Author’s response to reviews

Title: Intensive, personalized multimodal rehabilitation in patients with primary or revision total knee arthroplasty: A retrospective cohort study

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Intensive, multimodal rehabilitation in patients with persistent pain and functional disability after primary or revision total knee arthroplasty: An observational cohort study
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Technical Comments:
Editor Comments:
Major concerns must be addressed in the next revision.

Answer: We thank Dr Fitzpatrick (editor), Dr Sanchetti, and Naylor (reviewers) for their valuable feedback, which has given inspiration to thorough revision of the manuscript. We have addressed all comments in our point-by-point responses. The manuscript has gained in clarity and readability. We have highlighted all changes to facilitate the editor and reviewer’s work.

Reviewer reports:
Parag Sancheti (Reviewer 1): Need more literature review

Answer: The literature has been reviewed again and further references have been included as requested. Page 3-4, line 67-77

2.Inclusion and exclusion criteria not well defined

Answer: Issue related to inclusion and exclusion criteria has been clarified. Page 5, line 94-101

3.More elaboration of type of physiotherapy given required
Answer: The intervention has been described thoroughly and the TIDieR checklist has been submitted along with the revised manuscript version to further highlight the description of the intervention. Page 5-6, line 112-127 + additional file 1 and 2

Justine Naylor (Reviewer 2):
General
The issue under scrutiny is important. The idea - to provide intensive inpatient rehabilitation to people with complications 3 months post-surgery - is novel, but the design is very weak.

Answer: Thank you for noting the importance of our study. We agree that the design does not enable us to report the effectiveness of the rehabilitation program (the wording was changed accordingly in the abstract). Thus, we interpret our results very carefully and underline the need for further RCTs.

• The discussion and conclusion should be shortened and tempered by the fact the conclusions must be interpreted with caution. As the authors say, the results can be used to inform a larger more definitive study (RCT hopefully), but at best they show a weak signal of possible effect.

Answer: The discussion and conclusion have been shortened and the conclusion has been edited. Page 12-16, line 244-318

• The title is somewhat misleading.

Answer: The title has been changed to “Intensive, multimodal rehabilitation in patients with primary or revision total knee arthroplasty: A retrospective cohort study”. Title page

The intervention was given to those with complications. The patient may or may not have persistent pain as the title suggests. In fact, resting pain was not an issue as per Table 1. The title should reflect that this study was done using people with complications (and more problematic still, referred for unknown reasons as it is an assumption that all had a complication).

Answer: Under the “patient selection” section, it has been clarified that all patient had post-surgical complications based on clinical examination by their surgeon or family physician. Page 4-5, line 94-101

Ethical approval
It is unusual the study did not require ethical approval. I will leave it up to the Editor to decide whether this is fine.

Answer: It has been specified that due to the retrospective and register-based nature of the study, no approval from the ethics committee was required. Page 5, line 105-107 and page 17, line 345-349. This is based on the Act on Research Ethics Review of Health Research Projects, section 14, (2) “Notification of questionnaire surveys and medical database research projects to the system of research ethics committee system is only required if the project involves human biological material” (http://en.nvk.dk/rules-and-guidelines/act-on-research-ethics-review-of-
health-research-projects). Still, it is important to note that the study was conducted in agreement with ethical guidelines (participation, withdrawal, etc.).

Abstract
• Change "Outcomes following total knee arthroplasty (TKA) are of high interest as recent..." to simply "Recent evidence has shown that many patients suffer from persistent pain and impaired function after their surgery.

Answer: Changes has been made. Page 1, line 15-18

• In the Abstract, you need to add people were referred to inpatient rehabilitation about 3 months after surgery.

Answer: It has been added that patients with primary TKA were 3.7 months post-operative and patients with revision were 2.7 months post-operative. Page 1, line 23-24

• You also need to state this is a retrospective study

Answer: Retrospective has been added to the abstract and to the title (see above). Page 1, line 22

Introduction
• Lines 49-54. This Needs rephrasing as things are around the wrong way - "Since end-stage 51 knee OA is often treated with knee replacement, the number of total knee arthroplasties performed 52 has drastically increased over the past years, and the increase is expected to continue due to a 53 growing elderly population, an increased prevalence of obesity as well as a sedentary lifestyle 54 among both elderly and young people (3). Suggest start with "Rates of TKR are increasing due to increasing prevalence of knee OA....."

Answer: Sentence has been rewritten and shortened. Page 3, line 50-52

• Lines 59-61 For this sentence - Only 33% of the patients reported no functional 60 disability after primary TKA and 20% of patients stated that their primary TKA was not successful 61 in allowing them to resume their regular physical activities (7). As" - What is the context? That is, how many yrs after TKR?

Answer: It has been specified that results are from patients 6 months post-operative. Page 3, line 56

• Line 68 - change "regime" to "regimen"

Answer: Changed. Page 3, line 65

• Lines 76 - 78 - "A case study has proposed that patients with complications after TKA, such as chronic pain, lack of 77 effect from initial rehabilitation, infection or revision surgery, requires a more intensive 78 rehabilitation than standard treatment (4). The" The sentence does not make sense
Answer: Sentence has been rephrased. Page 4, line 72-77

• Line 85 - "Given the lack of knowledge within this patient population, it is" Change to "Lack of knowledge about management of persistent pain,....."

Answer: The sentence has been rephrased. Page 4, line 78-79

Methods
• Lines 107 - 108 - "Patients without complete follow-up from baseline to re-test were excluded from analysis. Patients without complete follow-up from baseline to re-test were excluded from analysis. Overall, 166 patients with primary TKA and 109 54 patients with revision TKA were included in the analysis (figure 1). Since all patients are referred to rehabilitation and therefore, must receive the treatment, it is not possible to sample a control group." These are results unless you are saying this is a retrospective study and this is part of your inclusion criteria? (If retrospective, you need to specify this)

Answer: The study is retrospective and this has been clarified. Page 4, line 92

Lines 167-176 - The technique to measure active knee extension seems odd. It is possible the clinician could not stabilise the femur in lying. I suggest results concerning this outcome be regarded with caution.

Answer: It has been specified how the measurement was performed. Page 7-8, line 164-169. The method is found reliable, based on the study by Jakobsen TL, Christensen M, Christensen SS, Olsen M, Bandholm T. Reliability of knee joint range of motion and circumference measurements after total knee arthroplasty: does tester experience matter? Physiother Res Int 2010 Sep;15(3):126-134.

• Lines 185-186 - when discussing effect size, what is the unit of measure ie 0.5 SD????

Answer: For clarity, we have added the equation from which the effects sizes are calculated. Effect sizes is unit less so no unit of measure can be used. Page 8, line 182-184. Based on the comments regarding the effect sizes, we reviewed the effect sizes and observed some errors in the calculation of the effect sizes. We have corrected these errors and inserted the correct values. Page 10, line 211-213 and page 11, line 222-224, 229-231, 235-237 and page 13, line 252-259.

Discussion
Limitations
Add the following limitations -
1. Retrospective study

Answer: Point added to the limitations. Page 15, line 297

2. No control so the effect size could be an exaggeration of the intervention given time is not controlled for
3. People with complications comprised the population so you did not really target those specifically with chronic persistent pain. Thus, the angle of the paper needs to change - ie treatment for people with complications (unspecified complications) as opposed to those with persistent pain.

Answer: The entire manuscript has been amended so the focus is on patients with post-surgical complications and we have avoided using the word persistent pain since this could be interpreted as all included patients had persistent pain, which was not the case as observed.

Additional comments -

- Lines 247-248 - "The results indicate that patients with postoperative complications or lack of effect from initial 248 rehabilitation can benefit from intensive, multimodal rehabilitation. Both..." The study does not show this. You have no data on what happened in the first 3 months post-surgery. All you can conclude is that people referred for late-stage intensive, inpatient-based rehabilitation after TKR or revision TKR improve significantly after 3-weeks of therapy. You do not know what would have happened without therapy and you do not know if this changes the incidence of persistent pain longer term.

Answer: We have clarified that the results are based on patients with patients with post-surgical complications. We do not have information regarding previous rehabilitation or longer term follow-up results from, and this is clearly stated the limitations. Page 13, line 247-251.

- b) Lines 248-250 - "Both the primary and revision 249 TKA groups had significant improvement in all outcome measures, except pain at rest for the 250 revision TKA group." c) The TKR gp did not change either (table 3?)

Answer: As correctly stated in the manuscript, all outcomes except “pain at rest” for the revision group showed significant improvements. Table 3 also shows this with an * placed at all results except the above mentioned “pain at rest”. Page 12, table 3

- d) Lines 285-287 - The current study showed that a patient population with post-surgical complications could benefit 286 from intensive, multimodal rehabilitation over a three-week period, although their previous 287 rehabilitation often had only little or none effect. This" Again you don't know what initial rehab did or did not do.

Answer: The phrase “although their previous rehabilitation often had only little or none effect” has been deleted and the sentence rephrased. Page 14, line 279-282.

- e) Lines 303-304 - you should provide a table comparing characteristics of people included and excluded to show if similar or not.

Answer: In table 1, we have added patient characteristics for the excluded patients. Page 9, table 1