Author's response to reviews

Title: Acupuncture for the treatment of phantom limb pain in lower limb amputees: a randomised feasibility study

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Author's response to reviews: see over
Acupuncture for the treatment of phantom limb pain in lower limb amputees: study protocol for a randomized controlled feasibility trial

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Abstract

**Background:** Phantom limb pain is a prevalent condition which is difficult to manage, with a lack of robust evidence supporting the use of many adjunctive treatments. Acupuncture can be effective in the management of many painful conditions but little is known about its effectiveness for treating phantom limb pain. The aim of this study is to explore the feasibility of conducting a randomised controlled trial comparing acupuncture and routine care in a group of lower limb amputees with phantom limb pain.

**Methods / design:** An unstratified, pragmatic, randomised, two armed, controlled trial of parallel design comparing acupuncture and usual care control will be conducted. A total of 20 participants will be randomly assigned to receive either usual care or usual care plus acupuncture. Acupuncture will include 8 one hour treatments delivered pragmatically over four weeks by traditional Chinese medicine trained practitioners. Outcome measures including; Numerical Pain Rating Scale, Short Form McGill Pain Questionnaire 2, EQ-5D-5L, Hospital Anxiety and Depression Scale, Perceived Stress Scale 10 item, Insomnia Severity Index, Patient Global Impression of Change will be completed at baseline, weekly for the duration of the study and at one month post completion of the study. Post completion of the trial participants will provide feedback though semi-structured interviews. Feasibility will be determined through ability to recruit to the study, success of the randomisation process, completion of acupuncture intervention, acceptability of random allocation and completion of outcome measures. Acceptability of the acupuncture intervention will be determined by semi-structured interviews with participants. Appropriateness of outcome measures for a future trial will be addressed through completion rates of questionnaires and participant feedback.
**Discussion:** Data generated on effect size will be used for future sample size calculations and will inform the development of an appropriate and feasible protocol for use in a definitive multi-centred randomised controlled trial.

**Trial registration:** ClinicalTrials.gov identifier: NCT02126436; date of registration: 9\(^{th}\) April 2014.

**Key words**

Acupuncture, phantom limb, feasibility studies, pain.
Background

Phantom limb pain (PLP) defined as painful sensations perceived in the missing portion of the amputated limb [1] was medically recorded as early as the 16th Century by Ambroise Paré [2]. It is very common and prevalence may be as high as 75 - 80% [3, 4].

Treatment of PLP includes interventions such as pre-emptive analgesia, pharmacological interventions, neuromodulation and supportive non-pharmacological / non-invasive techniques such as mirror therapy, graded motor imagery and stump liners. Evidence suggests pre-emptive epidural and perineural analgesia may not prevent chronic PLP [5, 6]. Pre-emptive gabapentin has also been found to be ineffective [7]. Pharmacological interventions including morphine, gabapentin and ketamine may provide short term analgesic efficacy [8]. There is a lack of robust evidence supporting the use of neuromodulation [9] mirror therapy [10] and graded motor imagery [11]. One randomised controlled trial suggested stump liners may reduce PLP [12] but the sample size in this study was small.

Acupuncture has been shown be an effective intervention in the management of many pain conditions [13, 14, 15] but little is known about the effectiveness of acupuncture for the treatment of neuropathic pain [16]. Specifically, the effectiveness of acupuncture for treating PLP has not been widely assessed or documented, with most of the literature consisting of case reports [17, 18]. Although these studies generally report positive outcomes [17] they are at the bottom of the hierarchy of evidence [19]. A systematic review including English, Chinese and Korean databases identified only two non-randomised controlled trials evaluating the effectiveness of acupuncture. Although both these studies reported positive outcomes, both were deemed to have a high risk of bias and low
methodological quality [20]. Further research is needed to evaluate the effectiveness of acupuncture for treating PLP, but prior to a definitive trial a study is needed to inform on feasibility [21].

The objectives of this study are to: (1) explore the feasibility of recruiting, randomising and retaining participants, (2) evaluate the feasibility and acceptability of having a standard care control, (3) evaluate the adherence / compliance and acceptability of acupuncture as an intervention, (4) evaluate the appropriateness of outcome measures and their completion rates and explore participants experience in completing outcome measures, (5) identify appropriate primary and secondary outcome measures which could be used in future trials, (6) explore the perceived effectiveness of acupuncture for treating phantom limb syndrome, (7) generate data on effect size for use in future sample size calculations, (8) inform the development of an appropriate and feasible protocol for use in a definitive multi-centred randomised controlled trial.

**Methods / design**

**Design:** A comparative effectiveness feasibility study will be conducted, using a mixed methods approach, including a small randomised controlled trial and semi-structured interviews. The randomised controlled trial will be an unstratified, open pragmatic effectiveness trial, of parallel design, with two arms, balanced randomization between acupuncture and usual care and a usual care control. Cross-sectional interviews will be carried out at the end of the intervention period.

Ethical approval was granted from NRES Committee London – Bloomsbury in July 2014 and Guy’s and St Thomas’ R&D and London South Bank University in October 2014. The trial is
registered with ClinicalTrials.gov (NCT02126436) and will be conducted in compliance with the principles of the Declaration of Helsinki [22] London South Bank University Code of Practice, and London – Bloomsbury Research Ethics Committee.

**Study settings:** The study will be conducted at the Amputee Rehabilitation Unit (ARU), at Lambeth Community Care Centre, London, Guy’s and St Thomas’ NHS Foundation Trust. The ARU is a 12 bedded inpatient unit which provides specialist rehabilitation post major amputation. It accepts both primary and established amputees who have undergone a functional decline for approximately 7 weeks of evidence based care, including access to specialist medical, nursing, therapy and counselling professionals. Acupuncture will be provided at the Gateway Acupuncture Clinic (which is co-located in the same building) and provides an NHS acupuncture service through GP referral, in the area of Lambeth and Southwark. The clinic provides treatment for chronic long-term conditions, specialising in chronic pain, headaches, migraines and HIV.

**Recruitment:** Participants will be approached and recruited whilst they are inpatients at the ARU. Newly admitted potential participants will be identified by clinical staff (JG, CC), approached by the researcher (ET), initially screened, and provided with verbal and written information. Participants who pass initial screening and who are willing to participate will have a final eligibility check by ET before being enrolled in the study (fig. 1). Signed, informed consent will be obtained from all participants before enrolling them in the study. Those declining to participate will be asked briefly for their reasons. As the study is a feasibility study no sample size calculation has been performed [21]. An arbitrary number of 20 participants was deemed adequate to provide information on recruitment, randomisation and acceptability of acupuncture and answer the objectives of this trial [23].
Eligibility criteria: Participants will be included if they: (1) 18 years of age or above, (2) full cognitive ability and are able to communicate in English, (3) traumatic or medical amputation of a lower limb (greater than toes), (4) currently experiencing PLP of ≥5 on an eleven point verbal rating scale (i.e. moderate or severe PLP) [24]. Participants will be excluded if they: (1) have congenital limb absence, (2) medically too unwell (as advised by medical staff at the ARU), (3) pregnant, (4) where acupuncture is cautioned including, participants with poorly controlled epilepsy, severe haemophilia or other bleeding / clotting disorders, pacemaker (if using electro-acupuncture), undergoing or recently undergone chemotherapy or bone marrow transplant, any skin changes or removal of lymph nodes on the body, ear or scalp that would preclude placement of acupuncture needles [25].

Intervention (RCT): The acupuncture group (group A) will receive usual inpatient care and a course of acupuncture. The control group (group C) will receive usual inpatient care only. Usual care will include both medical intervention and daily physiotherapy / rehabilitation as routinely provided at the ARU.

All acupuncture practitioners involved in the study will be traditional Chinese medicine (TCM) trained. All practitioners will be members of the British Acupuncture Council, have ≥ 15 years clinical experience and will follow the safety guidelines according to the British Acupuncture Guide to Safe Practice [25]. Acupuncture needles will be single-use, pre-sterilised, disposable, solid, stainless steel needles (with pre-packed single use guide tubes if guide tubes are used). The acupuncture intervention will be pragmatic but will be guided by a protocol previously developed though a Delphi practitioner consensus study [26]. This protocol advises:

- Using a combination of body and auricular acupuncture.
• Treating the contralateral limb and possibly the ipsilateral limb.

• Including auricular acupuncture points such as shen men, sympathetic, points corresponding to the lower limb.

• Depending on the health of the tissue and the individual participant, needling around the stump.

• Mirroring local and distal points by needling the opposite limb.

• Including points on the lower back (taking a segmental approach to dermatomal pain).

• Including points such as LI4+LR3, LR3, GV20, SP10 and also specified points according to participants specific symptoms.

• Retaining needles for 20-30 minutes.

No set criteria will be followed when needling, other than to follow the guidelines of the protocol. Practitioners will assess and treat participants under the paradigm of TCM. Treatment may (depending on the practitioners diagnosis and treatment plan) include electro-acupuncture or other adjunctive interventions such as cupping. All participants in group A will receive eight one hour acupuncture sessions (twice weekly for four weeks) delivered during their inpatient stay.

**Withdrawals, discontinuation and post-trial care:** Acupuncture is a low risk intervention and any adverse effects are usually minimal and temporary. In the event of mild adverse effects (drowsiness, haematoma, bleeding from a point, stuck needle, pain after needling a point) participants will not be withdrawn but will be able to drop out if they so wish. In the event of the occurrence of more serious adverse events participants will be withdrawn. As evidence suggests acupuncture is a safe treatment [27, 28] and as this study is not assessing
effectiveness, no specific arrangements have been made to review interim safety and
effectiveness. However, in the event of 3 participants reporting prolonged aggravation of
pain or other potential serious adverse events, the trial will be stopped prematurely. Post
completion of the study participants will be offered access to acupuncture through their GP
/ physiotherapist.

**Concomitant care:** Participants will be asked to refrain from using other forms of
complementary therapy for the duration of the trial but may receive any intervention as
routinely prescribed by clinical staff at the ARU.

**Study restrictions:** Participants and practitioners will be asked not to disclose participant
allocation to the researcher (ET).

**Intervention (interviews):** Consecutive sampling will be used to recruit (n=5) participants
from group A to explore their experience of being in the trial, having acupuncture and
completing outcome measures. Participants will be interviewed once post completion of
the study. Semi structured interviews will be facilitated by ET, will follow a topic guide (fig.
2) and will be recorded and transcribed verbatim.

**Randomisation, allocation concealment and blinding:** Randomization and allocation
concealment will be used to ensure against selection bias [29]. Prior to commencement of
the study a researcher (NR) not involved in the day to day execution of the study will
randomly allocate and conceal allocation. A copy of the randomised sequence will be kept
in a locked cabinet and not shared with study personnel. The researcher (ET) who will enrol
participants and assign them to either acupuncture intervention or control will not know the
random sequence or treatment allocation.
Randomisation will be achieved using a computer generated random numbers table and will be unstratified and balanced (1:1). Permutted blocking will be used to achieve balance between study arms. A block size of 4 will be used in this study. Allocation concealment will be implemented using sequentially numbered, opaque, sealed envelopes. The envelopes will be opened sequentially only after participant details are written on the envelope.

Participants and practitioners involved in the study will not be blinded. However, the researcher collecting outcome measures (ET) will be blind to the participant’s allocation.

**Outcomes:** Recommendations from the Assessment Committee of the Neuropathic Pain Special Interest Group [30] and the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials [31] were taken into consideration when developing outcome measures for use in this trial.

The primary outcome measure will be an 11 point numerical rating scale (NRS) measuring pain intensity. Pain will be rated by a number describing average pain over the last week, using the anchors 0 meaning ‘no pain’ and 10 meaning ‘pain as bad as you can imagine’ [31]. The NRS is an appropriate measure of pain intensity [32] and is a recommended outcome measure for clinical trials of chronic pain treatment effectiveness [31].

Secondary outcome measures will include a NRS measuring ‘worst’ pain, the Short Form McGill Pain Questionnaire 2 (SF-MPQ-2), EQ-5D-5L, Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale 10 item (PSS-10), Insomnia Severity Index (ISI), Patient Global Impression of Change (PGIC).

The McGill Pain Questionnaire (MPQ) and its short form (SF-MPQ) are generic questionnaires (applicable to any pain) whose reliability and validity have been extensively documented [33]. The SF-MPQ-2 is a 22 item questionnaire which uses a 10 point rating
scale and measures the major symptoms of both neuropathic and non-neuropathic pain [34]. It is reliable and valid for measuring diverse chronic pain [35].

The EQ-5D measures health related quality of life and although not validated for use in neuropathic trials, results appear robust in neuropathic trials with a large sample size or recording a large pain relief response in the active group [30]. The EQ-5D-5L has the same core dimensions as the EQ-5D but instead of using a 3 point rating scale uses 5 levels.

The HADS measures emotional function and is responsive to change in neuropathic pain clinical trials [30]. The HADS includes 7 depression and 7 anxiety items measuring cognitive and emotional aspects of depression and anxiety and is reliable and valid for assessing emotional distress in a medical population [36].

The PSS is a 4, 10 or 14 item questionnaire which was designed to measure psychological stress [37]. It is reliable and valid and found to have acceptable psychometric properties across studies [38]. The PSS 10 has no loss of psychometric quality compared to the PSS 14 [39] and has in fact been shown to be superior [38].

The ISI measures perception of insomnia and degree of concerns or distress caused by insomnia and comprises of 7 items [40]. It has the advantage of measuring symptoms within a two week period and is recommended when insomnia is a secondary endpoint. It has been validated against both polysomnographic and prospective sleep diary measures [40, 41].

A PGIC scale is advised for use in clinical trials [30, 31] and provides a readily interpretable assessment of participants evaluation of the importance of their improvement [42]. The scale used in this study will be a 7 point scale that ranges from ‘no change or worse’ to ‘a great deal better’ [43].
**Assessment:** Participants will complete the outcomes 6 times in total. All outcomes (except the PGIC which will only be collected from end of week one) will be collected at time of enrolment and at the end of each week for the duration of the study. The primary endpoint will be at the end of the intervention (end of week 4). Outcome measures will also be completed one month post completion of the study. Outcome measures will be completed under the supervision of the researcher (ET) at baseline and during weeks 1-4 (whilst participants are inpatients at the ARU). Outcome measures will be posted to participants one month post completion of the study.

**Analysis:** As this is a feasibility study emphasis will be on feasibility and not on statistical significance of results [21]. Compliance with the protocol will be examined through number counts on drop outs / numbers of missed treatments, completion rates of outcome measures and their perceived appropriateness and deviation from the protocol. Data will be collected on the use of rescue medication and adverse events (captured through open ended prompts by practitioners at each intervention time point). Any participants who are excluded from the study will be reported and exclusion will be distinguished from attrition.

All statistical analysis will be undertaken using SPSS Version 21 software. The analysis will test for within patient and between group differences in measurements taken at the beginning of the study, during the study, at the end and one month post completion of the study. An intention to treat approach will be taken [44]. In order to include missing data it will be imputed using last observation carried forward [45].

The null hypothesis is ; there is no difference in change in the primary outcome between group A and C at the end of intervention (end of week four). Statistical analysis will be performed to verify rejection of the null hypothesis with a P value of 0.05 selected as
indicative of statistical significance. Nonparametric tests will be used in inferential analysis. The nonparametric Mann Whitney U test will be used for analysis between groups. Difference between baseline and last observation scores will be analysed using Wilcoxon signed ranks test. Effect size (Cohen’s d) will be calculated to provide information on the relative magnitude of difference [46]. All secondary outcomes will be treated as the primary outcome. Categorical and continuous baseline characteristics will also be analysed to test for between group differences.

Framework Analysis procedure [47] will be used to analyse qualitative data. NVIVO 10 will be used to develop the analytic framework and index transcripts. Excel will be used during charting. Interviews will be transcribed verbatim. Specific steps will be followed during data analysis including: familiarisation, coding, identifying an analytic framework, indexing, charting and mapping / interpretation. To ensure credibility peer debriefing will take place throughout the research process and to ensure dependability two researchers will separately code a selection of transcripts.

The trial will be considered successful if:

- Recruitment rate is ≥ 2 participants per month fitting the eligibility criterion.
- The study recruits ≥ 70% of all eligible potential participants.
- Of the participants recruited to group A ≥ 90% receive their first acupuncture treatment within one week of recruitment.
- Post randomisation and allocation ≥ 90% of participants receive treatment as initially intended.
- Of the participants recruited to group A ≥ 80% receive all eight acupuncture treatments.
• Of the participants recruited to group C ≤ 10% drop out of the study.
• At the primary endpoint of the study outcome measures are completed by ≥ 90% of participants.
• At one month post completion of the study, outcome measures are completed by ≥ 60% of participants.
• Qualitative data identifies that outcome measures are acceptable, appropriate and easy to complete and outcome measures can be identified for used in a definitive trial.
• Qualitative data implies that acupuncture is an acceptable and effective intervention for treating PLP ± other secondary symptoms.
• Qualitative and quantitative data implies the acupuncture protocol used in the feasibility study is appropriate for use in a definitive multi-centred RCT.

Data management and reporting: The Consolidated Standards of Reporting Trials (CONSORT) [48] and STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [49] will be adhered to when reporting. Data will be stored securely with no participant identifiers included and access to and handling of data will be restricted to those involved in the study. All disseminated findings will contain no participant identifiable data.

Discussion

Currently no genuine placebo-controlled acupuncture trials exist [50]. Different types of sham acupuncture have been implemented in acupuncture trials including; shallow needling of acupuncture points, using non-penetrating needles, needling non-acupuncture points and
needling acupuncture points which are not indicated for that specific condition, but none of these methods are physiologically inert [50] and sham acupuncture may have some level of effectiveness [51]. Therefore, despite lack of blinding introducing ascertainment bias, sham acupuncture will not be used in this study and will not be used in a future definitive trial. Inferential statistics / hypothesis testing will be completed only to pilot procedure and will not be interpreted as a measure of effectiveness of acupuncture. Effectiveness will only be established post completion of a fully powered randomised controlled trail.

Results of this study will be disseminated through publication.

**Trial status**

Recruitment commenced in October 2014 and it is anticipated that it will finish by August 2015.

**List of abbreviations**

PLP, phantom limb pain; PLS, phantom limb sensation; ARU, amputee rehabilitation unit; TCM, traditional Chinese medicine; NRS, numerical rating scale; SF-MPQ-2, Short Form McGill Pain Questionnaire 2; HADS, Hospital Anxiety and Depression Scale; PSS-10, Perceived Stress Scale 10 item; ISI, insomnia severity index, PGIC, Patient Global Impression of Change.

**Competing interests**

The authors declare that they have no competing interests.
**Authors contributions**

ET, WT and NR were involved in the design of the study. ET will enrol participants, collect outcome measures and analyse data. NR and WT will review quantitative data analysis. Qualitative data coding will be reviewed and discussed by WT and NR, and NR will act as a second coder, coding a portion of the data using the analytic framework. ET drafted the manuscript. All authors read and approved the final manuscript.

**Sources of funding**

Guy’s and St Thomas’ Charity. The funders had no role in the collection, management, analysis, and interpretation of data; writing of the report or the decision to submit the report for publication.

**Authors information**

ET is both a chartered physiotherapist (BSc Physiotherapy) and acupuncturist (MSc Chinese Medicine) and is currently completing a PhD at London South Bank University. NR completed a PhD in 1976, has been a licenced TCM acupuncturist since 1982, and is a professor of Chinese Medicine and Integrated Health at London South Bank University. WT is a podiatrist, he completed a PhD in 2001 and is Pro Vice Chancellor / Dean of the School of Health and Social Care at London South Bank University.

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References


**Figure Legend**

Figure 1. Participant flow through the study.

Figure 1 presents a flow diagram of the different phases of the study and participants flow through the study. It provides details on timings of the different phases of the study.

Figure 2. Summary of the interview topic guide

Figure 2 provides a summary of the interview topic guide which will be used to interview participants in the acupuncture group post completion of the randomised controlled trial.