Author’s response to reviews

Title: Fish oil supplementation in chronic obstructive pulmonary disease: feasibility of conducting a randomised controlled trial

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Author’s response to reviews:

We appreciate the time the reviewers spent reviewing our manuscript. As a result we have made a number of revisions and feel that the manuscript is vastly improved.

Fish oil supplementation in chronic obstructive pulmonary disease: feasibility of conducting a randomised controlled trial" (PAFS-D-17-00021)

Response to reviewers:

Our responses can be found directly under each reviewer comment (Author response).

Reviewer #1

This manuscript achieves its objectives of describing the results of a pilot trial, exploring logistical challenges in conducting the trial, and providing recommendations for a successful full-scale trial. It is extremely well written and has only a few errors (both on line 226). The only suggestion I have is to make a small table of the recommendations so they are easily identifiable;
however, this is not necessary and can be ignored if the authors choose. I recommend that this paper be accepted for publication with little to no revisions.

Author response: The paper has been reviewed and errors corrected. Recommendations (previously included in a section titled proposed protocol changes resulting from the study findings) have been put into a table (Table 3).

Reviewer #2

This is a useful paper describing a randomised feasibility study on people with COPD. That it concludes that a main trial cannot be conducted with a similar design to the feasibility study makes it particularly useful for the relevant research community. I have a number of suggestions for improvement.

1. Objectives. Table 1 is useful in providing a clear list of measures used to assess objectives and associated progression criteria but the division into process and scientific outcomes is confusing and appears inconsistent with the text at the top of page 6 where feasibility and scientific outcomes seem to be mutually exclusive? The text and table need to be made consistent and clearer. I could not see objectives actually listed on page 4 as suggested by the CONSORT checklist and there isn't any explanation as to why some of the objectives are considered "key" and therefore described in the abstract while others are not. It would also be useful to put some confidence intervals around some of the rates calculated.

Author response: At the time the protocol for this study was developed in 2012 and published in early 2013 a decision was made to divide the outcomes into those reflecting “process” and “scientific outcomes” based on the available literature at the time. We agree that this may not be clear in the manuscript (text and tables). We have revised the abstract, methods and results sections to focus on feasibility criteria. As recommended for reporting of clinical trials (to avoid selective reporting of planned outcome measures), we have retained the “scientific outcomes” (Table 1) as these were proposed a priori (published protocol) but have endeavoured to clarify that the end sample size precluded any meaningful analyses of these. We have included a statement indicating why some criteria were considered key (lines 128-129).

The introduction has been amended to include a list of study objectives (lines 71-76). Consort criteria have been checked against the revised manuscript (tracked changes were ‘accepted’ to do this).

2. Sample size. I wasn't convinced by the rationale for the sample size based on the Lancaster or Browne papers. I don't think the intention in the Lancaster paper is to suggest a specific sample size to be used in a study to estimate parameters for a sample size calculation, and there are a number of papers on the subject more recent than the Browne paper.
Author response: We agree that there are other available methods of calculating sample size. At the time the protocol was developed (in 2012) and published in early 2013 there was very little guidance on the appropriate method to calculate the sample size for pilot and feasibility studies. A section (lines 145-152) has been added in the manuscript to reflect the more recent literature.

3. Statistical significance tests. These are not appropriate in a feasibility study since the study will not be powered to detect differences. They should be removed from the paper. If effect sizes are to be presented or discussed, confidence intervals should also be presented.

Author response: We agree that tests for statistical significance are not appropriate for this feasibility study. The key issue here revolves around the discrepancy between the prospectively planned protocol (published 2013) and the outcome of the study. We had prospectively planned the scientific outcomes in the original protocol as a basis to explore variability and effect size differences between groups as a basis for estimating sample size for a larger well powered RCT, should the planned protocol be deemed feasible. As it turns out, this protocol could not be deemed feasible (recruitment, sample achieved etc). Given the sparse literature in this area, we think there is value in reporting the effect sizes (and confidence intervals) which would allow other investigators to see the size of change (within and between groups). We acknowledge that with such a small sample that any sample estimates based on this data are very conservative and likely to reflect the “worst case” i.e larger samples are likely to reduce the confidence limits and provide greater confidence of the real difference between groups. In order to address this, we have:

1) Clarified the issue between the proposed statistical analysis (protocol) as a basis for future sample estimates and the outcome of the feasibility study (data analysis section of methods)

2) We have revised the manuscript and tables in Appendix 2 to include effect sizes with confidence intervals for scientific outcomes (a consistent calculator has been used for confidence intervals and therefore the effect sizes have been updated)

3) Removed all results for tests of statistical differences

4) Explicitly addressed this issue in the discussion.

4. At the top of page 8 the sentence beginning "Of the 27 participants consented to participate ..." does not make sense.

Author response: The section describing participant flow throughout the study has been revised, including this sentence (Lines 174-194). Figure 1 has also been updated to better describe the recruitment and enrolment stages.
5. I expected the results section to be structured according to the objectives and think it would be clearer if it was. In particular, retention and inputs for sample size calculation for a larger study are not mentioned. The latter is mentioned in the discussion but as per comment 2, I think the rationale given needs to be rethought.

Author response: The results section has been restructured according to the feasibility criteria listed in the methods section. We have explicitly stated in the results that we were unable to do sample size calculations (line 270-273).

6. The last column in table 2 should be removed. Because of the small sample size it would be surprising if there weren't some differences between the groups and highlighting them in this way doesn't really serve any purpose.

Author response: The last column in table 2 containing effect size calculations has been removed. We have added Borg ratings of perceived breathlessness to the participant characteristics (table 2) and removed these from appendix 2 as it is not a scientific outcome (nor was it identified as such in the planned protocol).

7. I liked some of the suggestions for improving recruitment. Later in the discussion other research is mentioned; some of the studies reached their target recruitment, others did not. I would have been interested in knowing whether there are lessons to be learnt from these studies about strategies to improve recruitment in a future study. Can something on this be included?

Author response: This is a very good point. To date there are very few studies on this topic (omega 3 supplementation in people with COPD). Of the available studies, only the Thomashow et al. (2014) study reached the recruitment target but was published only as a conference abstract which lacks this detail. A combined therapy study has been described in this section and a new study that is underway in North America has been referred to (noting that the study is not yet completed). Additional sentences have been added (lines 391-403).

8. On page 14 the authors suggest that: "It is recommended that the primary outcome be chosen based on outcomes that are most likely to be affected by the intervention". if this stays in the paper, can the authors provide a reference for this statement? However, it wasn't clear how the following discussion related to the work contained in the paper and therefore whether it was relevant here?

Author response: We agree that this sentence was confusing and ambiguous. Our intent was to flag the need for future studies to clearly match the primary outcome to the proposed mechanism of the intervention. Following discussion, we have deemed this section does not add to the work presented in this paper and therefore it has been removed.