Author’s response to reviews

Title: Effectiveness, costs and cost-effectiveness of chiropractic care and physiotherapy compared with information and advice in the treatment of non-specific chronic low back pain - study protocol for a randomized controlled trial

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Version: 1 Date: 28 Sep 2017

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Detailed replies to the comments from the reviewers follow below (all the changes are highlighted in yellow in the manuscript):

Reviewer 1:

1) With reference to the statement in the background "With limited health care resources and stretched health care budgets, it is important to strive for efficient use of scarce resources". Clarification/justification for having the Chiro + Physio (+ info/advice) group is warranted.

Response: We have revised this as suggested by the reviewer - See line 177-193.

2) It is not clear in Fig 1 that treatment groups 2-4 also receive the same information and advice as in group 1. I would suggest that this is revised. Similarly under 'Study treatments', this fact needs to be made more clear.

Response: We have revised this as suggested by the reviewer - See new Figure 1.

Reviewer 2:
The present study aims to evaluate the effectiveness and cost-effectiveness of chiropractic care and/or physiotherapy with information and advice and information and advice only. This can help to reveal if one of the treatments is superior and results might be helpful in decision making processes. However, the importance and rationale of this trial should be discussed and highlighted more. Furthermore the cost-effectiveness analysis should be described in more detail. Because of these aspects and as well because of linguistic aspects the present manuscript needs some revision.

Major comments:

Title: 1) One aim of the study is to evaluate the cost-effectiveness: This should be mentioned in the title (not only "costs")

Response: We have revised this as suggested by the reviewer – see line 1-3.

Abstract: 1) In "Methods" it is not clear, that "information and advice" is present in all groups.

Response: We have revised this as suggested by the reviewer – see 54-56.

Background: 1) 84-94: More aspects of CLBP and its consequences should be discussed (more detailed).

Response: We have revised this as suggested by the reviewer – see 79-84.

Background: 2) 89: How high are the costs for this disorder? Examples would be helpful.

Response: We have revised this as suggested by the reviewer – See 74-76 and 81-84.

Background: 3) 102: "Physiotherapists typically also use different types of training and exercise, which is less frequently used by chiropractors." The meaning of this and the following sentence is very broad. The authors should specify these statements and refer to literature.

Response: We have revised this as suggested by the reviewer – See 95-101.

Background: 4) 108-110: The authors should specify their statement. Main results of the cited reviews should be summarized/reported.

Response: We have revised this as suggested by the reviewer – see 108-133.
Background: 5) 117: "costs within and outside the health care system" should be specified.

Response: We have revised this as suggested by the reviewer – See 141-143.

6) 123: "QALYs" are no type of analysis. The analysis is the cost-effectiveness- (or cost-utility-) analysis.

Response: We have revised this as suggested by the reviewer – see 149.

7) 131: High internal and external validity is mentioned. However, it should also be mentioned the limitation, that the study is not powered for an economic evaluation (maybe under "Methods").

Response: We have revised this as suggested by the reviewer – see 159-164.

8) There should be a more detailed rationale for the aim of this study. Why is it important to compare these treatments? Why is there a comparison to "only information and advice"? Is the hypothesis that information and advice might be enough and the other treatments could be used less often?

Response: We have revised this as suggested by the reviewer – see 177-193.

Methods: 1) Aim and research questions should be in the section before

Response: We have revised this as suggested by the reviewer – see 195-208.

Methods: 2) The research questions should be formulated more precisely. The group with "only information and advice" is "missing" in this research question. Why are there two research questions for QALYs/costs and cost-effectiveness? By conducting a cost-effectiveness-analysis the parameters of question 2 are included and can be discussed.

Response: We have revised this as suggested by the reviewer – see 201-208.

Methods: 3) 181: "Each participant's treatment is at the discretion of the individual chiropractor and/or physiotherapist." Are there (official) guidelines existing, that define what those treatments typically include or how many sessions are standard?

Response: No official guidelines exist. This is clarified in the manuscript – see 217-218.
Methods: 4) 204: This exclusion criteria should be specified: „patients with specific pathology or who in any other way are unsuited for the study treatments."

Response: The sentence “The inclusion and exclusion criteria were developed to include patients that regularly visit the PCRU for CLBP but screen out patients with specific pathology or who in any other way are unsuited for the study treatments” has been deleted – see 236-247.

Methods: 5) 230: What is the block size?

Response: We have clarified and revised this as suggested by the reviewer – see 285-286.

Methods: 6) To increase quality of the trial, it should be conducted and reported according to the CONSORT statement (guidelines for reporting parallel group randomised trials).

Response: We have clarified and revised this as suggested by the reviewer. We have added that “The trial will be conducted and reported according to the reporting of pragmatic trials: an extension of the CONSORT (Consolidated Standards of Reporting) statement” – see 219-221.

Methods: 7) 350: It should be described more detailed how quality of life values are generated with the mentioned instrument/question (SRH). The given reference is about the EQ5D. 368-370

Response: We have clarified that this information is available in the supplementary material, and we now write: “We use a pre-scored Swedish experienced-based value set (as presented in the Online Resource with supplementary material to Burström et al. 2014 [32]), to transform SRH severity levels into quality of life (time-trade off) values.” – see 355-356.

Methods: 8) 366: A societal perspective usually includes absenteeism and presenteeism costs. Do you also collect data, like days not worked because of sick leave or how productive they are at work?

Response: We collect data on absenteeism (working status but also hours absent from work during the past 7 days due to illness), but not on presenteeism (i.e., how productive they are at work). This is now clarified in the manuscript – see 370-371, 391-392, and 545-553.

Methods: 9) Is there a guideline or recommendation of an article for the calculation of indirect costs/value of production conducted in this trial?

Response: We have included a reference (Almbrand et al. 2000) to our calculations of indirect costs - see 402.
Methods:10) How are the direct and indirect costs assessed exactly? Are participants asked for it or is a questionnaire used?

Response: We have clarified this in the manuscript – see 377-389, 391-402, and 545-553.

Methods:11) There is no description of the statistical analysis for the cost-effectiveness analysis. This is only described under "Exploratory outcome measures". According to this section, only ICERs are calculated (no bootstrapping, acceptability curves, cost-effectiveness diagram). Is that right? If a cost-effectiveness paper is planned, the CHEERS guidelines should be followed (Husereau et al., 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force).

Response: We have clarified that the cost-effectiveness analysis will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al. 2013) and Ramsey et al (2015) and how uncertainty will be analysed and presented – see 425-427 and 535-553.

Methods:12) According to the SPIRIT-Checklist there are some aspects missing (e.g. aspects of the section „Monitoring“)

Response: We have added the items in SPIRIT-Checklist also for the monitoring part and intervention section.

We have clarified the monitoring part (21a,b, 22, 23 in the SPIRIT-Checklist) – see 433-442.
We have also clarified the items in the intervention section (11b-d in the SPIRIT-Checklist) – see 258-262.

The following items in the SPIRIT-Checklist (17b, 26b, 30 and 33) are filled in as “not applicable” in the SPIRIT-Checklist. (e.g. 17b is defined as not applicable because our study is not blinded).

Discussion 1) In the discussion there is a strong focus on the recruitment. Some parts would better fit into the section "Methods". It should be more highlighted what the strengths and limitations of this trial are. There is only one sentence about the impact of results. This should be discussed more detailed. At times, some of the phrasing was a bit unclear or difficult to follow.

Response: We have modified and changed the discussion – see 569-593.

Syntax/grammar/spelling should be checked and I think that the manuscript could benefit from proof reading by a native English speaker.
Response: We agree and the manuscript has been subject to proof reading by a native English speaker. The changes have been made throughout the manuscript.

Minor Comments:

1) 127: A better alternative to „an economic evaluation is integrated in a RCT" is „an economic evaluation was conducted alongside a RCT"
Response: We have revised this as suggested by the reviewer – see 155-156.

2) 254-257 and 258: The explanation of „information and advice" is given twice
Response: We have removed the part as suggested by the reviewer – see 301-303.

3) Missing references: 86-89, 105 (there should be the reference instead of the publication year), 111-112, 125, 320 (reference of the questionnaires)
Response: We have revised this as suggested by the reviewer - see 74-77, 79-84, 91-92, 135-138, 149-151, and 327-331.

4) 446: The authors of the studies should be written down (instead of only the reference numbers 39 and 40)
Response: We have revised this as suggested by the reviewer – see 479-480.

5) The order could be modified in some sections, e.g.:
182: A "similar RCT" is mentioned here. Results of this study could be better implemented and discussed in the background section,
Response: We have revised this as suggested by the reviewer – see 119-125.

320: Outcome measures could be described first (then data collection and timeline);
Response: We have revised this as suggested by the reviewer – see 325.

404: The information, that missing data will be imputed should be mentioned and described earlier, when the use of ITT analysis is described (right now it is in 440),
Response: We have revised this as suggested by the reviewer - see 492-493.

443: The calculation of the sample size should be mentioned earlier (according to the SPIRIT in „Methods: Participants, interventions, and outcomes“)

Response: We have revised this as suggested by the reviewer – see 476.