Author's response to reviews

Title: Effect of TENS on pain in relation to central sensitization in patients with osteoarthritis of the knee: protocol of a randomized controlled clinical trial

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Author's response to reviews: see over
To whom it may concern,

Dear reviewers,

First, we would like to thank you for critically reviewing our manuscript “Effect of TENS on pain in relation to central sensitization in patients with osteoarthritis of the knee: protocol of a randomized controlled clinical trial”.

It is without any doubt that your comments and remarks have led considerably to the improvement of our paper’s quality. All revisions can be found with track changes in the MS Word document.

Furthermore, we have added a point by point response to the concerns of the reviewers (new pagination of the document with visible tracked changes in response).

We hope the revised version of our manuscript will meet the standards of your journal.

With my sincere thanks,

Yours faithfully,

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<table>
<thead>
<tr>
<th>REMARKS FROM REVIEWER 1</th>
<th>New p.</th>
<th>RESPONSE TO THE REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>l54 ( remove bold</td>
<td>Line l58</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l85 change 1 to one</td>
<td>P4; l91</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l87 appear to appears</td>
<td>P4; l93</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l100 &quot;on&quot; TENS to &quot;to&quot; TENS</td>
<td>P4; l106</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l106 6 weeks to 6 week</td>
<td>P4; l112</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l107 12 weeks to 12 week</td>
<td>P4; l113</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l115 and a follow up period and randomisation should be changed to randomization to remain consistent with the rest of the manuscript</td>
<td>P5; l122</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l142 take to taking</td>
<td>P6; l149</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l146 Randomization needs to be described in more detail as well as how allocation will be concealed.</td>
<td>P6; l153</td>
<td>A detailed description of the randomization and allocation procedures have been added to the revised manuscript.</td>
</tr>
<tr>
<td>l205 Intervention group is described but how will sTENS be administered.</td>
<td>P8; l228</td>
<td>A description of the TENS administration has been added to the revised manuscript.</td>
</tr>
<tr>
<td>l227 secundary to secondary</td>
<td>P9; l260</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l230 GPE is an outcome measure in methods that should be reported in the abstract</td>
<td>P9; l263, &amp; P2; l32</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l240 Also, since this is a home based program, how will compliance, use of co-intervention and adverse events be measured? One call at 6w does not seem sufficient</td>
<td>p10; l273, &amp; p9; l241</td>
<td>We plan to call the participants weekly during the 6 weeks to ask for adverse events and co-interventions. Also, as a response to the comment of reviewer 3, we will ask patients to come back after two and four weeks.</td>
</tr>
<tr>
<td>l256-8 A regression......This is a confusing sentence.</td>
<td>P10; l282</td>
<td>In a response to the comments of reviewer 2, we changed some of the statistical analysis. We hope that these changes improved the readability of the revised manuscript.</td>
</tr>
<tr>
<td>l257 bmi to BMI</td>
<td>P10; l294</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
<tr>
<td>l289 remove during</td>
<td>P11; l330</td>
<td>The requested changes have been applied in the revised manuscript</td>
</tr>
</tbody>
</table>
| Reference 10 does not look complete and too many colons. | All references have been checked and formatted according to the journal's
REMARKS FROM REVIEWER 2
1. Page 2, paragraph 4, line 39. Suggest including a [,] after [i.e.].
   P2;140

2. P 2, p 5, l 1. Also include the date of trial registration and include the date the first patient was randomized if that has already happened. If the trial is completed, state the date the last patient was randomized.
   P2;142

   P2;148

4. P 2, p 6, l 47. Should this not be [OAk] rather than [OA]? Also l 48 on the same P.
   P2;149

5. P 3, p 1, l 60. Should [osteoarthritis] not be [OA] since it is already defined?
   P3;164

6. P 3, p 2, l 72 and 82. Should [WDR] on l 82 not be [WRD] as defined on l 72 as well as P 11, l 307?
   P3;177

7. P 3, p 2, l 77. [TS] is defined here but left out of the list on P 11.
   P3;182

8. P 4, p 1, l 87. Suggest adding [s] at the end of [appear] to read [appears].
   P4;193

9. P 4, p 3, l 94. Suggest adding a [,] after [i.e.]. Also P 10, p 3, l 274.
   P4;1100

10. P 4, p 4, l 107 to 11. Given that this variable is not yet standardized, should not a study of the measurement tool be conducted before doing a trial? As a primary outcome measure this tool should have stated reliability, validity and responsiveness in the hands of the people who are being used to measure outcomes of patients in this trial.
    P4;1117

11. P 5, p 4. What about patients who have had recent uses of hyaluronic acid products such as Synvisc or Durolane?
    P5;1137

12. P 6, p 1, l 148. How many and what are the age strata?
    P6;1156

13. P 6, p 2, l 156, 159, 160, 162, 163 should all use [,] rather than [,] to represent the decimal place.
    P6;173-184

RESPONSE TO THE REVIEWER
The requested changes have been applied in the revised manuscript

The requested changes have been applied in the revised manuscript
The study has not started yet.

The requested changes have been applied in the revised manuscript

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We added an extra exclusion criterion as it has been proven recently that these products may have an impact on pain during the 24 weeks following intra-articular injection.

Age-strata have been defined in the revised manuscript.

The requested changes have been applied in the revised manuscript
14. To properly inflate the size of 42 by a loss of 15%, you should divide by 0.85 to get 49.4 and round up to 50 per group. In addition, you have not accommodated the loss of degrees of freedom for the two stratification variables of age and sex. For sex, you should increase the total sample size by 1 and the increase for age will depend on the number of strata that you plan to use. See 12 above. Consider adding the two groups sample sizes and state the total sample size to be recruited.

15. Suggest dropping [OA] since osteoarthritis is already part of the [WOMAC] name. Moreover, we inflated the sample size by 10% per potential confounding factor as proposed by Krikwood and Sterne (2003).

16. Delete [in order] in front of [to] as the words are redundant in English.

17. What is the experience of the investigators in using the sensitization instrument? Provide data if you can.

18. Suggest replacing [average] by [mean].

19. Do you have a reference for this choice?

20. Insert a space to read [30 s].


22. Replace [parameter] by [variable]. A parameter is a characteristic of a distribution of a variable in a population; not another name for a variable in a sample.

23. Insert a space to read [100 Hz].

24. Replace [score] by [scale]. Also provide a reference to this method.
25. P 8, p 4, l 227. Replace [parameters] by [variables]. Also replace the [u] by [o] to read [Secondary].


27. P 9, p 6, l 249 and 250. The sample size is too small for the KS test of normality. Consider trying one of the other ones that work with small sample sizes such as Shapiro-Wilk and indeed it is important to test residuals from models, not basic data from groups. So this sentence should be modified.

28. P 9, p 6, l 250. It is not necessary to test baseline values. It is more important to measure the randomization integrity. Any differences in baseline variables should be due to chance. See Dore and Altman where this is discussed in detail.

29. P 9, p 6, l 251. You should consider replacing the Student’s t test by ANOVA since you should be taking the stratification factors into account in your analysis. Also for the logistic regression in l 257.

30. P 9, p 7, l 254. Suggest inserting a space to read [6 w].

31. P 9, p 7, l 256. Rewrite as [0.05].

32. P 9, p 7, l 257 and 258. Suggest inserting [;] after [state] and replacing [dependent] by [independent].

33. P 10, p 4, l 279. Why did you mention cost effectiveness? You have not proposed measuring any costs so how can this be done? Consider dropping this.

34. P 11, p 1, l 292. Since no subgroups are identified as yet, consider dropping this from your protocol. Subgroups should be defined in advance ideally with a literature reference as to why it should be considered, have power to be statistically significant in one subgroup and not the others, and have the ability to detect an interaction between the subgroups and the treatment factor.

35. P 11, p 2, l 307. WRD is defined differently here than on P 3, l 72.

The definition of WDR is adapted and homogenized through the whole manuscript.
reviewer likes to see issue numbers added as they help to find the article when a reader wants to read the R.

36. P 12, R 4, l 1. Delete [(Oxford)].

37. P 12, R 7 appears correct.

38. P 12, R 9, l 1. Delete [(80-)] and on l 2, insert [(694)] after [150].

39. P 12, R 10, l 2. There should be a location and city for this type of R.

40. P 12, R 12, l 1. Replace [p] by [Panel] as the author; and on l2, insert [(10)] after [81].

41. P 12, R 14. There is now a 5th edition of this classic book, and is also available online. It appears to also be Chapter 1. Should these issues be considered for a reader?

42. P 13, R 20, l 4. insert [(10)] after [59].

43. P 13, R 22, l 2. Insert [(1-2)] after [129].

44. P 13, R 23, l 3. Insert [(1-2)] after [109].

45. P 13, R 26, l 3. Insert [(2)] after [15].

46. P 13, R 28 appears to be correct.

47. P 13, R 30, l 2. Insert [(4)] after [24].

48. P 14, R 38, l 2. While [tens] is lower case in the database used for checking, you have used [TENS] in its conventional form in the rest of the text. What does the actual paper do? Also insert [(2)] after [35].

ALL REFERENCES HAVE BEEN CHECKED AND FORMATTED ACCORDING TO THE JOURNAL’S GUIDELINES.

REFERENCE 4
The requested changes have been applied in the revised manuscript.

REFERENCE 9
The requested changes have been applied in the revised manuscript.

REFERENCE 10
The requested changes have been applied in the revised manuscript.

REFERENCE 12
The requested changes have been applied in the revised manuscript.

REFERENCE 14
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REFERENCE 15
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REFERENCE 24
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REFERENCE 25
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REFERENCE 35
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REFERENCE 39
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REFERENCE 40
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REFERENCE 41
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REFERENCE 42
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REFERENCE 44
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REFERENCE 45
The requested changes have been applied in the revised manuscript.

REFERENCE 46
The requested changes have been applied in the revised manuscript.

REFERENCE 47
The requested changes have been applied in the revised manuscript.

REFERENCE 48
The requested changes have been applied in the revised manuscript.

REMARKS OF REVIEWER 3
it would be important to ask the patient to come back for two or three follow-up visits to assess its ability to precisely replicate, over the 12-week period, the TENS installation.

P9;I260 We agree with this remark and we have adapted the revised manuscript accordingly.