle pressure to the area until it stopped.

- **Cross infection:** because the needles break the skin, there is a theoretical risk for localised infection. Training in essential hygiene was completed by therapists prior to participation in the study as per Trust policy including, hand washing pre & post procedure, use of a clinically clean environment, use of sterile needles and an insertion technique to prevent de-sterilisation prior to skin contact.

The acupuncturist identified any AEs related to acupuncture prior to each weekly treatment and documented them on the primary data form. In addition, AEs were followed up one week post the final acupuncture session. This was undertaken over the telephone if the patient not attending clinic for a standard of care visit. Events were classified according to CTCAE v4.03, by the research nurse/clinician. There was no requirement within the protocol to capture AEs related to pre-existing conditions, with a causal relationship to chemotherapy or standard CIPN medication.

Participants randomised to Control were invited to access the site's existing acupuncture service provision after the 10-week study period was over.

2.4. Outcome measures

All outcome data was collected at baseline, 6 and 10 weeks. The primary outcome measure was pre-defined as the 10-week data from the Patient Reported Outcome Measure (PROM): "Measure Yourself Medical Outcome Profile" (MYMOP2), see supplementary material 1 (Paterson 1996). With this validated scale, participants identified and graded their own worst symptom, thus data capture was flexible enough to address the complexity of CIPN. MYMOP2 is scored on an integer 0–6 scale with higher scores denoting greater issues. The clinicians used standardised questions and visual assessments of function, in accordance with CTCAE v4.03. The secondary endpoint was functional improvement set at reduction of CIPN to grade ≤ I (CTCAE v4.03). Clinicians were blind to initial study allocation; however, as assessments were undertaken within a standard clinic setting, it cannot be guaranteed that participants did not disclose their study arm during the appointment.

Quality of life and symptom burden were monitored through completion of the EORTC QLQ-C30 and associated CIPN20 module. This was supplemented by participants being asked to complete weekly diaries throughout the study period to capture daily pain scores and CIPN medication usage.

2.5. Data analyses

Both randomisation stratification factors were collapsed to binary factors in the analysis as some levels had low frequencies. Approximately 50% of participants in both arms had a diagnosis of breast cancer, (see Table 2), therefore a decision was made to group diagnosis as breast cancer (yes/no). Equally, approximately 40% of participants had completed treatment on study entry therefore adjustment was made for treatment complete status (no/yes) (see Table 2). All analyses were carried out on an intention to treat basis i.e., as randomised and all reported p-values are two-tailed.

2.6. Primary outcome (Week 10)

The analysis of the primary outcome was undertaken with a logistic regression, the focus being on the trial arm effect after adjustment for diagnosis, treatment status and the baseline MYMOP2 score. In addition, a worst-best case sensitivity analysis was conducted in which any missing outcomes in 'Acupuncture' were imputed as "failures" and those

Table 2
Baseline characteristics of the sample.

Baseline characteristics	Control (n = 59)	Acupuncture (n = 61)
Age ^a	60 (29–79)	61 (37–76)
Diagnosis	Breast Multiple Myeloma	32 (52%) 6 (10%)
Cancer treatment [^]	Gastrointestinal	25 (42%)
	Gynaecological	2 (3%)
	On treatment	34 (58%)
	Suspended	2 (3%)
	Due to start	0 (0%)
Affected extremities	Complete	23 (39%)
	Upper limbs only	2 (3%)
	Lower limbs only	5 (8%)
	Upper & lower limbs	52 (88%)
		33 (54%) 0 (0%) 3 (5%) 25 (41%) 0 (0%) 5 (8%) 56 (92%)

[^] See methods for a fuller description of the treatment categories.

^a Median (range).

in 'Control' as "successes".

2.7. Secondary outcomes (week 10)

Physician assessed CTCAE CIPN grade ≤ 1: analogous analyses to those for the primary outcome were conducted for this binary outcome variable i.e., logistic regression with adjustment for diagnosis, treatment status and baseline grade. Again, a worst-best case sensitivity analysis was conducted in which missing outcomes in 'Acupuncture' were imputed as "failures" and those in 'Control' as "successes".

EORTC QLQ-CIPN20: During the data collection period of the study, advice was sought and received from the EORTC that previously proposed subscales for this PROM (sensory, motor and autonomic) had been found unreliable. The current EORTC recommendation is to use an overall score based on the first 18 of the 20 items in the questionnaire. This maps to a 0–100 scale with lower scores being better. An analysis of covariance (ANCOVA) model was used with adjustment for baseline score, diagnosis and treatment status.

EORTC QLQ-C30 Summary Score: The Summary Score was calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale were not included). Prior to calculating the mean, certain symptom scales are reversed to obtain a uniform direction of all scales. The summary score was only calculated if all the required 13 scale scores were available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed). This results in a 0–100 scale in which higher scores represents better overall quality of life. An analysis of covariance (ANCOVA) model was used with adjustment for baseline score, diagnosis and treatment status.

Participant reported pain scores: Participants were asked to complete diaries in which they recorded their worst pain daily on an integer 0–10 likert scale with landmarks (0 = "no pain at all", 10 = "the most intense pain I can imagine"). Within-subject weekly mean scores were calculated, and the week 1 means were taken as baseline as there was no true baseline i.e., no pre-randomisation diary. An analysis of covariance (ANCOVA) model was used with adjustment for baseline score, diagnosis and treatment status.

Longitudinal models: Outcome data were also recorded at week 6 and longitudinal models with both week 6 and week 10 outcomes were fitted in further exploratory analyses. These models again adjusted for baseline value, diagnosis, and treatment status. In addition, they included the week effect and the full interaction of week with each of the other model terms. With this approach we were able to assess differences in the trial arm effect between weeks 6 and 10.

2.8. Adverse events

Adverse events were collated and monitored on an ongoing basis throughout the trial. They were reported at the trial management meetings to provide opportunity for regular review.

3. Results

Recruitment was complete in November 2018 with 120 participants randomised. Sixty-one participants were allocated to Acupuncture and 59 allocated to Control. Diagnostic groups within the cohort are as follows: breast 61 (51%), multiple myeloma 9 (8%), GI 48 (40%), gynaecological 2 (2%). MYMOP2 score for most troubling CIPN symptom at baseline: 3–4 in 33 (28%), 5–6 in 87 (73%). CTCAE CIPN at baseline; grade II 103 (86%), grade III 17 (14%). Fig. 1 below shows the CONSORT flow diagram for participants.

Baseline characteristics were reasonably balanced between arms. This includes prescription of standard medication for CIPN as per local policy: G: Gabapentin: Acu (8/61), SC (4/59), P: Pregabalin: Acu (21/61), SC (19/59), A: Amitriptyline: Acu (8/61), SC (15/59). G and/or P and/or A: Acu (32/61), SC (30/59).

3.1. Descriptors used for ‘most troublesome symptom’ on baseline MYMOP2

Symptom burden and impact of CIPN was expressed in a variety of different ways. The specific descriptors used by participants were collated from the primary data forms and are shown in Table 3 below:

Table 3
‘Most Troublesome Symptom’ on baseline MYMOP2.

Descriptor	Number	Additional Descriptive Comments
Numbness^a (+cold)	40 (+2)	Feet, toes, fingers, face
Pain (+burning)	27 (+3)	Feet, hands, fingers, thumbs
Tingling/pins & needles	22	Fingers, numb, feet, hands, toes, heat
Mobility	14	Lumpy, unsteady, ‘gravel’, numb
Dexterity (+weakness)	5 (+5)	Buttons, jars, gripping
Cramps	2	Feet

NOTE: Often multiple issues ‘packed’ into one symptom.

^a In an attempt to reflect accurately participants descriptions, it can be seen that ‘numbness/numb’ appears as a descriptor, with the part of the body experienced as ‘numb’ being reported in the comments and also as a comment in relation to the cause of poor mobility.

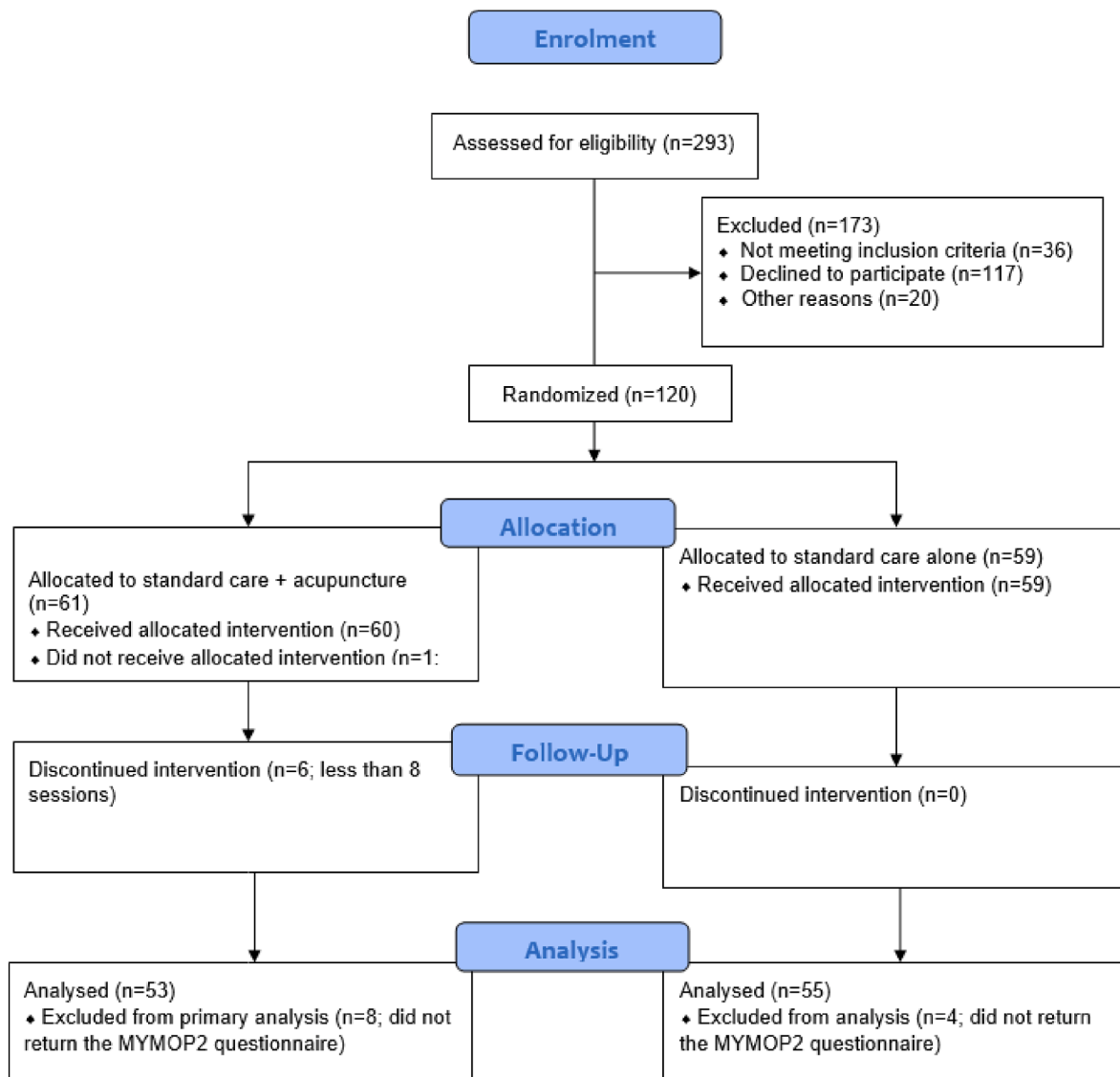


Fig. 1. CONSORT participant flow diagram.

3.2. Summary of baseline – week 10 outcomes

A summary of primary and secondary outcomes at week 10 compared to baseline with both simple descriptive statistics and fitted model effect size estimates is included in Table 4 below:

3.2.1. Primary outcome (Week 10)

Data was available for 108 of 120 randomised participants, which was above the 100 participants required to adequately power the study. Data showed 36/53 (68%) successes in the Acupuncture (A) arm compared to 18/55 (33%) in the Control (C) arm. The success odds ratio from a logistic regression model was 4.3 (95% CI 1.9 to 9.6; $p < 0.001$; A vs C) after covariate adjustment. With the worst-best case sensitivity analysis the 8 missing outcomes in the Acupuncture arm were imputed as “failures” and the 4 in the Control arm as “successes”. There were 36/61 (59%) successes in the Acupuncture arm compared to 22/59 (37%) in the Control arm and the adjusted success odds ratio was 2.4 (95% CI 1.1

Table 4
Primary & Secondary Outcomes, Baseline v Week 10.

	Control (n = 59)		Acupuncture (n = 61)		Effect size (95% CI)
	Baseline	Week 10	Baseline	Week 10	
MYMOP2 Score, Symptom 1					
0	0	3	0	2	
1	0	3	0	8	
2	0	8	0	13	
3	5	9	2	14	
4	14	9	12	10	
5	21	12	28	4	
6	19	11	19	2	
missing	0	4	0	8	
≥ 2 point improvement		18/55 (33%)		36/53 (68%)	OR = 4.3 (1.9–9.6) $p < 0.001$
CTCAE CIPN					
Grade 1	0	4	0	27	
Grade 2	48	44	55	26	
Grade 3	11	8	6	0	
missing	0	3	0	8	
≤ Grade 1 at week 10		4/56 (7%)		27/53 (51%)	OR = 13.1 (4.1–52) $p < 0.001$
EORTC QLQ-CIPN20	45.1 (21.3)	37.0 (20.8)	51.4 (16.4)	29.9 (19.0)	MD = -11.7 (-17.3 to -6.1) $p < 0.001$
missing	0	5	1	8	
EORTC QLQ-C30 Summary Score	63.8 (19.5)	70.2 (17.8)	60.8 (16.8)	76.9 (16.3)	MD = 9.5 (5.0–14.0) $p < 0.001$
missing	2	4	2	12	
Participant reported pain scores	5.0 (2.9)	4.7 (3.1)	5.8 (2.2)	3.8 (2.3)	MD = -1.45 (-2.25 to -0.65) $p = 0.001$
missing	1	12	2	11	

Entries are frequency or mean (sd) as appropriate. OR = Odds Ratio (Acupuncture to Control) from a logistic regression model adjusting for the two stratification factors and baseline score. MD = Mean Difference (Acupuncture – Control) from an ANCOVA model adjusting for the two stratification factors and baseline score.

to 5.0; $p = 0.02$; A vs C). Therefore, as is displayed in Fig. 2 below, the substantive finding of benefit of the intervention for the primary outcome is unaffected by missing data.

In addition, exploratory sub-group analyses were performed on the primary outcome data (≥ 2 -point improvement in MYMOP2 at week 10), for the two stratification factors (diagnosis and treatment status) and the troublesome symptom of numbness. These analyses are displayed in Fig. 3 below:

3.2.2. Secondary outcomes (week 10)

Physician assessed CTCAE CIPN grade ≤ 1 : Data was available for 109 participants with 27/53 (51%) successes in the Acupuncture arm compared to 4/56 (7%) in the Control arm. The adjusted success odds ratio from a logistic regression model was 13.1 (95% CI 4.1 to 42; $p < 0.001$; A vs C). Using the worst-best case sensitivity analysis, the 7 missing outcomes in Acupuncture were imputed as “failures” and the 3 in Control as “successes”. With these pessimistic assumptions there were 27/61 (44%) successes in the Acupuncture arm compared to 7/59 (12%) in the Control arm and the adjusted success odds ratio was 5.9 (95% CI 2.3 to 15; $p < 0.001$; A vs C). The substantive finding of benefit of the intervention for this secondary outcome is therefore unaffected by missing data.

EORTC QLQ-CIPN20: Data were available for 107 participants. In an analysis of covariance (ANCOVA) model the adjusted mean difference in week 10 outcome values using the overall score from the first 18 questions was estimated to be -11.7 (95% CI -17.3 to -6.1; $p < 0.001$; A vs C).

EORTC QLQ-C30 Summary Score: Data was available for 103 participants and in an analysis of covariance (ANCOVA) model the adjusted mean difference in week 10 outcome values was estimated to be 9.5 (95% CI 5.0 to 14.0; $p < 0.001$; A vs C).

Participant reported pain scores: Data was available for 97 participants and the adjusted mean difference in week 10 outcome values was estimated to be -1.45 (95% CI -2.25 to -0.65; $p = 0.001$; A vs C).

3.2.2.1. *Longitudinal models - (Weeks 6 & 10).* Trial arm effects were also statistically significant at the week 6 time point (data not shown). They tended to be of a smaller magnitude than the week 10 effects though not statistically significantly so for CTCAE CIPN ≤ 1 (see Table 5 below).

3.2.3. Safety data

No serious adverse events and only 16 adverse events (11 participants), were documented (tingling, ache/pain, bruising & ‘spotting’ of blood). Of these 16, none required intervention or withdrawal from the trial, 12 (75%) were recorded as mild and 4 (25%) were moderate.

3.2.4. Feasibility and acceptability data

The post-hoc, minimum threshold for acceptability was set at $\geq 80\%$ acupuncture delivery; 54/61 (88.5%) received ≥ 8 of the planned 10 sessions. Based on this, the study design was confirmed as acceptable to participants.

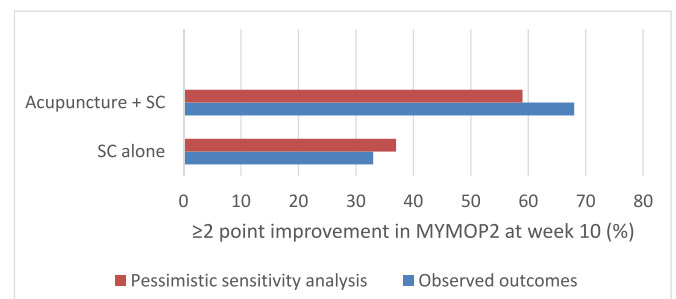


Fig. 2. Diagrammatic representation of primary outcome data.

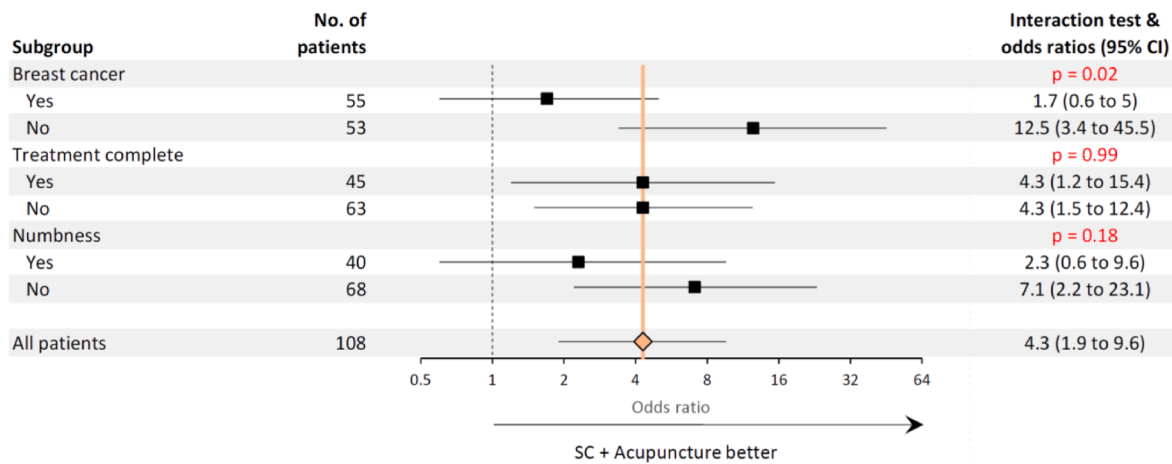


Fig. 3. Exploratory sub-group analyses: Forest Plot for the primary outcome (≥2 point improvement in MYMOP2 at week 10) including the stratification factors and numbness.

Table 5

Trial arm effect summaries from longitudinal model fits.

Effect (SC + Acu v SC alone)	Week 6	Week 10	Interaction Test (Week 6 = Week 10)
Odds ratio of a ≥2 point improvement in MYMOP 2 score	3.75 (1.64–8.56) p = 0.002	4.27 (1.89–9.64) p < 0.001	p = 0.74
Odds ratio of a CTCAE CIPN score ≤1	3.52 (1.15–10.70) p = 0.027	10.50 (3.67–30.02) p < 0.001	p = 0.047
Difference in mean QLQ-CIPN score	-11.71 (-16.29 to -7.14) p < 0.001	-12.66 (-18.11 to -7.21) p < 0.001	p = 0.95
Difference in mean QLQ-C30 summary score	7.27 (3.21–11.33) p < 0.001	9.25 (4.79–13.70) p < 0.001	p = 0.30
Difference in mean pain score	-1.19 (-1.75 to -0.64) p < 0.001	-1.61 (-2.39 to -0.83) p < 0.001	p = 0.15

Notes:

Entries are point estimate, 95% CI and p-value.

Odds ratios are from Generalised Estimating Equation (GEE) model fits.

Mean differences are from General Linear Model fits with no random effects and an unstructured covariance matrix for the within subject residuals.

All models adjusted for baseline value, diagnosis (breast v other), treatment complete (yes v no) and their interactions with time point (week 6 v week 10).

The post-hoc, minimum threshold for feasibility was set at ≥ 80% retention (i.e. return of the primary outcome). Therefore, 53/61 (86.9%) return of the primary outcome was taken to confirm feasibility.

4. Discussion

Studies to date would suggest acupuncture may be beneficial for treatment of CIPN. However, because of the complexity of symptom load it is a challenge to validate effectiveness for all presentations (e.g., thermal control and paraesthesia). To capture preliminary data encompassing impact of acupuncture on all aspects of CIPN in a way that was meaningful to the participants, the primary outcome measure for this study was the self-reported MYMOP2. Participants identified their own most challenging symptoms, described and scored in a way that was relevant to them. ‘Success’ of acupuncture as an intervention was set as a ≥ 2-point improvement in symptom score, with this being accepted as a clinically significant reduction in symptom burden. The results from this

study showed a highly significant level of benefit, with double the number of participants in the Acupuncture arm showing a ‘success’ at week 10 compared to those in the Control arm. Secondary outcome data from clinicians’ functional assessments also showed a significant level of benefit for participants receiving acupuncture in addition to standard medication compared to those receiving standard care alone. The results from the clinician rated outcome appear to endorse the suggested 2-point reduction in MYMOP2 scores as indicating a clinically meaningful response to treatment, as CTCAE grade ≤1 is often the threshold to recommence treatment. Additional secondary outcome data from the EORTC-QLQ-C30 and associated CIPN-20 was collected to facilitate a more comprehensive data set, as it is recognised that the impact of CIPN is notoriously difficult to capture using only one measure (Molassiotis et al., 2019a). This is as has already been alluded to, in large part because although many cases CIPN involve painless sensory loss, there is a significant minority of patients suffering painful symptoms, both of which negatively impact quality of life (Bonhof et al., 2020). Importantly, this study shows that in this cohort of patients, acupuncture proved to be a safe addition to the treatment package for patients with CIPN, even for those on active chemotherapy.

Evidence of effective pharmacological interventions for CIPN, such as tricyclic antidepressants, antiepileptics and opioids, is limited and inconclusive (Li et al., 2019; Jordan et al., 2020) and there is a risk of potential side effects including nausea, constipation and changes to sleep patterns (Desforgues et al., 2022). The exception is the use of Duloxetine, which has appropriate evidence of efficacy from clinical trials and is approved as a treatment for established painful CIPN by the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO), albeit with a limited amount of benefit (Desforgues et al., 2022). Whilst there continue to be challenges to pharmaceutical management of CIPN, in recent years, acupuncture has been identified as a possible alternative, non-pharmaceutical approach (Chien et al., 2019; Bao et al., 2018). There is increasing evidence in the literature supporting the benefits of acupuncture in related fields such as pain related conditions, including neck pain (Blossfeldt 2004; Vickers et al., 2012, British Acupuncture Council, 2021a), tension-type headaches (Linde et al., 2016, British Acupuncture Council, 2021b) and lower back pain (Liu et al., 2015, British Acupuncture Council, 2021c). Our findings are in line with these findings and indicate there was a significant level of benefit from adding acupuncture into routine pharmaceutical treatment of patients with CIPN, with improved quality of life and reduced symptom burden in this cohort. These results are in line with studies utilising similar choices of acupuncture points, such as the work by Molassiotis et al., (2019a) and recent meta-analyses of multiple smaller studies (Jin et al., 2020).

Whilst there is a growing body of evidence supporting the benefit of acupuncture in CIPN, the studies tend to be small, there is little consistency in design and no long-term outcome data. In order to provide preliminary data looking at the length of treatment required to afford benefit from acupuncture for symptoms of CIPN, longitudinal models were used to compare effects of the acupuncture at week six and ten. Significant benefit was seen at both time points however, the magnitude was less at week six. It will therefore be appropriate to undertake further exploratory analyses to better understand whether there are certain subsets of patients, who will require a longer course of acupuncture, such as those on certain chemotherapy protocols, or with a specific symptom burden. Exploratory sub-group analyses suggests that participants with breast cancer may have a lower odds ratio of achieving a successful outcome as defined by the ≥ 2 point improvement in MYMOP2 at week 10 than those in the other disease groups (OR = 1.7 vs 12.5, test for interaction; $p = 0.02$). In addition, these exploratory analyses showed that participants who described 'numbness' as their most troublesome symptom also appeared to have a lower odds ratio for successful outcome than those that did not, though this was not statistically significantly (OR = 2.3 vs 7.1, test for interaction; $p = 0.18$).

Using a Patient Reported Outcome Measure to power the study and provide primary data was key to the study design as it ensured that the data captured was person specific for all participants and flexible enough to facilitate them describing their symptoms in a way which was meaningful to them. Whilst MYMOP2 is a well validated tool, this is to our knowledge, the first time it has been used in a study looking at CIPN. Here we have shown the tool is capable of identifying clinical relevance in symptom burden, and in view of the increasing importance on patient reported outcomes for both regulatory and commissioning bodies (European Medicines Agency, 2016), it would be appropriate to continue its use in future studies, alongside more traditional measures.

4.1. Limitations

Reported benefit by participants from the addition of acupuncture, appeared to be part-validated by the clinicians' grading of motor skills. Unfortunately, due to the nature of the intervention and communication between participant and clinician within the clinic environment, it was impossible to guarantee blinding of clinicians to study arm during the week 6 & 10 assessments. For any future study, it is recommended that data be triangulated with an objective outcome such as nerve conduction studies.

Inclusion of multiple disease groups, at different stages of their treatment and being treated using multiple drug regimens, may be seen as a limitation. However, this facilitated inclusion of the three main classes of drugs known to cause the highest levels of neurotoxicity: platinum-based drugs (e.g., colorectal), taxanes (e.g., breast) and thalidomide (multiple myeloma) (Banach et al., 2017). Additionally, the inclusion of participants who were being treated with chemotherapy as well as those for whom chemotherapy was complete, could be seen as over-complicating the design, however it did facilitate the potential to explore response to acupuncture for both 'acute' and 'chronic' CIPN.

The decision not to incorporate sham acupuncture as a control was not straight forward and may be a limitation. It was made to avoid control participants having to attend for 10 weekly sessions. This was a concern highlighted in a pre-study survey of patients being treated with acupuncture within the clinical service, asked for their opinion of the study design. Because the study site was a tertiary centre, many participants lived a long distance away, had poor mobility and felt that inclusion of an arm giving sham acupuncture would have put them off taking part. From a clinical perspective, there were concerns regarding unmasking, given the complexity of delivering a sham treatment in a clinical setting, as well as the constraints of limited resource of acupuncturists, whose time was not funded within the trial. Finally, there are criticisms of various sham acupuncture methods in the literature, with debate as to whether they can elicit therapeutic responses, thus

compromising interpretation of results (Franconi et al., 2013; Freed et al., 2021, Molassiotis et al., 2019b). The decision about whether to include sham acupuncture in future studies will be revisited. The decision will in part be informed by the results of a nested qualitative study within this current trial, which sought to gather additional data about feasibility and user acceptability of being in the trial and receiving acupuncture, in addition to exploring the impact of living with CIPN.

4.2. Clinical implications and future work

The study set out to explore whether acupuncture could, alongside commonly used pharmaceutical options, maintain/improve physical functioning/mobility, reduce symptoms relating to sensation (including pain and dexterity), enhance wellbeing and when appropriate, facilitate ongoing treatment with drugs designed to reduce mortality from cancer. The results from this cohort suggest short-term clinical benefit from acupuncture and add to the growing evidence base for this non-pharmacological treatment as a treatment for CIPN. The data from this study has provided additional evidence, which both patients and healthcare professionals can use to inform decisions regarding the possible use of acupuncture in this context. However, the design of the study was such that only short-term benefit (10 weeks) was evidenced. For assessment of longer-term value, a defined follow-up period would be required.

To address some of the issues highlighted by this study, it is proposed that a larger multicentre study be undertaken. The authors propose that the design of any future trial incorporates protocols to monitor continuation of effect (e.g. teaching self-needling or offering less frequent 'maintenance' sessions). In addition, further exploration of factors, which could potentially alter the optimum length of treatment required (e.g. identifying numbness as a key symptom), would be a reasonable consideration. Finally, a full cost-benefit analysis is proposed to strengthen the case for the adoption of acupuncture as a potential patient care pathway for CIPN within the NHS.

5. Conclusion

In summary, the data from this study have corroborated the results from a previous service evaluation and other smaller studies in the literature (Molassiotis et al., 2019b), confirming that this cohort of participants benefited from the acupuncture they received. Specifically, the current data set also suggests acupuncture can impact the complex symptom burden associated with CIPN, not just the pain. However, sustainability of any improvements in symptoms requires further investigation.

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CRediT authorship contribution statement

Jacqui Stringer: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **W. David Ryder:** Formal analysis, Data curation, Writing – review & editing. **Peter A. Mackereth:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Funding acquisition. **Vivek**

Misra: Investigation, Writing – review & editing. **Andrew M. Wardley:** Methodology, Investigation, Writing – review & editing, Supervision, Funding acquisition, All authors read and approved the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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