Author's response to reviews

Title: Derivation and validation phase for the development of clinical prediction rules for rehabilitation in chronic nonspecific low back pain patients: a protocol of a randomized controlled trial

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Author's response to reviews: see over
Concerns: revision manuscript MS: 6518630951397356 Derivation and validation phase for the development of clinical prediction rules for rehabilitation in chronic nonspecific low back pain patients: study protocol for a randomized controlled trial.

Dear Dr. Doug Altman,
Dear Dr. Curt Furberg,
Dear Dr. Jeremy Grimshaw,
Dear reviewers,

Thank you for your interest in our manuscript. We have read your remarks and suggestions carefully and have modified the manuscript according to your review. Our responses to your remarks are presented below in a point-by-point discussion: remarks are cited in bold, while our responses are given in italic. We have highlighted the changes in the main text as well. When line numbers are changed we added the new line number in our answer.

We hope this revised version meets your expectations and look forward for your reaction.

On behalf of all authors,
Yours sincerely,

Mrs. Lenie Denteneer
Editorial requests:

1) Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?__________: study protocol for a randomized controlled trial
   We changed the title as requested:

   L3 “Derivation and validation phase for the development of clinical prediction rules for rehabilitation in chronic nonspecific low back pain patients: study protocol for a randomized controlled trial.”

2) Please reformat the Abstract. This section should be composed of the following sections: Background, Methods/Design, Discussion, Trial Registration.
   L35-L58 We changed the sections into the requested ones.

3) Please include the date of registration with the trial registration number at the end of the Abstract.
   L56 “This trial is registered at ClinicalTrials.gov on February 10, 2014 with the ID number: NCT02063503”

4) Please include the reference numbers provided with ethical approval with your ethics statement in the Methods section.
   L121 “Ethical approval (B300201215600) was obtained from the local ethics committees of the University of Antwerp, the Antwerp University Hospital and APRA rehabilitation hospital.”

5) Please include a figure title and legend section after the reference list.
   L602 “Figure title and legend
   Figure 1: Flow chart, representing the design of the derivation phase
   Figure 2: Flow chart, representing the design of the validation phase”
1) The power analysis to calculate sample size contains unclear two-tailed hypothesis statement in derivation phase. The sample size calculation may be different depending on what hypothesis is: a one-tailed or a two-tailed hypothesis. The comment made on the one-or two-tailed hypothesis is correct. Indeed in the derivation phase we use a two-tailed hypothesis. We changed the text as such:

L253  “Because we can’t predict therapy effect in the derivation phase, we use a two-tailed hypothesis to calculate the power. A pilot study showed that the standard deviation of our primary outcome measure, the MODI, is comparable to the results of Brennan et al. [15]. Given these estimates, 120 patients are needed to detect a minimum clinically important difference (effect size 0.43) with 80% power using a two-tailed hypothesis. This means that 3 X 40 patients need to complete the whole trial. Since Van der Wouden et al. [32] mention a dropout rate of 54%, we aim to include 260 patients.”

2) In the study design, the interest is that treatment success will be higher in the matched group than in the unmatched group which means a one-tailed hypothesis. However in the validation phase, when sample size is calculated using power analysis, a two-tailed hypothesis is presented to determine if there is a difference in matched and unmatched therapy for success Where is the discrepancy?
Thank you for your comment. You correctly state that a one-tailed hypothesis should be used. We have recalculated our power analysis for the validation phase and adjusted the text:

L262  “In the validation phase the intervention therapy stays the same but new patients will be included. In this study design, the interest is that treatment success will be higher in the matched group than the unmatched group which means a one-tailed hypothesis is used to calculate the power. In the validation phase we need 105 patients to detect a minimum clinically important difference (effect size 0.43) with 80% power using a one-tailed hypothesis. This means that 3 X 35 patients need to complete the whole trial. Again we take a dropout rate of 54% into account and aim to include 229 patients.”

3) In figure 2, letter “B” was dropped out of intervention group
We adjusted the mistake in figure 2.

4) Third paragraph in discussion section mentioned “1,5 year” being taken to finish each phase for collecting samples. Does it mean 18 months?
1,5 year was indeed meant as 18 months. We adjusted the text to 18 months:

L345  “This means that we need around 18 months to finish each phase.”
Reviewer’s report Dr. Nithima Vichatrong:

1) **Comment:** This research paper is quite interesting. It tried to create a new way of clinical prediction rule in order to choose exercise therapy method. However, the author should address one important point on a concern that this CPR may be used to choose patients for only one method of exercise. In reality combination of methods may be used according to condition of patients and judgment of physiotherapists. Moreover, the author should indicate and give rationale on research design and reason for choosing these three types of exercises. Also, implication for future use in clinical trials should be given.

Ł To answer the first question regarding the rationale on research design and reason for choosing these three types of exercises we would first like to refer to the text:

L71 “The large group of patients meeting these criteria is heterogeneous and therefore these patients represent a treatment challenge for every clinician. There is a consensus that exercise therapy should be used as a therapy approach [2] but little consensus has been reached about the preferential type of therapy [3-14]. There appears to be a wash out effect due to the heterogeneous character of CLBP patients. In response to this, the European guidelines [2] express the need for the development of tools which improve the classification and identification of specific clinical sub-groups of nonspecific CLBP patients.”

The three chosen types of exercises all have been proven effective in research (see references 3-12 in text). The problem is that no type of specific exercise approach could be pointed out as superior. We are aware of the fact that often a combination of methods are used, but we have chosen to work with exercise therapy since it is advised as preferential therapy approach for chronic LBP in the European guidelines. If we can validate a CPR for chronic non-specific LBP this would not mean all patients who match the CPR should only get the matched therapy form, but the matched therapy could be emphasized in the therapy/revalidation.

Ł The implication for future use in clinical trials should indeed be given. We added this in the discussion section:

L347 “The current study protocol describes only the derivation and validation phase, and not the impact phase. Future research should target this impact phase. The impact phase needs a totally different approach since it investigates the economic consequences of the implication of the CPR. It also depends on the outcome of the derivation and validation phase. Consequently, it is beyond the scope of the present paper.”

1) **Objectives:** should delete the word in blankets: derivation and validation phase
We deleted the two words in the abstract.
2) **Objectives:** the second objective should be “to validate a clinical prediction rule for the three forms of exercise therapy for patients with chronic non-specific LBP”

   We changed the sentence as suggested:

   \[L40\] “Secondly, to validate a clinical prediction rule for the three forms of exercise therapy for patients with nonspecific CLBP.”

3) **Background:** the author is interested in these three forms of exercise for the treatment of chronic non-specific LBP. In my opinion, the motor control exercise and isometric training of lumbar trunk muscle are acceptable as a form of CNLBP therapy but not for general active exercise. Please give rationale for using this intervention.

   Rationale for each treatment group is based on previous intervention studies using these types of exercise therapy. These references are added in the intervention section of the text.

   - **For motor control exercise:** \[L216\] “…and has proven to be effective in nonspecific LBP [4-7, 10].”
   - **For general active exercise:** \[L230\] “General active therapy has proven to be an effective therapy approach in nonspecific LBP [5, 6, 14].”
   - **For isometric training:** \[L236\] “Effectiveness of isometric training therapy has been proven in nonspecific LBP [11-13].”

   We added the following references:

4) **Background:** in the fourth paragraph: please provide the meaning of the abbreviation “LR+” in the first use.

   \[L89\] “Presence of three or more of the predicting factors leads to a positive likelihood ratio (LR+) of 4.0 (95CI: 1.6 – 10.0) and increases the post-test probability of success with motor control therapy from 33% to 67%.”

5) **Background:** Figure 1 (it is a table not figure) should be deleted since readers can find those detail from provided references.

   We deleted the figure.
6) Methods/design: Study design  
no need to mention too much on the third phase or impact analysis in the part of study design
We agree with this statement and have deleted the information on these phases.

7) Methods/design: Intervention  
No need to give the detail regarding another twelve sessions after nine weeks of intervention of RCT. It has no impact on the result.
We agree with this statement and have deleted the information regarding the additional 12 treatment sessions.

8) Methods/design: Motor control therapy  
should deleted “…” from the sentence. Please put the name of the whole target muscles.
We are unsure if we fully understand your question but we have rewritten the sentence using “such as”. If we name all the target muscles involved in lumbar stabilization we feel this would be too much information. Therefore we only named the most important ones:

L211 “The local stabilizing muscles (such as M. Multifidi, M. Transversus abdominis, pelvic floor muscles and diaphragm) together with the global muscles (such as M. Erector spinae and M. Rectus abdominis) are important in creating spinal stability [23-25].”

9) Method/design: Please provide the references for general active exercise and the Isometric therapy.
We would kindly like to refer you to our answer in question 4.

10) Method/design: Table 4  
a. Please provide the meaning of MCT
We added the meaning of MCT below the table:

"*MCT (Motor control therapy), **ADI (Abdominal drawing in), ***DTM (dimensional trunk movements), ****TD (Tergumed device)"

b. Several names of exercise the author provided in your table is unclear, for example: Reverse lunge, Lat pull down, Low row, Front raise, Side raise, please rewrite or put another column to explain how to conduct the exercises.

We searched for a convenient way to provide an explanation for the given exercises in Table 4. Instead of rewriting the table, we decided to provide this information in an additional file (additional file 1). We hope this gives a suitable answer to your question.

L247 “Exercises mentioned in Table 4 are further explained in an additional file (Additional file 1) which explains the performance of each exercise.”

L756 “Additional files
Additional file 1: Performance exercises Table 4”
c. Please indicate the use of Tergumed device for flexion/extension/rotation/lateroflexion in which part of body? 

*We adjusted this within the table:*

<table>
<thead>
<tr>
<th>Tergumed Device</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TD**** for lumbar flexion</td>
<td>X</td>
</tr>
<tr>
<td>TD for lumbar extension</td>
<td>X</td>
</tr>
<tr>
<td>TD for lumbar rotation</td>
<td>X</td>
</tr>
<tr>
<td>TD for lumbar lateroflexion</td>
<td>X</td>
</tr>
</tbody>
</table>