PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rotator Cuff Related Shoulder Pain: Does The Type of Exercise Influence The Outcomes? – Protocol of a Randomized Controlled Trial
AUTHORS	Dubé, Marc-Olivier; Desmeules, François; Lewis, Jeremy; Roy, Jean-Sébastien

VERSION 1 – REVIEW

REVIEWER	Daniel Cury Ribeiro University of Otago, New Zealand
REVIEW RETURNED	20-Jul-2020

GENERAL COMMENTS	Thank you for inviting me to review this interesting protocol. I have only minor comments that, I hope, may help to improve the protocol. 1) I would suggest you using the TIDieR checklist for ensuring description of interventions are provided in detail (some info covered by the TIDieR checklist is not presented in the protocol). 2) Introduction: I wonder whether you should discuss in your intro & possibly discussion: - the findings from the trial by Bennell and colleagues (https://www.bmj.com/content/340/bmj.c2756.short), which showed exercise therapy and manual therapy was not superior to placebo, - the recommendations from a Cochrane Review (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012224/abstract), which were divergent to other systematic reviews in this topic. The Cochrane review also suggested that future trials assessing the effectiveness of exercise therapy interventions should include a placebo arm. Adding these references and discussing these findings/recommendations would strengthen the rationale for conducting your trial (and your discussion section - if you decide to discuss the strengths and weaknesses of not including a placebo arm). 3) Line 211: what happens if participants have pain 3/10 at rest? How will you define the number of repetitions? 4) Line 215: how will participants complete the digital record? Which instrument/app will they use? Apologies, but that was not clear. 5) Line 299: Are you planning to adjust alpha for multiple comparisons? Seems you are keeping the baseline measurement within the response vector. I would suggest you to re-consider this, and use baseline as a covariate in your model. (e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1121605/pdf/1123.pdf). Alternatively, you could use the 'constrained' longitudinal data analysis (e.g. https://bmjopen.bmj.com/content/bmjopen/6/12/e013096.full.pdf and

	https://onlinelibrary.wiley.com/doi/full/10.1111/j.1541-0420.2009.01332.x?casa_token=AkW7UUG757YAAAAA%3Agpa1ukjXE-Em-H3KeM_OfxbQGdenaMMZ7E1e2uom-GRIX1yB4UumeFHzzBFLYt6c2xDZtZY1iPXaPpHx), which has the advantage of increasing statistical efficiency if you have missing data at baseline or follow-up. 6) Apologies if I missed it, but I could not find information regarding how you will monitor, record and report harms. Similarly, item 21 was not addressed – the recommendation is to explain why a DMC is not necessary. I wish you all the best with this trial and look forward reading the results.

REVIEWER	Ian Horsley English Institute of Sport, UK
REVIEW RETURNED	31-Jul-2020

GENERAL COMMENTS	This is a welcomed study whose outcomes should help inform the future treatment of RCRSP. The study is well put together, but there are just a few comments I have about the design; Will you be excluding traumatic causes of RCRSP? Will you exclude patients who demonstrate a Beighton over 4- ie hypermobile patients? With exclusion criteria what will you use as you definition for adhesive capsulitis; will there be a percentage loss of passive Abd/ER ? Will you exclude patients who are diabetic? With respect to the strengthening exercises external rotation(ER) at 0° abduction with a towel has been reported to produce activation up to 41% of maximum voluntary isometric contraction (MVIC)(. Reinold et al.2007), so it may be more suitable to modify the external rotation exercise? And similarly for internal rotation. I would be keen to know the reason that exercise E Shoulder extension is bilateral exercise and the others unilateral? Finally, exercise D) shoulder protraction I would be interested in the rationale for selecting this exercise; protraction which elicits serratus anterior, also recruits pectoralis minor, which is a scapular downward rotator and internal rotator, which both have been implicated in reducing AHD and thus contributing to SAIS

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments

General comment 1: I would suggest you using the TIDieR checklist for ensuring description of interventions are provided in detail (some info covered by the TIDieR checklist is not presented in the protocol).

- **Authors response:** Added precision on interventions such as:
  - material provided: *The necessary equipment (dumbbells, elastic bands) will be provided to the patients.*
  - intervention provider: *treating physiotherapist.*

TIDierR is presented in annex of this document.

General comment 2: Introduction: I wonder whether you should discuss in your intro & possibly discussion:
- the findings from the trial by Bennell and colleagues (https://www.bmj.com/content/340/bmj.c2756.short), which showed exercise therapy and manual therapy was not superior to placebo,
- the recommendations from a Cochrane Review (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012224/abstract), which were divergent to other systematic reviews in this topic. The Cochrane review also suggested that future trials assessing the effectiveness of exercise therapy interventions should include a placebo arm.
Adding these references and discussing these findings/recommendations would strengthen the rationale for conducting your trial (and your discussion section - if you decide to discuss the strengths and weaknesses of not including a placebo arm).

- **Authors response:** Thank you for the suggestions. We added both references as well as a sentence summing up the conclusions from these studies: "*There is even some evidence in the literature suggesting that some types of exercise may not be more effective than a placebo.*[16,17] *These findings highlight the need for higher quality studies evaluating the effect of different exercises for RCRSP*.

"We also added sentences in the discussion to explain our reasons for not including a true placebo arm: *A true control group (wait-and-see approach) will not be included as it would be difficult to maintain a high retention and avoid co-interventions during the mid- and long-term follow-up. We also chose not to include a placebo group, as it is hard to have a real placebo for this type of study and it is not really ethically fair for the participants given that they will be followed for the 6 months and that the exercises used in the programs have been shown to be superior to placebo.*[14]

General comment 3: Line 211: what happens if participants have pain 3/10 at rest? How will you define the number of repetitions?

- **Authors response:** As seen in supplementary file 3*: Feeling pain in the shoulder is permissible and even encouraged during the exercise program. Any level of pain is permissible as long as it is tolerable for the individual, and, that there is no increase or exacerbation in pain in the evening and the following day.* Number of repetitions will be based on this if pain is at or exceeds 3/10 at rest. Participants will start with a lower number of reps at pain levels of 4 or 5/10 and increase or decrease depending on their pain behavior in the following hours and the next day. We added a sentence in order to explain this element.

General comment 4: Line 215: how will participants complete the digital record? Which instrument/app will they use? Apologies, but that was not clear.

Authors response: Sentences was changed to: "Participants will be requested to complete a diary of their exercise adherence."

General comment 5: Line 299: Are you planning to adjust alpha for multiple comparisons? Seems you are keeping the baseline measurement within the response vector. I would suggest you re-consider this and use baseline as a covariate in your model. (e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1121605/pdf/1123.pdf).
Alternatively, you could use the 'constrained' longitudinal data analysis (e.g. https://bmjopen.bmj.com/content/bmjopen/6/12/e013096.full.pdf and https://onlinelibrary.wiley.com/doi/full/10.1111/j.1541-0420.2009.01332.x?casa_token=AkW7UUG757YAAAAA%3Agpa1ukjXE-Em-H3KeM_OfxbQGdenaMMZ7E1e2uom-GRIX1yB4UumeFHzzBFLYt6c2xDZtZY1iPXaPpHx), which has the advantage of increasing statistical efficiency if you have missing data at baseline or follow-up.

- **Authors response:** Thank you for your suggestions. We have decided to use nparLD package (R software) if parametric criteria are not met since it is not possible to assume that the covariance matrix is a compound-symmetry matrix. For the multiple comparisons, we will run post-hoc tests such as Bonferroni test. Statistical analyses section has been modified in order to reflect these changes: *If data are normally distributed, a 2-way repeated-measures ANOVA (3 interventions [Control or Strengthening or Motor control] x 5 Time [0, 3, 6, 12 and 24 weeks]) will be used to analyse and compare the effects of the three programs on primary outcome (quick-DASH) as well as secondary outcomes (X 2 time for the US-based outcomes* [0 and 12 weeks]*). Analyses will be made using nparLD package (R software) if parametric criteria are not met since it is not possible to assume that the covariance matrix is a compound-symmetry matrix. For the multiple comparisons, Bonferroni post-hoc test will be used. Alpha level was set at 0.05.*

General comment 6: Apologies if I missed it, but I could not find information regarding how you will monitor, record and report harms. Similarly, item 21 was not addressed – the recommendation is to explain why a DMC is not necessary.

- **Authors response:** Information about harms is found at line 296. We added a sentence to explain how we will report them*: If a participant presents with an adverse event, the primary investigator will report it to the Ethics Committee.* Added a sentence on DMC: *A Data Monitoring Committee is not necessary as this trial is low risk since it is not a very large RCT. The research team has opted not to undertake interim analysis.*

Reviewer 2 comments

General comment 1: Will you be excluding traumatic causes of RCRSP?

- **Authors response:** Participants with a fracture, dislocation or massive rotator cuff tear will be excluded. Also, to be included, participants must have had pain for at least 3 months. However, RCRSP arising from falls or traumas will not be excluded.

General comment 2: Will you exclude patients who demonstrate a Beighton over 4- ie hypermobile patients?

- **Authors response:** No we will not exclude them, except if they have a history of dislocation.

General comment 3: With exclusion criteria what will you use as your definition for adhesive capsulitis; will there be a percentage loss of passive Abd/ER?

- **Authors response:** Added the following precision: *restriction of passive glenohumeral movement of at least 30% for 2 or more directions.*

General comment 4: Will you exclude patients who are diabetic?

- **Authors response:** No, we will not exclude diabetics patients, if they don't present any other exclusion criteria.

General comment 5: With respect to the strengthening exercises external rotation (ER) at 0° abduction with a towel has been reported to produce activation up to 41% of maximum voluntary isometric contraction (MVIC)(Reinold et al.2007), so it may be more suitable to modify the external rotation exercise? And similarly, for internal rotation.

- **Authors response:** Although not shown on this picture, we suggested the use of a towel between the arm and the body during both rotations exercises.

General comment 6: I would be keen to know the reason that exercise E Shoulder extension is bilateral exercise and the others unilateral?

- **Authors response:** We chose to do it bilaterally in order to prevent trunk rotation compensation during the exercise.

General comment 7: Finally, exercise D) shoulder protraction I would be interested in the rationale for selecting this exercise; protraction which elicits serratus anterior, also recruits pectoralis minor, which is a scapular downward rotator and internal rotator, which both have been implicated in reducing AHD and thus contributing to SAIS

- **Authors response:** The aim of the strengthening program is to gradually load the important muscles of the shoulder in order to increase strength, load tolerance as well as induce changes in the tendon structural properties. Since the serratus anterior is an important scapula stabilizer we chose to include it. We feel that if this exercise is performed adequately (as prescribed by the treating therapist), it should not lead to reduction of AHD. Recruiting scapular downward rotators and internal rotators should not directly lead to reduced AHD. Patients should have to change their recruitment pattern to have a decreasen AHD.

VERSION 2 – REVIEW

REVIEWER	Daniel Ribeiro University of Otago, New Zealand
REVIEW RETURNED	11-Oct-2020

GENERAL COMMENTS	Thanks for your responses. Best of luck with your trial! Look forward reading the findings.