Trials

Acupuncture for the treatment of phantom limb syndrome in lower limb amputees: a randomised controlled feasibility study

--Manuscript Draft--

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Abstract:	Background: Post amputation, the complication phantom limb pain (PLP) is prevalent and difficult to manage. This study aimed to determine whether it was feasible and acceptable to undertake a definitive multi-centred randomised controlled trial assessing the effectiveness of acupuncture for treating lower limb amputees with PLP. Methods: A mixed methods embedded design including a randomised controlled trial and semi-structured interviews was undertaken. A total of 15 participants with PLP were randomly assigned to receive either 8 pragmatic Traditional Chinese Medicine acupuncture treatments and usual care or usual care alone over four weeks. Outcomes measures were completed at baseline, weekly throughout the study and at one month post completion of the study and included; a 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. Post completion of the trial, participants in the acupuncture group were interviewed about their experience. Feasibility specific data were also collected. Results: Of 24 amputees meeting the study inclusion criteria 15 agreed to participate (recruitment rate 62.50%). Qualitatively acupuncture was perceived to be beneficial and effective. Quantitatively acupuncture demonstrated clinically meaningful change in average pain intensity (raw change=2.69) and worst pain intensity (raw change = 4.00). Feasibility specific data identified that before undertaking a definitive trial, recruitment, practitioner adherence to the acupuncture protocol, completion of outcome measures at one month follow up and blinding should be addressed. Appropriate outcome measures were identified for use in a definitive trial. Data were generated for future sample size calculations (effect size 0.64). Allowing for a 20% dropout rate, a sample size of 85 participants per group would be needed in a future definitive trial. Conclusions: A future definitive trial may be possible if the areas identified in this study are addressed. As acupuncture may be effective at treating PLP and as this feasibility study suggests a definitive trial may be possible, a multi-centred trial with adequate sample size and blinding is now needed. Trial registration: ClinicalTrials.gov: NCT02126436. Registration date: 9.4.2014.	
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Response to Reviewers:	REVIEWER 1: Methods: 1. In the discussion, you state that only 1 practitioner was involved. It would should be noted in the methods that only 1 practitioner performed the intervention. Their level of training should be described. The methods section now states: 'Acupuncture was provided by an NHS clinic co-located in the same building by one British Acupuncture Council registered acupuncture practitioner (BSc (Hons) acupuncture) with more than 15 years clinical experience.' 2. A short description of the intervention protocol would be helpful so the reader does not need to refer to the protocol paper. A description of the intervention has now been provided: Acupuncture was delivered pragmatically under the Traditional Chinese Medicine (TCM) paradigm. A protocol developed prior to the study, using Delphi consensus methodology was used to provide guidelines[14] and included: •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 and 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; •Try and obtain deqi; •Retaining needles for 20-30 minutes. Treatment could include electro-acupuncture or other adjunctive interventions including cupping, exercises and lifestyle advice. 3. More information on the outcome measures would be useful: the range, which direction indicates worse outcome, references to questionnaires. More details have been provide on the range and direction of NRS and PGIC scale. References have been provided for all outcome measures. 4. More information on the interviews is required. Who conducted them? Was it a semi-structured process? Were they transcribed and coded? The following information has been provided about the interviews and qualitative analysis: 'Interviews were conducted by the researcher who enrolled participants and collected outcome measures. Interviews were semi-structured, audio-recorded, followed a topic guide and transcribed verbatim.' 'Specific steps were followed during data analysis including; familiarisation, coding, identifying an analytical framework, indexing, charting and mapping / interpretation. All codes and themes were developed inductively during analysis of the data.' 5. It would be useful for the proposed sample size to be reported (corresponding to an effect size of 0.35 using 0.8 power and 0.05 significance). The pooled standard deviation used to calculate the effect size should also be reported. Details are now provided on a sample size calculation in the methods and results section of the paper. In the methods section the following details are included: 'Using effect size data generated from this study and taking the assumption that a future study would: (1) use an 11 point NRS measuring average pain over the last

week, (2) have normally distributed data, (3) use a two tailed independent samples T Test to compare acupuncture versus usual care, (4) set power and level of significance / α-level at 0.8 and 0.05 respectively, a sample size for a future definitive trial was calculated[27]:'

In the results section the following details are given:
'A sample size for a future trial was calculated corresponding to an effect size of 0.64 and pooled standard deviation of 1.36. A total of 71 per group (142 in total) would be needed. According to findings from this feasibility study, the follow up rate at four weeks was 80%. Therefore, considering a 20% dropout rate, 170 participants (85 per group) are recommended to detect a significant change in a two armed, parallel group randomised controlled trial comparing acupuncture and usual care as measured using an 11 point NRS measuring average pain at four weeks.'

Results:
6. Baseline imbalances (e.g. gender, ISI) should be discussed.

These have now been discussed:
'Between groups there were differences in gender. In the acupuncture group six were males and in the usual care group five were females. In the acupuncture group the majority of participants were below knee amputees, whereas in the usual care group the majority were above knee amputees. Baseline primary and secondary outcome measure scores were similar between groups.'

7. Add label to y-axis of figure 1.

A label has been added to the y axis of figure 1.

8. Add percentages to Table 1 with baseline demographics.

Percentage values have been added to table 1.

9. There should be some brief comment on the results of secondary outcomes.

Secondary outcomes have been commented on:
In the acupuncture group decrease in mean worst pain was found to be clinically meaningful (raw change = 4.00) but this was not so in the usual care group (raw change = 1.00). The SF-MPQ-2 identified a small effect between groups at day 28 (d=0.46). Mean HADS anxiety and depression scores were normal throughout the study in both groups (score ≤ 7). As with the HADS, little change was observed in PSS-10 scores over the course of the study. Both groups at baseline had sub-threshold insomnia (ISI score 8-14) which improved by day 28. Throughout the study EQ-5D-5L scores were stable across dimensions. At the primary end point of the study the PGIC identified that participants in the acupuncture group rated themselves as 'better' whereas participants in the usual care group rated themselves as 'a little better'.

10. In the qualitative results, you state "The acupuncturist where the acupuncture was conducted were considered to affect the effectiveness of treatment." Do you feel you can say this when only one practitioner was involved in the study?

This has now been changed to:
'The environment where the acupuncture was conducted were considered to affect the effectiveness of treatment.'

REVIEWER 2:
The study's primary endpoint simply shouldn't be calculated before the completion of management of these patients. End of treatment must be considered the period after all acupuncture and/or conventional therapy has sessions have been made; therefore the primary endpoint should be sought after that. When patients answer questionnaires after just a week of treatment should not be considered a primary endpoint.
In this regard, only one patient from the acupuncture group completed his follow-up and was able to provide feedback, which should be the endpoint. Even feasibility studies shouldn't come to any conclusions when only one patient from one group and four from the other group complete the follow-up. No results can be translated into

knowledge for future studies from this work unfortunately.

It has now been clarified in the article when the study's primary endpoint was. The primary end point was, as stated in the protocol, after completion of the intervention at day 28 (after completion of the acupuncture intervention). At the primary end point (day 28) 7 participants in the acupuncture group and 5 in the usual care group completed outcomes.
'The intervention was discontinued after week 4 and this was chosen as the primary end point of the study (day 28).'
'A total of 12 participants were still enrolled and completed outcomes at day 28, the primary end point of the study (7 acupuncture group and 5 usual care group).'
The participant flow diagram has also been amended to highlight the primary endpoint of the study.

REVIEWER 3:
Firstly, regarding randomisation, please clarify that opaque envelopes were used for randomisation as stated in the protocol as this will be helpful for future readers.

It has now been included that the envelopes were opaque.
'allocation concealment was implemented using sequentially numbered opaque envelopes which were only opened once participants had been enrolled.'

Secondly, in light of the study not meeting a number of its success criteria, particularly regarding recruitment and retention, the feasibility of a larger study seems doubtful. The conclusion in the abstract that a larger study is warranted therefore needs to be stated more cautiously.

The conclusion of the abstract has been stated more cautiously:
'A future definitive trial may be possible if the areas identified in this study are addressed. As acupuncture may be effective at treating PLP and as this feasibility study suggests a definitive trial may be possible, a multi-centred trial with adequate sample size and blinding is now needed.'

As a number of problems were identified with feasibility, please provide further elaboration in the discussion as to why a definitive trial would be justified despite these issues.

The discussion section has been rewritten focusing on feasibility and steps which would need to be put in place when designing a definitive trial.

Additionally, though improving retention is highlighted as an issue, suggestions for improving this are not discussed and this would be helpful for those designing a future study in this area.

Suggestions for improving retention have now been included in the discussion:
Although participants adhered to completing outcome measures, this was not sustained post the primary end point of the study. This lack of long term retention needs addressing as poor retention has implications on statistical power and the internal and external validity of a study[43]. Strategies could be implemented such as including; a follow up contact, pre-notification reminders, mentioning an obligation to respond[44]. In randomised controlled trials offering and giving small monetary incentives has been found to be successful in improving response[43].

EDITORS COMMENTS
I am concerned that the primary endpoint is not clearly defined in the paper and in particular within the results section and flowchart.
The trial was registered on ClinicalTrials.gove which states: "Primary Outcome Measures: Change in Numerical Rating Scale [Time Frame: Change from baseline at four weeks]...An eleven point scale will be used.... Participants will be asked to rate their average phantom pain over the last week". The primary endpoint specified prior to commencement of the study is clearly given as four weeks from baseline. However the results section of the paper states that: "A total of 10 participants [from 15] did not complete the one month follow up questionnaire". A check of the flowchart also shows that at one month follow-up only one participant from the acupuncture group, and four

	from the control group, provided outcome data. Any attempt to draw conclusions regarding the clinical impact of the intervention using data from just one participant is clearly not sound. With regard to the conclusions, in the absence of any mention of this, or indeed the lack of any observed statistical difference in outcomes between groups, the statement that "The study identified that acupuncture may cause clinically meaningful change" appears to be cherry picking. The primary end point of the study was after completion of the intervention (four weeks from baseline). All data analysis was completed at this time point (data from 7 participants in the acupuncture group and 5 in the usual care group completed outcomes at this time point). Data were only collected at one month post completion of the intervention to inform on dropout rate at this time point. To address this particular issue please: 1.Rewrite the analysis and results section of the paper. For this I would recommend approaching a different statistician for support. Please note this will be subject to further statistical scrutiny on submission of the revised manuscript. On obtaining further advice we have been advised that as the study is a feasibility study with no sample size calculation it is inappropriate to include any significance tests or report on hypothesis testing. Therefore all details on significance testing has been removed from the paper. 2.Provide a table of results for outcome data in the main body of the paper rather than supplementary materials. This should clearly show the actual number of participants in each group who provided complete data for each measure at each endpoint. These numbers are not currently given in the supplementary tables. A table of results for outcome data has now been included in the main body of the paper and shows the actual number of participants in each group who completed outcomes at these time points. 3.Use means and 95% CIs when presenting results wherever possible. Data has been changed from median (quartiles) to mean (±95% CI). Also, as mean and 95% CI have been used, Cohen's d effect size has been used to calculate effect size. 4.Revise the flowchart, including defined endpoints in days or weeks. The flow chart has been revised to include defined endpoints. 5.Rewrite the discussion and conclusions sections. I suggest removing the above statement, or at least balance it, by giving priority to results for the primary outcome/endpoint. Obviously as a feasibility study the intention was not to demonstrate effectiveness, but rather was a toe in the water for a bigger RCT. It achieved that purpose. The discussion section has been rewritten to focus on feasibility. Given that 12 participants were enrolled at the primary end point of the study the conclusion has not been changed. 6.Further issues to address: The acupuncture intervention that was actually delivered is not clearly described in the manuscript. The reader should not have to refer to another paper describing a protocol, which may or (indeed as the manuscript alludes to) may not have been followed. Please complete the STRICTA checklist (http://www.stricta.info/checklist.html) and attach it to the submission, revising the manscript accordingly. The manuscript has been revised and a STRICTA checklist included.

Acupuncture for the treatment of phantom limb syndrome in lower limb amputees: a randomised controlled feasibility study

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ABSTRACT

Background: Post amputation, the complication phantom limb pain (PLP) is prevalent and difficult to manage. This study aimed to determine whether it was feasible and acceptable to undertake a definitive multi-centred randomised controlled trial assessing the effectiveness of acupuncture for treating lower limb amputees with PLP.

Methods: A mixed methods embedded design including a randomised controlled trial and semi-structured interviews was undertaken. A total of 15 participants with PLP were randomly assigned to receive either 8 pragmatic Traditional Chinese Medicine acupuncture treatments and usual care or usual care alone over four weeks. Outcomes measures were completed at baseline, weekly throughout the study and at one month post completion of the study and included; a 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. Post completion of the trial, participants in the acupuncture group were interviewed about their experience. Feasibility specific data were also collected.

Results: Of 24 amputees meeting the study inclusion criteria 15 agreed to participate (recruitment rate 62.50%). Qualitatively acupuncture was perceived to be beneficial and effective. Quantitatively acupuncture demonstrated clinically meaningful change in average pain intensity (raw change=2.69) and worst pain intensity (raw change = 4.00). Feasibility specific data identified that before undertaking a definitive trial, recruitment, practitioner adherence to the acupuncture protocol, completion of outcome measures at one month follow up and blinding should be addressed. Appropriate outcome measures were identified for use in a definitive trial. Data were generated for future sample size calculations (effect size 0.64). Allowing for a 20% dropout rate, a sample size of 85 participants per group would be needed in a future definitive trial.

Conclusions: A future definitive trial may be possible if the areas identified in this study are addressed. As acupuncture may be effective at treating PLP and as this feasibility study

suggests a definitive trial may be possible, a multi-centred trial with adequate sample size and blinding is now needed.

Trial registration: ClinicalTrials.gov: NCT02126436. Registration date: 9.4.2014.

Key words:

Phantom limb, randomized controlled trial, acupuncture, amputation, mixed methods research.

BACKGROUND

Phantom limb pain (PLP) is defined as painful sensations in the missing portion of the amputated limb. It is neuropathic in nature and caused by a lesion of the somatosensory nervous system[1]. It can be chronic and has been found to influence individuals subjective well-being affecting both physical and mental components of quality of life[2].

Currently, PLP is not well managed. A systematic review evaluating the use of pre-emptive analgesia found only one case-controlled study supported combined bupivacaine, diamorphine and clonidine. Epidural and perineural infusions containing local anaesthetic +/- opiates were deemed only effective for treating acute perioperative pain[3]. A small randomised controlled trial found intravenous ketamine could significantly reduce PLP during and for 30 minutes after infusion[4]. However, a subsequent systematic review found it ineffective[5]. The most commonly used first line treatment is gabapentin[6] but a systematic review found this beneficial for short-term analgesic efficacy only[7]. Many case studies report positively on the effectiveness of mirror therapy[8] but few randomised controlled trials have been completed and adverse effects have been reported.

Acupuncture has been found to be effective for treating a variety of chronic pain conditions[9] but little quality evidence is available on the use of acupuncture for PLP. A recent systematic

review identified only two non-randomised controlled trials[10] and 26 case studies[11]. 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.

This study aimed to evaluate the feasibility and acceptability of completing a small randomised controlled trial in preparation for a definitive multi-centred randomised controlled trial[12]. Objectives were to; (1) explore the feasibility of recruiting, randomising and retaining participants, (2) evaluate the feasibility and acceptability of having a usual care control, (3) evaluate adherence / compliance and acceptability of acupuncture as an intervention, (4) evaluate the appropriateness of 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 PLP, (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

A comparative effectiveness study using a mixed methods embedded design including a small randomised controlled trial incorporating semi-structured interviews was undertaken. The randomised controlled trial was unstratified, open, pragmatic, with two parallel arms, balanced randomization and usual care control. Interviews were cross-sectional. The study protocol has been published[12]. The trial was registered with ClinicalTrials.gov (NCT02126436). A CONSORT checklist is included within the articles additional files (additional file 1, CONSORT 2010 checklist of information to include when reporting a randomised trial.pdf). Ethical approval was granted from NRES Committee London – Bloomsbury (14/LO/0817) and London South Bank University, the trial commenced in October 2014 and closed one year later in October 2015.

Participants were recruited from an NHS inpatient amputee rehabilitation unit in London. All participants were provided with information and were required to consent orally and in writing. Participants were included if they; (1) 18 years of age or above, (2) full cognitive ability and able to communicate in English, (3) traumatic or medical amputation of a lower limb (greater than toes) (4) currently experiencing worst pain PLP of ≥5 on an eleven point verbal rating scale. Participants were excluded if they: (1) had congenital limb absence, (2) medically unwell, (3) pregnant, (4) where acupuncture is cautioned[13].

Participants were randomly allocated to either receive usual care and acupuncture or usual care alone. A usual care comparator was chosen as the study was undertaken under the Medical Research Council guidelines for developing and evaluating complex interventions. Usual care included pharmacological medical intervention, physiotherapy and occupational therapy. Acupuncture was provided by an NHS clinic co-located in the same building by one British Acupuncture Council registered acupuncture practitioner (BSc (Hons) acupuncture) with more than 15 years clinical experience. Acupuncture was delivered pragmatically under the Traditional Chinese Medicine (TCM) paradigm. A protocol developed prior to the study, using Delphi consensus methodology was used to provide guidelines[14] and included:

- 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 and 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;
- Try and obtain deqi;

- Retaining needles for 20-30 minutes.

Treatment could include electro-acupuncture or other adjunctive interventions including cupping, exercises and lifestyle advice. All participants in the acupuncture group were allocated eight one hour sessions (twice weekly for four weeks).

Outcome measures were completed at baseline, weekly for the duration of the trial and one month post completion of the study. The primary outcome measure was an eleven point numerical rating scale (NRS) capturing average PLP over the past week, using the anchors 0 meaning 'no pain' and 10 meaning 'pain as bad as you can imagine'[15]. Secondary outcome measures included; NRS capturing worst PLP over the past week, the Short Form McGill Pain Questionnaire 2 (SF-MPQ-2)[16], EuroQol-5 Dimensions (EQ-5D-5L)[17], Hospital Anxiety and Depression Scale (HADS)[18], Perceived Stress Scale 10 item (PSS-10)[19], Insomnia Severity Index (ISI)[20] and a seven point Patient Global Impression of Change (PGIC) scale ranging from 1 meaning 'no change' to 7 meaning 'a great deal better' Phrasing of PGIC question was similar to the phrasing used by Hurst and Bolton[21] and stated 'since being enrolled in this study how would you describe the change (if any) in activity limitations, symptoms, emotion and overall quality of life in relation to your phantom limb pain. Feasibility specific data were collected (table 4) and post completion of the study, participants in the acupuncture group were interviewed. Interviews were conducted by the researcher who enrolled participants and collected outcome measures. Interviews were semi-structured, audio-recorded, followed a topic guide and transcribed verbatim.

No sample size calculation was undertaken but a sample of 20 was deemed adequate to inform on feasibility[22]. Interim safety and effectiveness were not formally evaluated but data were collected through participant interviews. Randomisation and allocation concealment was undertaken by a researcher not involved in the study using a computer generated random numbers table. Randomisation was unstratified and balanced using a block of four and allocation concealment was implemented using sequentially numbered opaque envelopes which were only opened once participants had been enrolled. The researcher collecting

outcome measures and analysing data enrolled participants and was blinded to the participant's allocation. Participants and acupuncture practitioners were not blinded.

Quantitative data analysis used an intention to treat approach and missing data were imputed using last observation carried forward. The intervention was discontinued after week 4 and this was chosen as the primary end point of the study (day 28). As this was a feasibility study no significance tests were performed and no hypothesis testing is reported. Raw change, the difference between mean baseline and subsequent scores was calculated for the NRS and considered meaningful / clinically significant when ≥ 1.80[23]. Cohen's d effect size was calculated using the calculation; $d = M_1 - M_2 / \sigma$ pooled using Cohen's criteria; 0.2, small effect, 0.5, medium effect and 0.8, large effect[24]. Framework Analysis[25] was used to analyse qualitative data. Specific steps were followed during data analysis including; familiarisation, coding, identifying an analytical framework, indexing, charting and mapping / interpretation. All codes and themes were developed inductively during analysis of the data. Inferences were drawn from analysis of qualitative and quantitative findings. Meta-inferences were drawn through combining qualitative and quantitative findings using side-by-side comparison[26].

Using effect size data generated from this study and taking the assumption that a future study would: (1) use an 11 point NRS measuring average pain over the last week, (2) have normally distributed data, (3) use a two tailed independent samples T Test to compare acupuncture versus usual care, (4) set power and level of significance / α-level at 0.8 and 0.05 respectively, a sample size for a future definitive trial was calculated[27]:

$$n = \frac{2\left(Z_a + Z_{1-\beta}\right)^{2\sigma 2.}}{\Delta^2}$$

RESULTS

A total of 36 lower limb amputees were identified of which 12 were ineligible. Of those eligible, 9 refused to participate. A total of 15 participants were enrolled, and their data analysed within their originally assigned groups. Before the primary end point 2 were withdrawn due to being medically unwell and 1 dropped out having been randomised to usual care. A total of 12 participants completed outcomes at day 28, the primary end point of the study (7 acupuncture group and 5 usual care group). A total of 10 participants did not complete the one month follow up questionnaire and 2 participants refused to be interviewed at the end of the study (figure 1).

Demographic details are presented in table 1. Between groups there were differences in gender. In the acupuncture group six were males and in the usual care group five were females. In the acupuncture group the majority of participants were below knee amputees, whereas in the usual care group the majority were above knee amputees. Baseline primary and secondary outcome measure scores were similar between groups.

Figure 1. Participant flow through the trial

Table 1. Participant demographics

Quantitative findings

In the acupuncture group mean average pain decreased from 5.44 to 2.75 and in the usual care group from 5.43 to 4.43 (figure 2). In the acupuncture group decrease in average pain was found to be clinically meaningful (raw change = 2.69), but not in the usual care group (raw change = 1.00). At day 28, a medium effect was found between groups (d = 0.64).

In the acupuncture group decrease in mean worst pain was found to be clinically meaningful (raw change = 4.00) but this was not so in the usual care group (raw change = 1.00). The SF-MPQ-2 identified a small effect between groups at day 28 (d=0.46). Mean HADS anxiety and depression scores were normal throughout the study in both groups (score ≤ 7). As with the HADS, little change was observed in PSS-10 scores over the course of the study. Both groups

at baseline had sub-threshold insomnia (ISI score 8-14) which improved by day 28. Throughout the study EQ-5D-5L scores were stable across dimensions. At the primary end point of the study the PGIC identified that participants in the acupuncture group rated themselves as 'better' whereas participants in the usual care group rated themselves as 'a little better'. The datasets supporting these findings are included in table 2.

Figure 2. Box plot of 'average pain' intensity at baseline and day 28

Table 2: Summary statistics at baseline and day 28 expressed as mean and between group effect sizes

Qualitative findings

Six themes were identified through interviews with participants who received acupuncture (table 3). Participants were initially sceptical and apprehensive about being involved in the trial, had low expectations of acupuncture and hoped to be randomised to usual care. However, these views changed, participants liked treatment (even if not being physically needed) and found it relaxing. Electro-acupuncture was considered beneficial and pleasant and receiving two treatments a week was considered acceptable though some participants found this tiring. Acupuncture was perceived to be effective at resolving or reducing PLP and other health problems and 4-6 treatments were needed for it to be effective. Acupuncture was not perceived to cause any adverse effects. The environment where the acupuncture was conducted was considered to affect the effectiveness of treatment.

Completing outcome measures was considered acceptable, and relevant, but the SF-MPQ-2 included words which some participants did not understand. Length of time and frequency of questionnaire completion was acceptable with only one participant thinking they were given too often. Overall being involved in the study was considered a good experience and acupuncture was perceived to be beneficial. Participant quotes are included in table 3.

Table 3. Acupuncture group participant quotes from semi-structured interviews

Feasibility specific findings

Recruitment was problematic, clinicians sometimes failed to identify suitable participants, the unit did not always run at full capacity and potential participants were often unwilling to be involved having just had a major amputation. Of those identified, 12 were ineligible for inclusion, mainly due to PLP being < 5/10 intensity and of the remainder n=24, 62.50% consented to be enrolled. Randomisation worked well with only one participant dropping out due to being randomised to usual care and all participants were treated in the group they were allocated into. Those enrolled reported being happy to be randomised to either acupuncture or usual care. Blinding was unsuccessful, with both participants and practitioners unintentially informing the researcher which group they had been allocated to.

Participant compliance to the protocol was good[14]. The four participant deviations were due to; tiredness, forgetting appointments, appointments coinciding with another medical appointment, not wanting further treatment as PLP had resolved. Practitioner adherence to the protocol was poor and no participant received all 8 treatments (mean total number of treatments 5.14 (4.02 – 6.27)). Despite the protocol[14] advising using a combination of auricular and body acupuncture this was only given to one participant on two occasions. Both lower limbs were treated 66.67% of the time whereas the contralateral limb only 8.33%. Needle retention time and adverse events were not reported. For the dataset on acupuncture points used by practitioners in this feasibility study, see additional file 2 (Acupuncture points used by practitioners during the feasibility study.pdf).

Outcome measures were identified which would be appropriate for a definitive trial. The NRS, SF-MPQ-2 and PGIC captured change. Baseline HADS scores were normal and little change was observed in the PSS-10 and EQ-5D-5L suggesting these outcomes may be inappropriate. The ISI may not be appropriate in an inpatient setting as anecdotally noise and medication affected sleep. Retention of participants up until the primary end point of the study was good, but at one month follow up was poor.

A sample size for a future trial was calculated corresponding to an effect size of 0.64 and pooled standard deviation of 1.36. A total of 71 per group (142 in total) would be needed. According to findings from this feasibility study, the follow up rate at four weeks was 80%. Therefore, considering a 20% dropout rate, 170 participants (85 per group) are recommended to detect a significant change in a two armed, parallel group randomised controlled trial comparing acupuncture and usual care as measured using an 11 point NRS measuring average pain at four weeks.

Using the criteria set *a priori*[12], as shown in table 4 the study was found to be successful in relation to participants receiving the intended intervention, outcome measures being considered acceptable and appropriate and being completed at the primary end point of the study and the intervention being considered acceptable and appropriate for use in a definitive trial. The study was unsuccessful in relation to recruitment, practitioner adherence to the protocol, completion of outcome measures at one month follow up and blinding.

Table 4. Success of feasibility study

DISCUSSION

The study did not meet its target of recruiting ≥ 2 participants per month or 20 participants in total. This is not unusual and other studies have also reported recruitment as being slower or more difficult than expected[28]. It has been suggested that clinical staff have limited time to undertake research activities[29] and this may have influenced the identification of potential participants. A future trial would need to ensure trial centres allocated adequate time and personnel. Potential participants should be provided with some education about the intervention as a brief introduction may make participants less sceptical and more willing to consent. Recruitment could be enhanced by a multi-centred approach. Intensity of PLP was a major barrier to recruitment. Although PLP can be severe, this may only be in approximately

30% of amputees[30, 31] explaining why this inclusion criterion excluded 9 participants. Future studies may consider lowering or excluding the severity of this criterion.

The study did not meet its target of recruiting ≥ 70% of all eligible participants. However, this criterion was unrealistically high and 62.50% of all eligible participants were recruited. Other CAM studies report a lower participation rate[32] and studies evaluating the effectiveness of interventions for treating PLP also report a lower participation rate[33]. This study may not have met its target recruitment rate because it was set unrealistically high. Participation rate was good suggesting a future trial would be possible.

Amputees have often undergone extensive unpleasant interventions prior to amputation, and this may partly explain the reason for those refusing to consent. The study site may not have been optimal for recruiting with it being a busy unit providing rehabilitation care for those at a key life point. Although, overall, recruitment was good, future studies may benefit by including amputees who are not in an inpatient unit receiving multiple interventions at a key life point and by making the proposed intervention less intensive.

Blinding was unsuccessful. A future study may benefit from clearly including information on the participant information sheet about the necessity of blinding and should ensure that the outcome measures used are reliable and objective. Additionally, a future trial could use duplicate assessments of outcomes and report the level of agreement between assessors[34]. Also, different data analysts to data collectors could be used.

Establishing acceptability and compliance to an intervention is vital, as if the intervention is unacceptable and participants not compliant, the study will fail. This study suggested acupuncture and usual care were acceptable and participants were compliant with the protocol. Unlike usual care alone, acupuncture did appear to be clinically effective at reducing pain intensity and findings suggested a ‘meaningful change’[23]. This is in keeping with results from case studies[11] and non-randomised controlled trials[10]. Clinically meaningful change is important as this is relevant to patient care. Across a diverse patient group a change of 1.74 on an eleven point NRS has been associated with ‘much improved’ and a change of 2.76

'very much improved'[35] suggesting that by the primary end point participants in the acupuncture group average pain was 'much improved' and worst pain was 'very much improved' but this was not so in the usual care group for either average or worst pain. In keeping with quantitative findings, qualitatively acupuncture was perceived to be effective at resolving symptoms. Findings from this study support the need for a definitive trial to determine effectiveness. As less than 8 treatments may be effective this may be a more appropriate and cost effective dosage. A usual care control should be used in future studies as it has the advantage of being safe (physicians make individualised treatment decisions about participant care) and unlike efficacy trials ensures the intervention can claim to be superior to usual practice[36].

Unexpectedly practitioners were found to not adhere to the acupuncture protocol. This lack of adherence may have been partly due to tensions between clinical and research workload[29] and due to poor communication with the research team. This would need addressing before undertaking a future trial as lack of participants receiving the full intervention as intended could lead to reduced effectiveness, a decrease in study power and inappropriate conclusions[37]. Robiner[38] provides a table of adherence enhancing strategies which could be used in a future trial, including; promoting collaboration and good communication between acupuncturists and research staff, providing feedback on adherence, promoting non-judgemental discussion around adherence, and addressing adherence problems proactively.

Although adverse events were captured during semi-structured interviews, practitioner compliance of capture of adverse effects was poor. This is not uncommon[39] but would need addressing before undertaking a definitive trial. Recommendations of capture of adverse events include capturing the frequency, incidence, timing and severity of each event[40]. A future study may benefit from giving practitioners a log book designed to capture this information.

The study identified appropriate outcome measures which could be used in a future trial. However as the SF-MPQ-2 included some terminology which was not understood, an

alternative outcome measure may be more appropriate such as the neuropathic pain scale, the neuropathic pain symptom inventory, or the Pain Quality Assessment Scale[41, 42]. Although participants adhered to completing outcome measures, this was not sustained post the primary end point of the study. This lack of long term retention needs addressing as poor retention has implications on statistical power and the internal and external validity of a study[43]. Strategies could be implemented such as including; a follow up contact, pre-notification reminders, mentioning an obligation to respond[44]. In randomised controlled trials offering and giving small monetary incentives has been found to be successful in improving response[43]. However, lower limb amputees tend to be a frail population and long term survival post amputation, is poor. By one year post amputation almost half (44%) of lower limb amputees will have died and by five years 77%[45]. Additionally, major amputations are associated with high morbidity and complication rates. This would need to be taken into consideration when designing a definitive trial.

Limitations

This study did not consider the effect of attention on symptoms and did not include a control that mimicked the theoretically inactive elements, but not the active elements of acupuncture. Further research needs to be carried out to identify optimal dosage, which aspects of acupuncture intervention causes change and whether environmental factors affect outcomes. The study did not recruit the number of participants it initially aimed to recruit and quantitative findings reported in this study should be interpreted with caution. Only one practitioner was involved in this study and as differences in effectiveness is known to occur with different practitioners[46] future studies would benefit from use of multiple practitioners. Practitioners did not adhere to the acupuncture protocol and participants were not offered 8 treatments, making it difficult to determine the effectiveness of the protocol. Two participants in the acupuncture group were not interviewed and data saturation of qualitative data cannot be assumed.

CONCLUSIONS

The study provides novel data on the feasibility of conducting a randomised controlled trial to establish the effectiveness of acupuncture for treating lower limb amputees with PLP. The study identified that acupuncture may cause clinically meaningful change. The protocol used in this study was acceptable and data on effect size was generated allowing for a sample size calculation. Areas which would need addressing prior to undertaking a definitive trial were identified.

LIST of ABBREVIATIONS

PLP, phantom limb pain; TCM, Traditional Chinese Medicine; SF-MPQ-2, Short Form McGill Pain Questionnaire 2; EQ-5D-5L, EuroQol-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; PSS-10, Perceived Stress Scale 10 item; ISI, Insomnia Severity Index; PGIC, Patient Global Impression of Change.

DECLARATIONS

Ethics approval and consent to participate

Ethical approval was granted from NRES Committee London – Bloomsbury (14/LO/0817) and London South Bank University. All participants consented to participate both orally and in writing.

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in the design of the study and analysis and interpretation of data. All authors reviewed and commented on the manuscript and gave final approval of the version to be published.

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Participant demographics	Acupuncture group (n=8)	Control group (n=7)
Age mean (± 95% CI)	51.63 (40.38 – 62.87)	55.71 (40.17 -71.26)
Gender n (%):		
Male	6 (75)	2 (28.57)
Female	2 (25)	5 (71.43)
Ethnicity n (%):		
White British	7 (87.5)	4 (57.14)
Black Caribbean	1 (12.5)	1 (14.29)
Black African	0 (0)	1 (14.29)
White other	0 (0)	1 (14.29)
Employment status n (%):		
Student	0 (0)	1 (14.29)
Unemployed	1 (12.5)	0 (0)
Sick leave	5 (62.5)	3 (42.86)
Retired	2 (25)	3 (42/86)
Time since amputation in days mean (±95% CI)	25.63 (18.43 – 32.85)	29.43 (13.12 – 45.74)
Level of amputation n (%):		
Above knee	2 (25)	4 (57.14)
Below knee	6 (75)	3 (42.86)
Reason for amputation n (%):		
Vascular	5 (62.5)	3 (42.86)
Trauma	2 (25)	2 (28.57)
Infection	0 (0)	1 (14.29)
Other	1 (12.5)	1 (14.29)
History of past amputations n (%):		
Yes	2 (25)	1 (14.29)
No	6 (75)	6 (85.71)
General health n (%):		
Diabetes I	1 (12.5)	0 (0)
Diabetes II	3 (37.5)	2 (28.57)
Cancer	1 (12.5)	0 (0)
Osteoarthritis	1 (12.5)	0 (0)
Epilepsy	1 (12.5)	0 (0)
Nil	1 (12.5)	5 (71.43)
Mobility level n (%):		
Wheelchair	8 (100)	7 (100)

Table 2 Statistical data

Outcome measure	Group	Baseline mean (± 95% CI)	Between group effect size (Cohen *d*)	Day 28 mean (± 95% CI)	Between group effect size (Cohen *d*)
Number of participants who provided complete data	Acupuncture Usual care	8 7		7 5	
NRS average pain	Acupuncture Usual care	5.44 (3.90 - 6.98) 5.43 (3.75 - 7.11)	0.00	2.75 (0.31 - 5.19) 4.43 (2.37 - 6.49)	0.64
NRS worst pain	Acupuncture Usual care	8.00 (6.21 - 9.79) 7.29 (5.80 - 8.77)	0.38	4.00 (0.40 - 7.60) 6.29 (4.54 - 8.03)	0.69
SF-MPQ-2	Acupuncture Usual care	2.55 (1.70 - 3.40) 2.85 (1.22 - 4.47)	0.21	1.06 (0.13 - 2.24) 1.89 (0.07 - 3.85)	0.46
HADS anxiety	Acupuncture Usual care	6.38 (2.75 - 10.00) 5.29 (2.33 - 8.24)	0.29	5.25 (1.97 - 8.53) 4.86 (1.38 - 8.34)	0.10
HADS depression	Acupuncture Usual care	6.63 (3.34 - 9.91) 5.14 (0.99 - 9.29)	0.35	5.75 (1.35 - 10.15) 5.14 (0.99 - 9.29)	0.12
PSS-10	Acupuncture Usual care	15.25 (10.90 -19.60) 17.28 (10.11 - 24.46)	0.31	11.63 (5.43 - 17.82) 15.57 (7.35 - 23.79)	0.48
ISI	Acupuncture Usual care	13.50 (5.96 - 21.04) 9.14 (0.93 - 17.35)	0.49	8.50 (1.65 - 15.35) 7.42 (0.61 - 14.24)	0.14
EQ-5D-5L mobility	Acupuncture Usual care	4.88 (4.58 - 5.17) 4.88 (4.58 - 5.17)	0.00	3.75 (2.88 - 4.62) 4.29 (3.13 - 5.45)	0.47
EQ-5D-5L self care	Acupuncture	1.75 (1.16 - 2.34)	0.24	1.63 (1.00 - 2.25)	0.09

	Usual care	1.57 (0.84 - 2.30)		1.57 (1.08 - 2.07)	
EQ-5D-5L usual activities	Acupuncture	3.75 (2.68 - 4.82)	0.45	2.88 (2.18 - 3.57)	0.84
	Usual care	4.29 (3.26 - 5.31)		3.71 (2.69 - 4.74)	
EQ-5D-5L pain - discomfort	Acupuncture	3.50 (2.87 - 4.13)	1.24	2.88 (2.18 - 3.57)	0.44
	Usual care	2.71 (2.26 - 3.17)		2.57 (2.08 - 3.07)	
EQ-5D-5L anxiety / depression	Acupuncture	2.00 (1.11 - 2.89)	0.46	2.00 (1.23 - 2.77)	0.50
	Usual care	1.57 (0.84 - 2.30)		1.57 (0.84 - 2.30)	
EQ-5D-5L health today	Acupuncture	63.13 (46.41 - 79.84)	0.21	74.63 (58.49 - 90.76)	0.15
	Usual care	67.14 (50.29 - 84.00)		77.14 (63.05 - 91.23)	
PGIC	Acupuncture			5.71 (4.23 - 7.20)	1.27
	Usual care			3.20 (0.37 - 6.03)	

Theme	Quote
Scepticism and lack of expectations	*"I was a bit worried about what it was all about. You said acupuncture and I said I'm not keen on that. And then I thought I'll try it I'll try it out."(Interviewee 1)* *"Didn't expect it to work. Very, very very sceptical me, very. That's how ignorant I was…. I didn't think it would work, I thought it was all nonsense."(Interviewee 4)*
Being treated	*"it was so relaxing…. and um I was just lying there and I could have quite easily gone to sleep! It was so relaxing, so sort of peaceful"(Interviewee 2)*
Changes in phantom limb pain	*" I said well, it's good. It's very good..... It works good and then last time she came she said aren't you going to have it? I said no, no, it's got rid of that pain that was down there."(Interviewee 1)*
Factors affecting treatment	*"She [the acupuncturist] looked after you well and I think that was a lot of it, her personality and the way she treated you and everything."(Interviewee 2)* *"I think because of the environment it was being done in and the timing more than anything, I think it wasn't really a positive thing. It might have been a different story in another setting, if I had more time around my schedule"(Interviewee 3)*
Completing the outcome measures	*"[SF-MPQ-2] A couple of the wordings were a bit weird. I didn't get some of the words on the describe the pain, gruelling and what was the other one, there were a couple of them I didn't understand what these words meant."(Interviewee 4)*
A good experience	*"it's been very positive.... it's been an extra benefit I would definitely say that…. I couldn't criticise anything to be perfectly honest."(Interviewee 5)*

Table 4 Success of the feasibility study

Click here to download Table Table 4. Success of the feasibility study.pdf

***A priori* criteria**	**Findings**	**Objective met (yes / no)**
Recruitment rate was ≥ 2 participants per month fitting the eligibility criteria.	Recruitment rate was 1.36 eligible participants per month.	No
The study recruited ≥ 70% of all eligible potential participants.	62.50% of all eligible participants were recruited.	No
Of the participants recruited to acupuncture group ≥ 90% received their first acupuncture treatment within one week of recruitment.	All participants received their first acupuncture treatment within a week of recruitment.	Yes
After randomisation and allocation ≥ 90% of participants received treatment as initially intended.	All participants received treatment as intended and the study protocol was considered acceptable.	Yes
Of the participants recruited to acupuncture group ≥ 80% received all eight acupuncture treatments.	No participants received all 8 treatments (mean total number of treatments 5.14 (4.02 – 6.27)).	No
Of the participants recruited to usual care group ≤ 10% dropped out of the study.	One participant (14.29%) of participants dropped out of the usual care group.	No
At the primary endpoint of the study outcome measures were completed by ≥ 90% of participants.	100% of participants still enrolled on the study completed all outcome measures by the primary endpoint of the study.	Yes
At one month after completion of the study, outcome measures were completed by ≥ 60% of participants.	Outcome measures were completed by 5 participants (33.33%)	No
Qualitative data identified that outcome measures were acceptable and appropriate, that questionnaires and rating scales were easy to complete and that outcome measures could be identified for use in a definitive trial.	Outcome measures were considered acceptable, appropriate and easy to complete. The HADS, PSS-10, EQ-5D-5L and ISI may not be appropriate for use in a definitive trial.	Yes
Qualitative data implied that acupuncture was an acceptable and effective intervention for treating PLP with or without other secondary symptoms.	Acupuncture / electro-acupuncture was considered acceptable. Acupuncture was perceived to be effective at treating both PLP and other secondary complaints.	Yes

Data was collected on the primary outcome measure (NRS) and effect size was calculated to inform a sample size calculation for a larger trial.	Considering a 20% dropout rate, 170 participants are recommended to be recruited to detect a significant change in a two armed parallel randomised controlled trial comparing usual care and acupuncture as measured using an 11 point NRS measuring average pain at four weeks.	Yes
Qualitative and quantitative data implied the acupuncture protocol used in the feasibility study was appropriate for use in a definitive multi-centred randomised controlled trial.	Participants did not drop out of the acupuncture group suggesting it was acceptable. Participants symptoms generally improved over 6 treatments suggesting 8 treatments was adequate. Acupuncture and electro-acupuncture were considered acceptable, effective and relaxing.	Yes
The researcher was not aware which group participants had been enrolled to 100% of the time.	Blinding was not successful and the researcher knew through both participants and clinical staff at the amputee unit their group allocation.	No

Figure 1 Participant flow

Click here to download Figure Participant flow chart (1).pdf

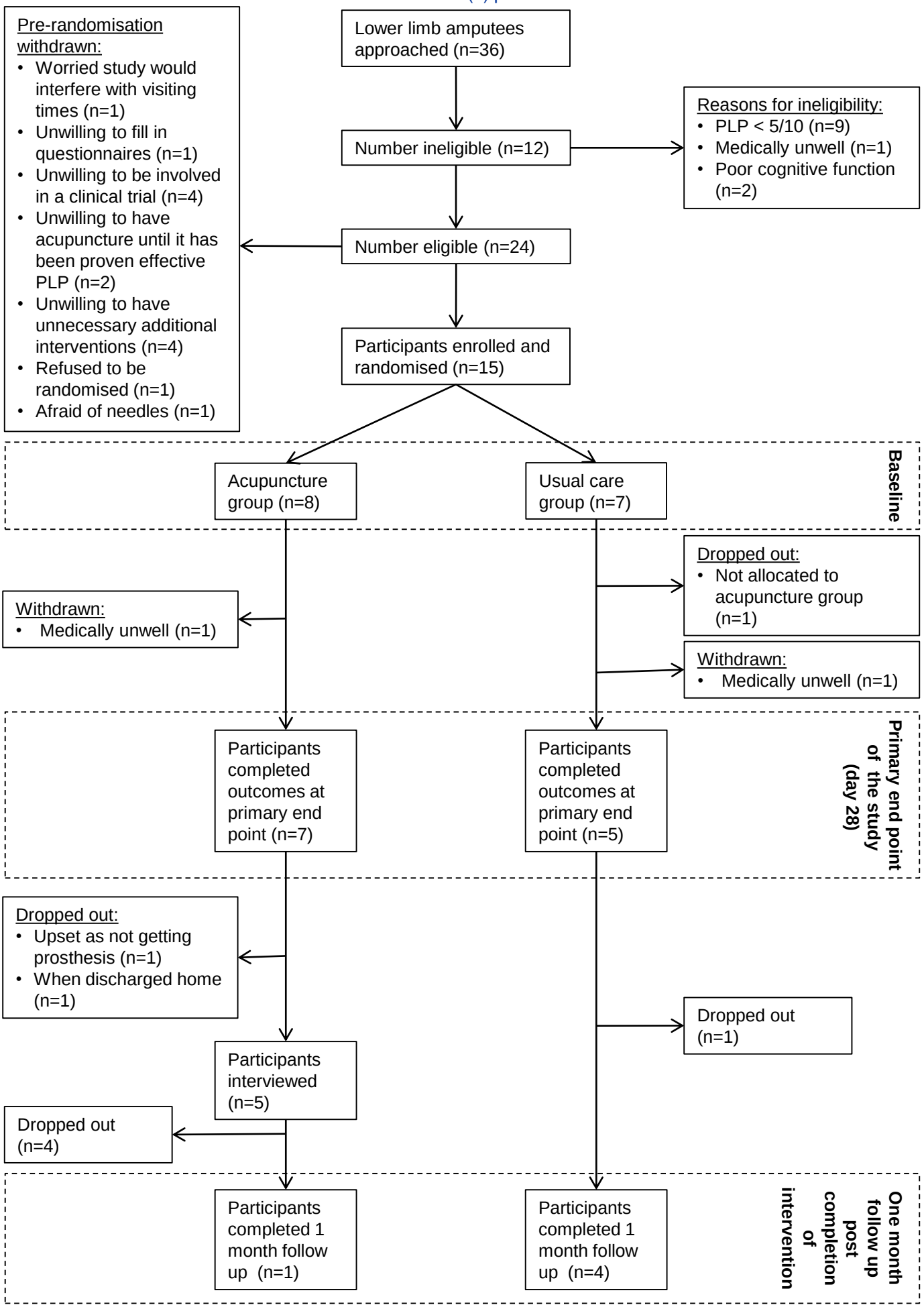

Figure 2 Boxplot average pain intensity

Click here to download Figure Box plot NRS average pain intensity.pdf