Author’s response to reviews

Title: Home management of lower limb lymphoedema with an intermittent pneumatic compression device: A Feasibility Study

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Author’s response to reviews:

Dear Editor,

Subject: Submission of revised paper PAFS-D-18-00147

Home management of lower limb lymphoedema with an intermittent pneumatic compression device: A Feasibility Study – Pilot and Feasibility Studies

We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes to the manuscript can be found using the page and line references below. We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,

Nyree Dunn

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Reviewer 1

Thank you for your ongoing and helpful review. The authors have addressed your points below:
1) Table 1 - as you have taken out the p-values as suggested, the footnote about statistical tests is now redundant (page 6, line 23-24). This has been removed.

2) The only p value you have now included is for comparison of QoL scores (page 11, line 4). If, as the previous reviewer suggested, it is not appropriate to discuss statistical significance for limb volumes in light of the small sample size then presumably it is not relevant for the QoL results either? – P value has been removed (page 11, line 13). If this is the case the section on 'statistical analysis' (page 8, line 11) also needs amending. This has been removed since the advice of a previous reviewer we removed all stats as results were not a focus of this feasibility study.

3) I still think table 3 is unclear. Is it showing the mean differences between R leg and L leg over time such that over the first 3m, the difference between the affected and unaffected limbs increased by 300 in the control group and 78 in the intervention group i.e the lymphoedema worsened in both groups but more so in the control group? If so, it would be clearer to show the mean absolute differences for each group at baseline, 3m and 6m timepoints and the change. The table has been amended to clarify these points.

4) In a related point linked to the clarity of table 3, in your results section you state "The largest changes were seen at 3-6 months; for the control group the mean difference in volume was +128 mls, 95% CI [-303, +560] and for the intervention group, +311 mls, 95% CI [-226, +848] (Table 3)". I'm not clear in what way this was the largest change as from the figures given, these are neither the largest numbers nor the greatest differences. Agreed, this point has been removed.

5) Page 13, line 9 - there is a 's' missing off the end of week. This has been amended (page 13, line 19).

Reviewer 3

Thank you for your thorough review and helpful points. The authors have addressed your points below:

Abstract:

Well-written and appropriate, containing the relevant information. The authors could add one sentence in the Results section (around line 18) about the trend in outcomes/efficacy to support the feasibility of a future study, assuming that the trend in outcomes is positive. Results indicate that there isn’t any trend but that this could actually be due to confounding factors (which are discussed later in the paper). The authors believe that this is too complex to allow adequate description/explanation within the context of an abstract.

Introduction
Appropriate and concise Introduction. My comment is around the final paragraph attending to the Aim/Purpose and Objectives of the study. The Aim is well-written, but does suggest "efficacy" although the purpose is clear about the feasibility of the study. The authors could clarify this statement of the purpose by saying:

The purpose of this study is to evaluate the feasibility of the study design and to gather insight/trends into the possible outcomes, with a view to support the design and implementation of a future definitive study.

The objectives of this study are to:

1. Conduct a pilot RCT using established outcome measures;
2. Evaluate the research design and process;
3. Explore possible outcomes and offer insights into possible results/outcomes;
4. Provide recommendations related to the sample size, design and implementation of a definitive RCT.

The aim of this study is stated as ‘to evaluate a proposed methodology of a study design’. The main section of the paper has been written to correspond with the objectives as set out in this paragraph.

Methods

Randomisation (page 6 line 28)

I suggest sentences to provide more detail regarding randomisation would be appropriate, cover the additional topics of: who did the randomisation (independent researcher/administrator, or the researchers themselves?), how was the randomisation determined (use of random numbers? Out of a hat?). This information is useful for a pilot study as evaluation of the randomisation process and approach is part of feasibility assessment and to ensure the reduction of researcher or selection bias. More information has been added (page 7, lines 14-16)

Control group (page 7 line 11)

There is some variation to the control group intervention(s), which may confound the effect of determining the effect of each intervention. This variation of intervention in the control group suggests that the sample size in the future definitive trial would need to be larger to smooth out or accommodate for these confounding factors. The authors should consider this and include this insight into the sample size determination of a future trial. Consideration of these points has been added to pg. 14, line 24.
Intervention Group (page 7 line 21)

How and where were the patients trained to use the equipment and apply the treatment schedule - did they attend a workshop? Was training done at the same time as the assessment consultation with the appointment being longer so to do the equipment training on a one-to-one basis? A longer appointment was not necessary, an hour was allocated to each participant, the whole hour was not always used. Was each patient checked to see if they could and were using the equipment properly? Is any of this was done then it should be described in this section. If not, then this should be recommended as improvement to the future study design. This has been added (page 8, line 12-15).

Outcome Measures (page 8 line 9)

The outcome measures and tools/questionnaires are mentioned in the Methods section towards the beginning, but not in very much detail. The authors should offer a description of the Primary Outcome Measure(s) (the most important ones and the ones that will be used to base effect size calculations/estimates and sample sizes for future studies will be based) and Secondary Outcome Measure(s) (useful and informative, but no critical to the study). Then, each outcome measure should be briefly described and why it/they were chosen. A paragraph has been added to pg. 5. Line 18-23, addressing these points.

Statistical Analysis (page 8 line 12)

Authors should make it clear in this section that inferential statistics is an adjunctive process in this study and not a key objective - to provide insight and trends to possible outcomes.

However, if the authors want to conduct some level of inferential statistics, the process and methods should be described in more detail here, and should include: the statistical methods used and a rationale why; how both the summary statistics and statistical results were interpreted and the benchmarks/levels of significance; how was the data managed and by whom; were effect size calculations done; was there a sample size calculation or estimate for this pilot study and also for a future study - what methods and why; how was the sample size estimated, what is the proposed sample sizes; what type of statistical correlation was chosen and performed; confidence intervals?

Knowing the statistical methods used for this pilot study, then insight and recommendations could be made regarding the statistical methods and approach for a definitive study in the future, which is part of determining feasibility of a future study.

As the focus of this study was to assess a proposed study methodology, statistical analysis of results relating to proposed outcome measures have not been included (this was on the advice of a previous reviewer). All references to statistical analysis have therefore been removed.
Retention (page 9 line 2)

Retention, Drop-outs, loss to follow-up, subject allocation, and distribution of type of lymphadeodema are all important components to this section, because known then drop out or loss plus condition distribution enables the researcher to estimate the time needed, number of patients and resources/funding required to conduct a fully powered definitive RCT in the future - all important information in planning and implementing a future study.

The authors should elaborate on the above topic in this section over 4-5 sentences.

Noteworthy, if the dropout or loss to follow up can have a dramatic impact on results and inferences if there is small sample size, as in this study, of 10/group - the authors may end up trying to make inferences and decision based on data from 4-5 patient, which may not be enough. The authors believe that this has been covered in the paper.

Discussion

Feasibility

The authors discussed the relevant issues and insights related to the study and make good recommendations for a future definitive study/RCT.

I note there is no sample size estimate, which may be useful. However, the sample size was seemingly too small in this study, with too low a Power, and too high a drop out and missing data, that the results of this pilot study is confounded i.e. this pilot study is in itself too small to make reasonable inferences around feasibility and viability of a future larger study. The authors should offer some insight and suggestions around this problem so to convince readers that this pilot study was sufficient in itself to offer advice on feasibility. The focus of the paper is to help define the structure and duration of a future RCT and was not designed to provide an estimate for a power calculation.