Author's response to reviews

Title: A comparison of isometric, isotonic concentric and isotonic eccentric exercises in the physiotherapy management of subacromial pain syndrome/rotator cuff tendinopathy: study protocol for a pilot randomised controlled trial.

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Author’s response to reviews:

Cindy Gray, PhD
Associate Editor
Pilot and Feasibility Studies

September 6th 2017

Dear Dr Gray,

Re: PAFS-D-17-00006R1

“Comparison of isometric and isotonic (concentric and eccentric) exercises in the treatment of patients diagnosed with rotator cuff tendinopathy/subacromial pain syndrome: feasibility study protocol for a randomised controlled trial.”

Rita Kinsella, BSc (Hons), MMACP; Sallie M Cowan, PhD, Grad Dip (Manip Physiotherapy); Lyn Watson, Grad Dip (Manip Physiotherapy); Tania Pizzari, PhD

Thank you for your detailed letter and very thorough review of our manuscript. We have made the required amendments and believe that our manuscript is much improved as a result.

The following documents the changes we have made in response to your comments.

Comment 1 * Line 38: the authors state the study is to determine "feasibility" but it is unclear what "feasibility" is or how it is defined. A sentence here on indeed how feasibility is measured/determined would be useful to inform the reader;
Response: Thank you for this comment. The following text has been added in the background and aims section to further inform the reader: “Various key parameters including ease of recruitment, suitability of the assessment algorithm, adherence to the exercise intervention including home based exercises, compliance with log-book completion, retention rates and, nature of adverse events will determine whether this study design can feasibly be undertaken as a full-scale RCT.” Line 114-117.

AE COMMENT: The reviewer was asking for text to be added to the abstract, not the background and aims section. I agree that the specific aim of the study needs clarified in the abstract. In addition, (ln43) you don’t need to repeat that this is a protocol for a feasibility study.

R2 AUTHOR RESPONSE: Thank you for this comment. The repetition in line 43 has been removed and the following text has now been added to the abstract:

“The primary outcome measure will be feasibility which will involve evaluation of key study parameters including (a) ease of recruitment (rate and number as well as suitability of the assessment algorithm); (b) adherence to all phases of the exercise intervention including home program compliance and log-book completion, (c) participant non-completion (drop-out number and rate) and (d) adverse events (nature and number)". Line 48-52.

Comment 3 * Line 44: the sample size of 36 is indicted. I assume that this sample size was estimated using some list of criteria, or was it arbitrary? Note that performing inferential statistics n a total sample size of 36 (12 per group over 3 groups) very unlikely to offer meaningful results, so the authors should consider outcomes with great caution and should not be the focus of this pilot study;

As per our response to comment 2 above, the authors agree that the primary focus of this study is to determine feasibility and that any inferential statistics should be treated with caution. Line 40-43

AE COMMENT: I think the sentence starting ‘the analysis…’ is still too definitive for a feasibility study and should be removed

R2 AUTHOR RESPONSE: The authors agree with this comment and the sentence has been removed.

Comment 4 * Line 51: the authors state the outcome measures being used. It would be useful for the authors to divide the outcome measures into primary outcome measures and secondary outcome measures, based on the clinical importance or clinical relevance of each outcome measure. This pilot study would then focus on using the primary outcome measures to inform the design of a future study and the data from these primary outcome measures could be used to estimate or calculate the sample size needed for a future definitive study (based on calculated effect size). I am assuming that sample size estimates will be discussed in the body of the paper;
Response: Thank you for this comment. As this is a feasibility study, the authors consider that the primary outcome is whether the study in its current form is feasible to undertake in terms of ease of recruitment, suitability of the assessment algorithm, ability of the participants to comply with both stages of the exercise intervention, compliance with completing questionnaires, ease with which the assessment and treatment components are fitted into clinic schedules etc. The secondary outcomes have been listed in order of clinical relevance, as the reviewer suggests, and are being used to inform the design of the future study as well as to make some preliminary observations of clinical outcomes.

AE COMMENT: I agree with the response, however, please could you describe the method used to capture the primary outcomes as well as the secondary outcomes

R2 AUTHOR RESPONSE: Thank you for this comment. Further information has been added to the abstract and main text regarding the capture of the primary outcomes measures:

“The primary outcome measure will be feasibility which will involve evaluation of key study parameters including (a) ease of recruitment (rate and number as well as suitability of the assessment algorithm); (b) adherence to all phases of the exercise intervention including home program compliance and log-book completion, (c) participant non-completion (drop-out number and rate) and (d) adverse events (nature and number).

Line 48-52.

“The primary outcome measure will be feasibility which will involve evaluation of key study parameters including (a) ease of recruitment (rate and number as well as suitability of the assessment algorithm); (b) adherence to all phases of the exercise intervention including home program compliance and log-book completion, (c) participant non-completion (drop-out number and rate) and (d) adverse events (nature and number). The regular monthly research staff meetings will provide an opportunity for continual evaluation to gauge whether the various components of the study work well together as well as allowing collection and monitoring of data relating to the key parameters that have been identified in point (a-d) above.

Line 225-233

Comment 6 Background & Aims * The authors offer a convincing literature review in support of the pilot trial, and common sense tells us that isometric exercises would be useful in patients where their shoulder pain would prohibit full range-of-motion exercises; * Line 96: I can't help but feel that high-load isometric exercises may lead to tearing of relevant rotator cuff muscles. How would this risk be reduced or mitigated? A brief sentence here would informative;

Response: Thank you for allowing us to clarify this point. Although in the abstract the authors refer to a previous study published by Rio, E., et al., Isometric exercise induces analgesia and reduces inhibition in patellar tendinopathy. Br J Sports Med, 2015. 49(19): p. 1277-83 that investigates the use of high load isometric contractions in patella tendinopathy, in this present
rotator cuff study, the isometric exercises being undertaken are not highload and are not described as such. The isometric contraction is undertaken using a rigid band and held for up to 10 seconds. Repetitions are progressed in accordance with patient ability and symptom response. Indeed, isometric exercises are increasingly supported in the treatment of tendinopathy in different body regions and although only a small pilot study, recent findings from Parle PJ, Riddiford-Harland DL, Howitt CD, et al. Br J Sports Med 2017; 51:208–209 suggest that isometric exercises for rotator cuff tendinopathy may positively influence pain and tendon thickness. In this study, as in ours, high-load isometrics were not used.

AE COMMENT: There needs to be something added to the manuscript to make this clear (probably at this point and perhaps in the abstract too).

R2 AUTHOR RESPONSE: Thank you for this comment. The authors agree this needs clarity and the following text has been added to the abstract:

“Rotator cuff tendon responses to isometric loading are not yet established in the literature hence individualised, progressive loading will be used in this pilot study in accordance with symptoms.”

Line 43-45

and body of the text:

“Findings from a small pilot study [37] suggest that isometric exercises for rotator cuff tendinopathy may positively influence pain and tendon thickness but little has been established in the literature regarding rotator cuff tendon responses to varying isometric loads, Hence, the dosage in this present study will be semi-tailored, as per clinical practice, according to pain, severity and irritability.”

Line 117-120

Comment 10 * Line 138: the authors offer a rationale that a minimum of 30 subjects per group would be required for a definitive, fully powered RCT. Although this estimate is based on a published trial, the sample seems very low and, in my view, unlikely to offer robust data for a full-scale RCT as suggested. Calculated samples sizes for musculoskeletal disorder RCT are usually underestimated and a sample size per group of around 120 is more likely to offer valid and reliable data in a definitive clinical trial. The minimum sample per group in a decent pilot trial is generally considered to be 30 /group, so the authors need to think carefully about the sample size per group chosen for their study (at 12 per group). Julious et al (2005) offers justification for a sample size per group as low as 12, but this is within the context of highly controlled laboratory or pharmaceutical settings, and does not account for the variance found in real-life clinical practice (Julious, Steven A. "Sample size of 12 per group rule of thumb for a pilot study." Pharm Stat 4, no. 4 (2005): 287-291). If the authors are going to stick to their stated sample size then a stronger argument is needed to support the sample size, particularly since a great deal of the inferences will be drawn from hypothesis test and outcomes. Amorin-Woods et al. (2016) paper offers a good approach to pilot study design (Lyndon G. AmorinWoods, Lee
Response: Thank you for this comment. Please see our response to comment 3 above for the justification of the sample size chosen for this study.

“It is anticipated that this sample-size will provide the opportunity to observe suitability of the assessment algorithm, compliance with the exercise intervention, including any adverse responses, and enable preliminary evaluation of outcome trends, while saving the costs associated with a full-scale trial”.

AE COMMENT: the above does not reflect the full suite of primary outcomes that the authors have identified in the aim.

R2 AUTHOR RESPONSE: Thank you for this comment. The full suite of primary outcome measures has now been included in the text as follows:

“It is anticipated that this sample-size will provide the opportunity to observe: recruitment rates using the assessment algorithm; adherence to and compliance with the various components of the intervention; numbers of participants lost to follow up; nature and number of adverse events as well as; enable preliminary evaluation of clinical outcome trends while saving the costs associated with a full-scale trial.”

Line 153-157

Comment 11 * Line 156: an exclusion criteria is GHL and/or AC joint moderate-severe degeneration, which is quite sensible, but I do think that all participants would need a recent x-ray (if they do not have one) to determine the extent of degeneration. This would ensure consistency and reliability on the recruitment process;

Response: The authors agree that a recent x-ray to exclude OA of the GHJ/ACJ is appropriate. Generally the patients present with an x-ray report or images. Since we do not wish to expose our patients unnecessarily to radiation, if they have shoulder pain and have not undergone a shoulder x-ray within the previous 12 months, recommendation will be made that they discuss this with their GP. In the absence of an x-ray within the previous 12 months, they will be excluded from the study. The text has therefore been amended to: “To determine the severity of OA, a shoulder x-ray within 12 months is required for inclusion in the study”. Line 170-171

AE COMMENT: In the exclusion criteria ln 159 you have (x-ray report ≤ 12 months). Should it be > 12 months? If this is corrected, do you need “To determine the severity of OA, a shoulder x-ray within 12 months is required for inclusion in the study”. Line 170-171, as this is repetition, also it is confusing as at the start of the paragraph, you say inc/exc will be primarily based on clinical decision making.

R2 AUTHOR RESPONSE: Thank you for this comment. The sentence in line 159 has been removed and the text has been amended to reduce confusion as follows:
“To determine the severity of OA, a shoulder x-ray undertaken within the previous 12 months is required for inclusion in the study.”

Line 185-186

Should you also reference Figure 2 and the assessment algorithm around ln 183.

R2 AUTHOR RESPONSE: Yes, the authors agree and this has now been added to the text as follows:

“Eligibility will be confirmed through a clinical assessment (using the assessment algorithm shown in Fig 2)…….”

Line 197-198

Comment 14 * Line 198: the authors offer the criteria for feasibility in this section, which appear sensible - (a) ease of recruitment (b) adherence to treatment, (c) non-compliance/dropout, and (d) adverse events. These are entirely appropriate, but there is very little justification or expansion on these feasibility criteria in the paper. The authors should offer some benchmark or threshold levels for each criterion, which in turn would inform the authors/reader if a future study is indeed feasible. For example, what does "ease of recruiting mean" - 1 recruit per day? 10 per fortnight? To what degree do the participants need to be non-adherent before they are excluded? What adverse events would exclude them from the study, or is this about serious adverse events? The devil is in the detail here, which I turn will inform the authors if a future definitive trial is feasible, more so than the treatment outcomes themselves;

Response: Thank you for this comment. The authors agree that this criteria for feasibility information is important to include. The text has been amended as follows: “Participant compliance will be obtained by recording the number of physiotherapy sessions attended (out of a maximum number of 5). They will be provided with a daily log-book to record the number of home exercise sessions completed as well as adherence to the home exercise program. Adverse events and the use of cointervention will also be recorded in the log-book along with further questioning by the assessor at trial completion (6 months). All adverse events will be documented by the treating physiotherapist and the project coordinator informed (RK). Line 205-210 And: “In order to meet the target sample size, it is planned that the recruitment coordinator will achieve a telephone screening percentage of 75% and the assessors at each site will achieve a clinical assessment screening percentage of 50%; screening will continue until the target population is reached (12 participants per site (Chan 2013). Making a diagnosis of subacromial pain syndrome/rotator cuff tendinopathy is complex and an assessment algorithm has been designed in order to ensure the appropriate participants are included in this study. Part of the feasibility of this study relates to the assessment algorithm and its influence on recruitment rates. Calculating the time it takes to recruit will facilitate planning for the full-scale RCT. For completeness of data collection and improved statistical analysis, we seek to maximize study retention and adherence. In accordance with the Pedro Scale criterion, we plan for a retention rate of at least 85%. By keeping the intervention period relatively short to reduce the patient burden as well as by contacting participants to remind them of their treatment and assessment
appointments, we anticipate this will be achievable. In studies that have investigated exercise interventions in participants with Subacromial pain syndrome/rotator cuff tendinopathy, adherence to intervention protocols has been reported as 80% and over (Blume 2015, Holmgren 2012, Bennell 2010). We consider this will be achievable in our study with the exercise check-review during week 9, specifically designed to ensure ongoing compliance. All groups in our study will undertake an exercise-based intervention only and we therefore do not anticipate any serious adverse events. Increased short term pain during and following performance of exercises has been reported in other exercise based studies (Bennell 2010). As all of our participants will undergo a structured semi-individualised exercise program, with progression governed by symptoms and stage of tendon pathology, we anticipate minimal reporting of these kinds of minor adverse events.” Line 213-234

AE COMMENT: For ease of reading I wonder if the above should be re-written in the order of the key parameters as presented in the aim: ease of recruitment, suitability of the assessment algorithm, evaluation of the randomisation process, adherence to the exercise intervention, compliance with log-book completion, retention rates and, nature of adverse events.

Also it is not clear how the randomisation process will be evaluated.

The description of the Primary outcome should be coherent both with the aim and the procedures (at the moment there are discrepancies). Attention should also be paid to the secondary outcomes to make sure these are coherent throughout the manuscript.

R2 AUTHOR RESPONSE: Thank you for this comment. The above section of text has now been re-written in the order of the key parameters. Also, it has been repositioned in the body of the text in a more logical place below the Primary Outcome.

“Primary Outcome: feasibility of a full-scale RCT.

The primary outcome of this study is to determine feasibility for a full-scale RCT. As outlined above, this will involve an evaluation of: (a) ease of recruitment (rate and number as well as suitability of the assessment algorithm); (b) adherence to both phases of the exercise intervention including home program compliance and log-book completion, (c) participant non-completion (drop-out number and rate) and (d) adverse events (nature and number). The regular monthly research staff meetings will provide an opportunity for continual evaluation to gauge whether the various components of the study work well together as well as allowing collection and monitoring of data relating to the key parameters that have been identified in point (a-d) above.

In order to meet the target sample size, it is planned that the recruitment coordinator will achieve a telephone screening percentage of 75% and the assessors at each site will achieve a clinical assessment screening percentage of 50%; screening will continue until the target population is reached (12 participants per site. As making a diagnosis of SPS is complex, an assessment algorithm (see Fig 2) has been designed in order to ensure the appropriate participants are included in this study]. Part of the feasibility of this study relates to the ease of use of the assessment algorithm by the assessor, their willingness to use it and, its influence on recruitment rates. Calculating the time it takes to recruit will facilitate planning for the full-scale RCT.
Participant adherence will be monitored by recording the number of physiotherapy assessment and treatment sessions attended. For completeness of data collection and improved statistical analysis, we seek to maximize study retention and adherence. In accordance with the Pedro Scale criteria, we plan for a retention rate of at least 85%. By keeping the intervention period relatively short to reduce the patient burden as well as by contacting participants to remind them of their treatment and assessment appointments, we anticipate this will be achievable.

Compliance with the exercise intervention will be monitored via therapist log-book sign-off at each treatment session. In studies that have investigated exercise interventions in participants with SPS, adherence to intervention protocols has been reported as 80% and over. We consider this will be achievable in our study with the exercise check-review during week 9, specifically designed to ensure ongoing compliance.

As well as participants recording adverse events in their log-book, further questioning regarding this will be undertaken by the assessor at trial completion. As all groups in this study will undertake an exercise-based intervention only, serious adverse events are not anticipated. Increased short term pain during and following performance of exercises has been reported in other exercise based studies. As all of our participants will undergo a structured semi-individualised exercise program, with progression governed by symptoms and stage of tendon pathology, we anticipate minimal reporting of these kinds of minor adverse events.”

Line 225-263.

The description of the primary and secondary aims/objectives and outcomes has been made consistent throughout the text as follows:

“The primary outcome measure will be feasibility which will involve evaluation of key study parameters including (a) ease of recruitment (rate and number as well as suitability of the assessment algorithm); (b) adherence to all phases of the exercise intervention including home program compliance and log-book completion, (c) participant non-completion (drop-out number and rate) and (d) adverse events (nature and number).

Secondary outcomes will include (i) shoulder related symptoms and disability (Western Ontario Rotator Cuff Index (WORC) and Shoulder Pain and Disability Index (SPADI)); (ii) perception of pain (11-point Numerical Rating Scale (NRS); (iii) shoulder muscle strength (hand hand-held dynamometer); (iv) perceived global rating of change score. These secondary outcome measures will be collected at the primary (6 weeks) and secondary (12 weeks) end-points of the study with additional within-treatment assessments of pain and muscle strength undertaken when the group-specific rotator cuff exercises are taught.”

Line 48-59

“The primary aim of this study is to establish the feasibility of running a large full-scale RCT that compares the effects of isometric, isotonic concentric and isotonic eccentric rotator cuff contractions when used as part of a structured semi-individualised exercise-based physiotherapy rehabilitation program in patients diagnosed with SPS. To achieve this aim, an evaluation of key
parameters including (a) ease of recruitment (rate and number as well as suitability of the assessment algorithm); (b) adherence to all phases of the exercise intervention including home program compliance and log-book completion, (c) participant non-completion (drop-out number and rate) and (d) adverse events (nature and number) will be undertaken and used to inform the implementation of a large-scale RCT.

The secondary aim is to offer insights into any potential trends in treatment effects observed between the groups, to explore whether faster gains in pain, strength and therefore function are achieved from either of the three exercise interventions. To achieve this aim and facilitate sample-size estimations for a large-scale RCT, data will be collected using the selected clinical outcome measures at specific study time-points, with within-treatment and pre - and post-intervention differences evaluated across the three groups.”

Line 122-135

Ln 251 should you write out NRS the first time it is used?

R2 AUTHOR RESPONSE: Thank you for pointing this out. This has now been done for initial time used.

Are Figures 3 and 4 in the wrong order?

R2 AUTHOR RESPONSE: Thank you for pointing this out – now corrected.

Comment 18* Line 305: there is not much detail here regarding the anticipated statistical analysis. Please elaborate more on aspects such as: what type of data is expected, who will the data be organised and tabulated, who will do the statistical analysis, why is the proposed analysis and statistics chosen, how will the results be interpreted, will there be consensus agreement related to the results/outcomes?

Response: Thank you for this comment. The text has been amended to inform the reader of the statistical analysis: “All analyses will be conducted on intention-to-treat principles with missing data replaced by the last-score-carried-forward technique. Analyses of variance (ANOVA) with repeated measures will be used to analyse trends in between-group changes in secondary outcome scores at baseline, and after six and twelve weeks of the exercise intervention. Continuous variables (SPADI, WORC, 11-point NRS, dynamometer and, GRCS) will be summarised using means and standard deviations, or medians and interquartile range, while categorical variables (gender) will be summarised using frequencies and proportions (and 95% confidence intervals).” Line 359-365

AE COMMENT: should ITT just be used as a sensitivity analysis, I am not sure it is necessary for a pilot study such as this one – especially as your numbers are really low and LSCF may really change the findings. What about post hoc tests following significant ANOVA outcomes? Also what analyses will you do on your primary outcomes.
R2 AUTHOR RESPONSE: Thank you for this comment. The authors agree that as the numbers are low, the use of ITT and LSCF are likely to influence the findings. The text has now been amended to reflect that ANOVA as per-protocol will be used as well as the addition of post-hoc analyses using Tukey’s test.

“Analyses of variance (ANOVA) with repeated measures will be undertaken to analyse trends in between-group changes in secondary outcome scores with post-hoc analyses using Tukey’s HSD test performed where significant between group differences are observed.”

Line 383-385

Comment 19 * I note there is no mention of sample size calculations or estimated in the methods section for a definitive study. This is a critical component to a pilot study and the methods that are anticipated to be used to calculate the sample size of a future definitive study should be provided. A great deal is published on sample size estimated/calculations, but at least a brief description and anticipated calculations should be offered in this paper.

Response: Thank you for this comment. Please see our response to comment 3 above which details the sample size justification used in this feasibility study. Line 134-142

AE COMMENT: I think the reviewer was asking for an indication of how you would use the findings of your study to inform your final calculations for a full RCT – this should probably be added to the aims with regards to the secondary outcomes. It is not clear what the primary outcome for an RCT would be – this should be made clearer throughout the manuscript.

R2 AUTHOR RESPONSE: Thank you for this comment. The text has been amended as follows:

“The secondary aim is to offer insights into any potential trends in treatment effects observed between the groups, to explore whether faster gains in pain, strength and therefore function are achieved from either of the three exercise interventions. To achieve this aim and facilitate sample-size estimations for a large-scale RCT, data will be collected using the selected clinical outcome measures at specific study time-points, with within-treatment and pre- and post-intervention differences evaluated across the three groups”.

Line 131-135.

Associate editor further comments to be addressed:

Comment 28  Is the research design for an RCT being tested as well as the intervention? If so, then is it a pilot trial rather than a feasibility trial?

Response: The authors understanding of a feasibility study is that it is used to gauge whether a study can be done and therefore it evaluates how the components of a study work together. In this study this includes an evaluation of the following parameters: ease of recruiting participants (number and rate); ease of using the assessment algorithm; ease with which participants complete the questionnaires; participant compliance with the exercise intervention including
phase 1 (individual treatment sessions) and phase 2 (progressive exercise sheet); participant adherence to the intervention (home-exercise program and daily log-book recording); non-completion (drop-out number and rate) and; adverse events (number and type).

AE COMMENT: The authors’ response is closest to the NIHR definition of a pilot study (https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/research-programmes/RfPB/FAQs/Feasibility_and_pilot_studies.pdf) Pilot studies are a version of the main study that is run in miniature to test whether the components of the main study can all work together. It is focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It will therefore resemble the main study in many respects, including an assessment of the primary outcome. In some cases this will be the first phase of the substantive study and data from the pilot phase may contribute to the final analysis; this can be referred to as an internal pilot. Or at the end of the pilot study the data may be analysed and set aside, a so-called external pilot.

R2 AUTHOR RESPONSE: Thank you for this comment. The authors agree that their intent is to test whether the components of the main study work together and have therefore changed the manuscript to a pilot study. As the authors are most keen to evaluate the way the components and processes of the study work as a whole, including the assessment algorithm, they have maintained the primary outcome as feasibility and the secondary clinical outcomes listed as per their relevance.

The manuscript title has also been changed to reflect it is a protocol for a pilot study:

“A comparison of isometric, isotonic concentric and isotonic eccentric exercises in the physiotherapy management of subacromial pain syndrome/rotator cuff tendinopathy: study protocol for a pilot randomised controlled trial.”

Line 1-3

Comment 29 How can analysis be conducted with group allocation undisclosed?

Response: Groups will be coded and analysis will be undertaken by a statistician who will not be made aware of what exercise program is used in each of the three groups.

AE COMMENT: Could this be made clear in the manuscript. At the moment it is not, an indeed the it is suggested that the statistician will not be aware of group allocation at all (this is different from intervention allocation).

R2 AUTHOR RESPONSE: Thank you for this comment. The text has been amended as follows:

“All data will be de-identified with analyses performed by an independent analyst. Groups will be coded and intervention allocation undisclosed so that the analyst is blind to the exercise program being used in any of the groups.”

Line 392-394
General additional comments

AE COMMENT: Please re-read the manuscript for typos (e.g. missing capital ln 63). Also consider where addition/ removal of commas would be helpful to aid reader’s understanding

Please also highlight all changes made in manuscript for ease of re-review.

R2 AUTHOR RESPONSE: Thank you – yes this has now been done.

Thank you again for your thorough review of our manuscript. We appreciate the time you and the other reviewers have taken and the advice you have provided.

We very much hope that you will be amenable to the amendments we have made. We look forward to hearing from you in due course and hope that our manuscript is now acceptable for publication in BMC Pilot and Feasibility Trials.

Yours sincerely,

Rita Kinsella.