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 are tracked. 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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Response to reviewer 2:

Reviewer #2: I found this manuscript to be concise and very to-the-point regarding the purpose, design, results, and discussion. However, on certain points I feel it was too concise and lacking
detail. I've commented below on areas that could be elaborated further to better explain or document the study. There are also a small number of grammatical or formatting issues, noted first.

Page 3, line 44: no period at end of "...successful lymphoedema management [4,5]" This has been added (page 3, line 15).

Page 13, line 24: no period at end of "...and viscoelastic properties [24]". This has been added (page 14, line 12).

Page 13, line 37: no closing single-quote for the full spelling of the Lymph-ICF-LL questionnaire; though it's not clear that you necessarily need an opening single-quote. This has been removed (page 14, line 18).

Both Table 1 and 2, in the lymphoedema stage row, 100% for stage II and 0% for stage III, but "(0)" in all cases for the number of participants. This has been changed (table 1, page 6. Table 2, page 9).

Figure 3 shows that 3 subjects were lost to follow-up in the control arm before the 3 month follow-up, but then has n=8 at the 3-month follow-up. This figure has been changed.

Page 4 identifies differences in IPC modality (proximal-distal vs distal-proximal, equivalency to manual lymph drainage technique). In the study design, could you clarify how the IPC device chosen in this pilot study works? Furthermore, it might be useful to comment on how the results of a larger study would or would not be generalizable depending on the nature of the device used. Also, you note that there is lack of consensus for treatment parameters using IPC; how was that overcome or addressed by this study, and in the next study? Information regarding how the utilised IPC device functioned has been added (pg. 4, line 12) and this has been further elaborated on (pg. 7, lines 16-17). Our subsequent study, which is currently recruiting, is evaluating both IPC compression modes by randomising participants to either mode for their intervention period; this information has been added to pg. 15, lines 13-17.

As participants utilised the IPC devices in their home environment, their safety was a prime concern and as such the devices was set to operate on the pressure and time duration recommended for home use by the device manufacturer (this information has been added to pg. 7, lines 17-20). Whilst there is a need for evaluation of different treatment parameters for IPC use, the study team believe that this should be undertaken in a supervised environment and therefore was not evaluated by this study or the subsequent study which focus on home use of IPC.

Page 6 notes that limb volume measurements were taken at baseline by an RN with experience in this area; how was this accuracy maintained at the follow-up visits? Follow up limb volume measurements were also undertaken by the same RN – this information has been added to pg. 6, line 2-3.
Also, Table 1 provides a comparison of demographics between control and intervention. With only 20 participants total, it does not seem that this study is sufficiently powered to have statistically significant outcomes or differences in participants, thus the p-values are not surprising, but nor are they relevant. Later, on page 10, the table of mean leg volume differences does not show p-values for comparison of means. I would suggest being consistent about this, either including or excluding them. The p values for Table 1 have been removed.

This also speaks to the manuscript not commenting on why 20 was the sample size for this study, or whether 20 would be sufficient/insufficient to show any statistical significance in outcomes. It's clearly stated that the objective of this study is feasibility, not treatment effect, but the choice of sample size and consequent power of the study should be commented on, if at least to inform how large a larger study would need to be to show significant treatment effect. The sample size was limited by the number of IPC devices we had to use – we had 10 machines and one year of funding. As there were no definitive change in limb volumes a power calculation was not informative, so we decided to include subjective measures and a more focused quality of life questionnaire for a larger study.

Page 8: could you comment on the pathophysiological difference between Stage II and Stage III lymphoedema and how this might impact the analysis of study outcomes with respect to use of the IPC device? This has been added to pg. 11, lines 10-15. It's explained in the Discussion how recruitment bias may have affected the demographics of the participants, but not whether IPC may be more or less feasible or acceptable for an individual with stage II vs stage III lymphoedema, thereby affecting the recruitment, retention, and analysis of a larger study that does include individuals at stage III.

Page 10: the mean leg volume differences table and analysis is confusing. Is this reporting an increase or decrease in volume over time? As in, between the 3 month and 6 month follow-ups, across the Control group, was there a mean leg volume increase of 128.42 mL? For some participants leg volumes increased whilst for others leg volumes decreased – the mean volume differences are stated in the Table (this has now been denoted using + or – signs in the table to make this clearer for the reader). There appears to be a very wide variation in volume change (again, on trends, considering that 5 of the 6 confidence intervals cross 0). If you could, please clarify further what these results are reporting and their significance. Information has been added to clarify this (pg. 10, lines 17-18).

Also, a table for the QOL scores would be helpful. This has been added (page 11). The study design also only notes the QOL questionnaire being completed at baseline, not at the 3 and 6-month follow-ups, yet here it was clearly was being completed at follow-up. It should be clarified in the study design when the questionnaire was being completed. (this information has been added to pg. 8, lines 3-5).

Page 12: to address participant apathy in the control group, consequent to not receiving an IPC device, you suggest using a cross-over design and five-week intervals. Considering that five weeks is less than the 3 month follow-up interval in this study, and not in accordance with the general follow-up schedule at the lymphoedema clinic, could you clarify why 5 weeks would be appropriate for the next study design (especially if 3-4 weeks is more common in clinical
practice when MLD is the treatment modality)? 5 weeks decided upon to allow the participants to have a week getting used to using the device and 4 subsequent weeks of IPC treatment to ensure any if there were short term effects they would be reflected in the results.

Furthermore, how will shortening the IPC intervention period to 3-4 weeks affect longer-term analysis? Would you still attempt 3 and 6-month follow-ups to assess for long-term impact on lymphoedema after a short-term intervention? How generalizable and clinically useful would the results of the next study be if the intervention period is shortened, for the sake of reducing participant burden? This has been addressed pg.13, lines 12-15.

Page 13: additional outcome measures important to participants were identified, including subjective 'limb heaviness' and 'tightness'. However, to address this, the use of the Myoton Pro is suggested and it is explained how it collects objective data. How will the next study address the subjective outcome measures? This information has been added to pg. 14, lines 12-13.

Regarding Intervention Feasibility, it might also be useful to clarify here (as opposed to above under Study Feasibility) how the next study would try to ensure, or at least assess, proper use of the IPC device, considering that lack of this was a drawback in this study. This has been addressed by using a shorter intervention period to minimise participant burden, study diaries have also been simplified – filling out a 5 week diary is less mundane than filling out a diary for 6 months.

Page 14: although this is a feasibility study and thus not intended to draw conclusions about the effectiveness of the intervention itself, I think it would be worth in the Discussion section either (a) commenting on any trends noted in the analysis of study outcomes, or (b) explicitly stating why there is no comment on any potential trends that speak to the effectiveness of the intervention. This has been commented on pg. 14, lines 1-4. Furthermore, considering that next study will be looking for effectiveness of the intervention, how does this study inform the nature of the intervention for that next study (e.g.: choice and modality of the IPC device itself, frequency of use, comparison to MLD and otherwise standard of care).

Answered above.