Author's response to reviews

Title: Effects of light-emitting diodes on muscle fatigue and exercise tolerance in patients with COPD: a randomized clinical trial

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Author's response to reviews: see over
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To the Editor in Chief
Doug Altman, University of Oxford

Re: Effects of light-emitting diodes on muscle fatigue and exercise tolerance in patients with COPD: a randomized clinical trial

Dear Professor,

We appreciate the reviewer’s extensive revision and suggestions to our manuscript which has improved it. Please find below a point-by-point response to each comment.

1. Page 5, paragraph 2, line 1. The sample size if 30 here while it is 35 on P 2, l 5 as well as P 10, p 4, l 3. Make them all agree.

   We have corrected the sample size in all parts mentioned by the reviewer.

2. P 5, p 2, l 1 and 2. Rewrite as [… FEV1 ≤ 70% predicted]…].

   Sorry, but we cannot understand why the reviewer asked us to change “≤” by “#”. We respectfully disagree with your suggestion because we do not use this symbol “#” to specify the severity of the pulmonary function for patients with COPD. The spirometric criteria for copd severity is FEV1 less than or equal to 70% of the predicted value. (Global Initiative for Chronic Obstructive Lung Disease. Global strategy of the diagnosis, management and prevention of chronic obstructive pulmonary disease updated. National Institutes of Health and National Heart, Lung and Blood Institute. Eur Respir J 2003; 22:1-95). Therefore, we have decided to keep the symbol “≤”.


   We did it.

4. P 5, p 3, l 2. Insert the date that the trial was registered.
We insert the number of the trial registered. (See P 5, p 1, l 3).

5. P 5, p 4. Multiple outcome measures are listed and just one can be the primary. Which one is the primary? Each outcome measure should have its scale stated, the MCID for it and some idea how long it takes to administer each measure as well as all of them. The sample size justification on P 10 does not state which outcome measure this is computed to handle. If multiple outcome measures are to be analysed, and tested, how will the conclusion be handled If there is conflict in the statistical significance of the multiplicity of measures?

We completely agree with you and we have specified the primary outcome (endurance time on cycling). We have added the scale for each outcome in the “Outcome measures” (P 5, p 3, l 1, 3 - 6). Unfortunately, we do not have the MCID for each outcome of our study. We have inserted the time of each measure according your suggestion (P 6, p 1, l 7; P 7, p 1, l 1-2; P 8, p 2, l 19; P 10, p 1, l 1-2). We have added that the sample size was calculated based on the endurance time (First sentence of the Statistical analysis - P 10).

Thank you for warning us about the implications of analysing multiple outcomes. Because of that, we have decided to specify our main outcome which was used to calculate the sample size. However, we will also look at the behavior of other variables described as secondary outcomes.

6. P 5, p 4, l 3. Replace [parameters] by [variables]. A parameter is a characteristic of a distribution of a variable in a population of patients and not another name for a variable in a sample. Also P 8, p 3, l 2.

We modified as suggested.

7. P 6, p 2, l 10. What happens if the variability is > 5%?

We have specified in the body of the text when the difference in strength of three contractions exceeding 5%, another measure of MIVC will be requested and also that the greatest value of these three contractions will be considered as the MIVC. (P 6, p 2, l 11-13)

8. P 7, p 3. There are too few R(eference)s to the methods used here. Each one should have a R.

We insert more references as suggested.
9. P 7, p 3, l 11. Who has validated the program? Is it published anywhere?

The matlab routine was developed specifically for our study. A professional specialist in this software was the one who developed the matlab routine for our study. We have used this routine in another study from our laboratory, but we still do not have published it (We are finalizing the discussion of that study for future submission).

10. P 8, p 1, l 18. Was this modified as well? Should R 23 be cited here?

*We cited the R 23 as you have suggested.*

11. P 9, p 1, l 6, 7, 8. Insert the company and city where these can be obtained.

*We insert the information you requested.*


*We did it.*

13. P 10, p 2, l 2. Rewrite as [1 h].

*We did it.*

14. P 10, p 3. The details of the randomization are not adequate. See CL Meinert’s clinical trials book on P 86 for how to do it. Stratification is mentioned in Figure 1. What is the stratification factor and how many levels does it have? This does not appear to have been considered in the sample size calculation below and is not mentioned in the statistical analysis section.

We made a mistake. *There is no stratification for randomization. We apologize for this. We have corrected the figure 1.*

15. P 10, p 5, l 1. Rewrite as [Assuming a Type 1 error rate of 0.05 and a Type 2 error rate of 0.2 …]. What is the justification for these choices? Also why is the MCID chosen as 55 sec and the sd of 79? Was the R 31 study done the same as you plan to do? Do you have any local pilot data to back these up? Was any software used to calculate this sample size? Document it. Does this apply to the other outcomes besides DET of the many listed on P 5? How has stratification been considered? Is this to be a one or two tailed test? What will you do if there are missing data? What about sample size for P 11, p 1 on endurance time?
We have re-written the sentence as your suggestion. We have opted for a Type 1 error of 0.05 because it is not only usual but also appropriated to assume a 5% chance that the observed result is not true. Usually the error type 2 is set at 0.2 which means that the probability of not committing a Type II error (false negative) is equal to 80%.

Because we have no pilot study, we assume the MICD and sd from the reference 31 which also used an electrophysical intervention (neuromuscular electrical stimulation) to increase the endurance time for a dynamic protocol on cycle ergometer (similar to ours).

We used the GraphPad Instat tm Program (version 2.0) to calculate the sample size. We have added this information (Page 11, p 4). We do not apply the sample calculation for the other outcomes.

About the stratification, we have already answered it (Please, see Comment number 14).

We have assumed a two-tailed test because it does not specify a direction. We want to know whether the endurance time is either higher or not after LED application in comparison with placebo.

It will be used the intention to treat analysis with the baseline data being used for missing data from patients who did not complete all assessments\(^35\). An additional analysis of the results involving only those patients who complete the treatment originally allocated will be also performed (per protocol). We have added this information in the Statistical analysis (P 11, p 1, l 2-5).

We have specified that the endurance time was used to calculate the sample size.

   
   We did it.

17. P 11, p 1, l 5. Rewrite as […] paired Student’s t-test.]
   
   We did it.

18. P 11, p 2, l 5. Rewrite as […] for normal distributions and Spearman’s correlation will be used for non-normal distributions.]
   
   We did it.

19. P 11, p 2, l 6 and 7. Rewrite as [The level of significance will be set at 0.05.] P values are compared to the level and if they are < than the level they are declared to be statistically significant. What do you plan to do about multiplicity from the multiple
outcomes? What do you plan to do about missing data if there are any? What software do you plan to use for data management and the statistical analyses?

We completely agree with you about the level of significance. However, as we have added the Type 1 error in the second sentence of the Statistical analysis, we believe does not need to include that “The level of significance will be set at 0.05.”

About multiplicity analysis, we have answered it in your Comment number 5.
About the missing data, we have answered it in your Comment number 15.
Surely we will use the SPSS software for data management and the statistical analyses.

20. p 13, p 1, l 5 to 7. Where are the Rs to justify this statement.
We have added more studies that justify that statement.

21. P 14. [SIC] is missing from the list of short forms. See P 22, Figure 2.
We have added it at the list of short forms.

22. P 14, last p. Given the number of statistical issues that were not used correctly in this protocol, you might consider adding a statistical consultant to your list of authors.
Thank you for your suggestion. We believe that with your comments/recommendations about the methodological and statistical analysis issues our study protocol has improved greatly. Possibly, when we have the data set we will consult a statistician.

23. P 15, R 4 appears to be correct.

24. P 16, R 11, 12 and 18 appear to be correct.

25. P 16, R 10, l 2. The author is [De Necochea-Champion R].
We corrected it.

26. P 17, R 20 and 21. Both of these were not verifiable and should be translated into English with the translation in [square brackets]. At the end of the citation enclose the (language) in round brackets.
We modified as suggested.
27. P 17, R 23 appears to be correct.

28. P 17, R 26, I 3. Insert [(4-5)] after [87].
   *We did it.*

   *We did it.*

   *We modified as suggested.*

31. P 20, R 44 and 47 appear to be correct.

32. P 20, last l. Replace [Parameters] by [Settings]. Also P 23 l 1.
   *We did it.*

33. Figure 2. Why is there a double randomization? Where does stratification take place?
   *Because we have two different protocols (isometric and dynamic). Then, the patients will be randomized to receive either placebo or LED for each protocol. As previously answered, there is no stratification.*

Yours sincerely,

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