Author’s response to reviews

Title: Supervised and home-based physical exercise in patients newly diagnosed with multiple myeloma – a randomized controlled feasibility study

Authors:

Rikke Faebo Larsen (rfl@regionsjaelland.dk)
Mary Jarden (mary.jarden@regionh.dk)
Lisbeth Rosenbek Minet (lisbeth.minet@rsyd.dk)
Ulf Christian Frølund (ucf@regionsjaelland.dk)
Niels Abildgaard (niels.abildgaard@rsyd.dk)

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Author’s response to reviews:

Reviewer reports:

Reviewer #1: This is a well-written and well-designed feasibility study in an important area. There is a strong need for research in this area, and demonstrating that myeloma patients are willing to be recruited just after diagnosis is very valuable. I only have minor comments for clarification.

Thank you.

The use of accelerometers and objective fitness is commendable. Are patient interviews planned? It would be particularly interesting to understand how patients felt about being approached so close to diagnosis and how they felt if randomised to the control condition.

Answer: Thank you. We certainly agree with the relevance of conducting patient interviews, but this was not included in the study. However, we would like to mention that we have not experienced that patients have withdrawn from the feasibility study due to allocation to the control group.
It seemed the information on accelerometers was missing from the methods. In addition, proportion of accelerometer data meeting compliance would be a useful addition to table 4 as useful to know how well they were tolerated by participants.

Answer: We have added information about accelerometer measurements in the methods section (p8, 197-198), as well as in the result section (p11, 275-277) and in Table 4 (p12).

Regarding the study timeline - recruitment began in June 2015 and the current paper presents data from 30 patients recruited between then and June 2016. The paper was submitted June 2019 stating the trial is still ongoing. One might have expected the main trial to be complete at this stage given the target sample was 102. Some clarification would be useful. Understanding timelines and recruitment are helpful data from a feasibility trial.

Answer: For sure, it is quite a long time since we had the feasibility data for our own use. It has taken some time to finalize and submit the manuscript Also, a previous lengthy review process and then rejection by another journal delayed the submission process. We would like to point out that the previous journal suggested that this paper would be a better fit for “Pilot and feasibility studies”. Study inclusion is now complete, and we are presently waiting for the final test sessions to be carried out.

Statistical comparison of demographics between intervention and controls seems unnecessary.

Answer: We have deleted the comparison of demographics from Table 2 (p9), as well as in the statistical analysis section (p8, 211-212) and results section (p8, 217-220). This correction answers the editors comment number 7, as well.

Who conducted the assessments? Were these trained researchers? Regarding blinding - was there any indication of how successful this was? It is very difficult to retain blinding in an exercise trial since patients will often mention having attended the hospital for an exercise session etc. Useful if this was recorded as helps the design of future studies.

Answer: Trained physiotherapists, who received a structured introduction in carrying out the assessments, conducted the assessments. This information is added to the methods section (p5, 127-128). We fully agree that blinding is a challenge and documenting the success of blinding would have been helpful. We did not do that, but we did make efforts to minimize the risk of allocation being revealed. First, the assessors reminded the patient not to tell about their allocation, and secondly the training facility for the intervention patients was located in an area where assessors would not typically be regular visitors.
Regarding the exercise intervention - who delivered the supervised sessions? Am assuming this was the study physiotherapist, but this could be explicitly stated beginning of the intervention paragraph. In addition, the figure was a little hard to follow so it was a little unclear how the weekly sessions took place. The hashtag seemed to suggest 4 sessions, but the other symbols suggested three. In addition, the fluctuating weekly pattern could have been further clarified.

Answer: Physiotherapists performed the supervised session. We have added this information, and furthermore added that they had a structured introduction to the intervention (p6, 166-167).

Figure 1 has been completely revised and changed. So regarding this figure, we have not made a regular track and change (see separate file), except for the legends (p5, 146 and p6, 147-156). In the revision process of figure 1, we decided to change the ‘naming’ of the time points. We have also changed the naming of time points throughout the manuscript. We hope this will make it clearer and more logical in this way.

Re the controls - was there any indication of how many participants took up a physician ordered exercise plan? Potential for contamination in terms of exercise?

Answer: We collect retrospective information of exercise after the final test session, and thereby we have that information to be used in the RCT paper (the main study), where the effect of exercise will be evaluated. We agree that there will be a risk of contamination of the results. The simple fact that patients participate in an exercise study may inspire them to be more active. The authors find it more relevant to include this information in the RCT paper than in this feasibility trial. We hope the reviewer can accept this decision.

Table 4 is a little unclear in terms of ns and labelling.

Answer: We have made some adjustments in Table 4. Both in labelling and in the legend (p12).

Reviewer #2: This is a relevant contribution to the field of exercise oncology, addressing a cancer population that has been under-researched - Multiple Myeloma (MM). The study is novel in examining the feasibility of a partially supervised, partially home based exercise intervention with NEWLY DIAGNOSED MM patients. It also provides and tests out a novel methodology for screening bone disease in order to evaluate and adjust the exercise testing if necessary.

Thank you.

The hypothesis, methodology and results in the paper are comprehensively and appropriately detailed. The percentage values for acceptance, attendance and adherence to the intervention clearly suggest that an exercise intervention near to time of diagnosis is feasible for many but not all patients with MM (high attrition rate).

Answer: We have made that perspective about attrition more explicit in the discussion section (p14, 333-334).
The authors mention that there was a very careful assessment of bone status which resulted in successful inclusion of patients with BD. In the methods there is a brief description of components of this systematic assessment to determine restrictions regarding the physical tests and exercise. Some additional information and/or examples to show how the assessments led to decisions on which restrictions were decided and implemented and what impact this had on test and exercise prescription would be of interest to readers.

Answer: We have elaborated on the bone assessment and its consequences for test and exercise (p5, 116-126).

The screening and monitoring for adverse events during the intervention and the exercise testing suggest that the testing and intervention was safe even in newly diagnosed older MM patients and in patient with bone disease

Associate Editor comments:

1. Abstract. Please use the structured headings: Background, Methods, Results, Discussion.

Answer: Thank you, we have changed the headings (p2) and deleted the heading “Conclusion” (p15, 368).

2. Please use “Background” instead of "Introduction".

Answer: We have changed the heading (p3, 54).

3. P3 line 52/79. Please describe the duration of intervention using weeks or months, but not both.

Answer: We have changed the text to weeks (p3, 79-80).

4. Introduction/Background, in addition to the stated aim, please list the specific feasibility objectives to be addressed by the research.

Answer: We have added the specific objectives after the overall aim (in the end of the background p4, 92-94).

5. Similar to the reviewer I found Figure 1 difficult to follow. Please review this and consider whether there is an alternative way to depict this information. Alternatively, consider including accompanying text to help guide the reader.

Answer: We have revised and changed the figure (see separate file).
6. The paragraph describing/comparing patient characteristics in intervention and control groups on P7 appears to be duplicated on P8.

Answer: The paragraph below Table 2 is deleted (p9, 229-233).

7. I am not convinced that the between group comparisons on demographic/clinical characteristics are helpful given such small numbers. Please consider removing these from Table 2 and paragraphs on p7 & p8.

Answer: Corrections are made in the statistical analysis section (p8, 211-212), Table 2 (p9) and the result section (p8, 219-220).

8. There are a large number of abbreviations and acronyms used in the manuscript, often multiple times within individual sentences. Please consider whether all of these are necessary.

Answer: We have reduced the use of abbreviations. See the list on p16, 416 and p17, 418-426.

Additional corrections from author:

Odense Patient data Explorative Network is corrected to Open Patient data Explorative Network, since the network has changed their name after submission (p8, 205-206).

We have added a reference (number 30) in order to comply to the comment from reviewer 2 about bone disease and restrictions (p5, 125).

Furthermore, we have checked the reference which was not validated (Elsawy), and now it is correctly stated (ref. nr.35, p20, 512).