Author's response to reviews

Title: A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease.

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Author's response to reviews: see over
Dear Prof Alam

Re: A randomised trial of three or one breathing technique sessions for breathlessness in people with malignant lung disease.

MS:  1671029929172375

Thank you for the opportunity to revise our manuscript taking into account the statistical and other two reviewers. We are grateful for their time and expert eyes. We think the message is now more strongly presented, and we have gone through the flow chart and text carefully to iron out the errors that had crept into the manuscript – very grateful to have had those spotted, thank you.

We present our responses below in blue italic text.

Yours sincerely

Miriam Johnson, on behalf of the investigator team.

Statistical Review

I would prefer to see a sentence justifying the 2:1 ratio of intervention allocation (unless I've missed it), though this does not affect the robustness of the conclusions at all.

Thank you – we have inserted the following, “This was done in order to minimise a potential increase in demand on usual services from participating in a trial actively seeking to recruit patients.”

2. I would prefer to see the estimate and confidence interval for the primary analysis in the abstract, though I recognize that interpretation of the AUC may make this less helpful than usual.

Apologies for this omission – now corrected.

3. Given the width of the confidence interval, I feel the conclusion that “three sessions conferred no additional benefits over one” is a bit strong. Would it not be safer to say “there was no evidence that three sessions conferred any additional benefits over one”?

Thank you – we have done as suggested in the abstract, discussion and conclusions

Reviewer SS

I have only minor/discretionary revisions:

Thank you for such an encouraging review. The suggested revisions are addressed point by point below.
Page 5, end of first paragraph: At what time did the re-calculation happen: June and/or July 2013?

Thank you. The review of attrition was conducted in June and the sample size recalculated in July. We have simplified this by removing (July 2013) in the subheading.

Page 8, sensitivity analysis: did the sensitivity analysis include the impact of different places of delivery (at home, in hospital) or which profession delivered the session?

This would have been interesting, but we did not look at this aspect.

Fig 1 (page 21 – the heading is placed on page 18): I am struggling with this figure because of a few points:

- 528 patients were not enrolled because the patients declined (they were asked but said no?)? Or was it a question of eligibility (did not full-filled inclusion criteria)?

All figures in the box entitled “excluded from enrolment” were those who were eligible (see previous box in flow chart) but who declined the invitation. To make this clearer we have inserted “invitation” to read: “Declined invitation no reason given by patient”

- Analysed group 3 session: n=43: although only 39 patients got the intervention (box above). Does this mean that 4 patients were included in analysis without getting the intervention?

Thank you so much for spotting this. There is an error in the text (page 6, first line of results): this has been corrected to “(52 to three session; 104 to single sessions)” which is now consistent with the Fig 1 flow chart and results Tables. There were two participants that withdrew from the trial prior to receiving intervention from each arm and were not included in the analysis. This is explained in the text in the sentence 2 in the results on page 6. We have clarified Fig 1 to reflect this more clearly.

- Allocation group 3 session: 39+11=50 – but n=52. What about the last two patients?

This has been addressed in the comment above.

Table 1: What does “preference” mean – preference for what? Preference for study allocation is mentioned later at the end of the table.

Thank you. We have now inserted “and pre-randomisation preference for study allocation.” in the text in the methods and results where this is mentioned to make this clear.

Reference 24: please check again: is “kind p” the author (because it is written in lower cases)?

Thank you for spotting this typo. Now corrected.

Reviewer MM

The trial concerns an important clinical question and the findings are likely to be useful to a large multidisciplinary audience. Major strengths of the trial are its external validity – participants from multiple settings were offered a pragmatic intervention – and the novel concept of an optimal dose of supportive care – considering adverse effects of excess treatment burden.
Thank you for such positive comments.

Major:

Different patient flow numbers are reported in the text, figure 1 and table 3,

Thank you for spotting these discrepancies. We have checked through again and corrected the errors, added a bit more explanation to the final 4 week analysis numbers in Fig 1 and also clarified table 3 for the same purpose. (also see comment to reviewer SS)

and the absolute numbers do not match percentages (e.g. page 6, para3, 131/156 does not equal 86%).

Apologies for this confusion. This was one of the errors – the final number of participants with sufficient data over the 4 weeks to perform an AUC analysis were 124/156 = 79%, as 7 (124 + 7 = 131) participants still in the study at 4 weeks did not have sufficient worst NRS scores over the first 4 weeks to allow an AUC calculation. We have changed this in Table 3 to make this clear.

In all cases there appears to be selective attrition of patients (worse performance status, worse breathlessness NRS) and higher attrition in the one session group, which would reduce the chance of observing a difference if three sessions were superior.

When the 2:1 randomisation is taken into account, there is no material difference – ie by 8 weeks 42 were lost to follow up or withdrew in the single session arm (41% attrition), and 23 from the three session arm (46%).

Minor:

The statistical methods text uses different tenses, refers to incorrect tables (Table 2 not Table 1),

These have been corrected

proposes analyses that are not to be presented (psychological traits),

We have removed this sentence

and repeats earlier text (stratification by site reported under randomisation).

In the statistical methods we are describing presentation – we have therefore changed “stratification” to “presented” to make this clear.

The planned use of imputation (primary outcome not secondary outcomes) does not match reported results, e.g. imputed QALYs, ‘sensitivity’ complete case secondary outcomes. Some re-ordering would improve readability.

We have added “Management of missing data for the cost-effectiveness analysis is described below” at the end of the statistical methods main section to make this clearer. In the statistical methods sub-section on cost-effectiveness analysis we have added “A sensitivity analysis using multiple imputation to account for missing data was performed” to reflect the results for the cost-effectiveness analysis.
The manuscript would benefit from more consistent terminology, e.g. shortness of breath vs. breathlessness; one session vs. single session; trial vs. study; patient vs. participant; arm vs. group; three then one session vs. one then three sessions. Table 3 introduces the terms high-intensity and low-intensity which don’t feature elsewhere.

Thank you – we have done a find/replace check for these issues. We could only find one “shortness of breath” in a reference title, but we have aligned session, trial, participant (once the patient had consented and was participating in the trial), arm and keeping the order of three vs one to reflect Fig 1 and Tables 2 and 3, and we have edited Table 4 to reflect the same pattern.

Page 5, para 1 – useful to specific what the authors mean by ‘earlier consent’

Thank you – we have added the following “(consent to trial participation even if their reported breathlessness intensity did not fulfil the criteria for randomisation).”

Page 7, para 4 – the text suggests weekly descriptive will be reported (graphical representation of the primary outcome may be interesting) thought only weeks 4 and 8 are offered.

This now reads, “Descriptive statistics for the summary weekly measures at week 4 and week 8 are shown in Table 4”

Page 9, para 4 – suggest insert ‘breathing’ before training in last sentence.

Done

Page 10, para 1 – suggest insert no ‘objective’ measure of physical activity.

Done

Page 11, para 1 – the final pre-conclusion point could be spelt out more. I read it that the authors are suggesting breathlessness services can serve more patients if they adopt a standard of one session of breathing training and assuming services are offering more than one session currently. This is an important point for readers but is only implicit in the current text.

Done