Author’s response to reviews

Title: Is heavy eccentric calf training superior to wait-and-see, sham rehabilitation, traditional physiotherapy and other exercise interventions for pain and function in mid-portion Achilles tendinopathy.

Authors:
Myles Murphy (myles.murphy1@my.nd.edu.au)
Mervyn Travers (mervyn.travers@nd.edu.au)
William Gibson (william.gibson@nd.edu.au)

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Author’s response to reviews:

Dear Dr Burke

We are grateful to both yourself, and your reviewers for taking the time to review this manuscript. The comments have helped increase the quality of the manuscript. We have provided a point by point response to your comments below and included highlights in the manuscript where changes have been made.

Associate Editor

1. Whilst parts of the protocol are well-written, and there is an intention to follow the PRISMA-P guidelines, there is a sense that this protocol has been submitted before it was ready. The PROSPERO registration number is missing.

a. Thank you for the feedback regarding the missing PROSPERO registration. At the time of submission, we had submitted our protocol but unfortunately it was some weeks before we received the registration number back and therefore we did not have the number at the time of submission. We have included this now into both the abstract and methods section. (Page 3 and 17)
2. There is also missing information regarding the storage of the data in which the authors have put ",(XXXX)" instead of waiting until there is a clear decision. Line 124: missing information in the reference. Line 175: the review authors are not specified. Rather than put "XX", leave this unstated (same for lines 179, 186, 189, 209, 211).

   a. Thank you, we did not realize that the manuscript did not need to be blinded for peer-review and hence author initials in regard to roles played in the methods section and papers written by the authors by included as “XX”. We apologise and have amended the manuscript to include all names and initials.

3. It is not clear if other types of observational studies could be included.

   a. We agree this was not clear and have included further information into the methods section. (Page 8)

   “Trials that are non-randomised observational trials, case reports/ series, clinical observations and systematic reviews will be excluded.”

4. In the "Types of outcome measures" section, the authors state "Only studies that have used a validated and reliable outcome measure of pain and function in mid-portion Achilles tendinopathy will be included." They also state that "The VISA-A has also been identified as the only reliable and valid measure of pain and function in the mid-portion Achilles". So, will the VISA-A be the only outcome measure? it is not clear. The information for the latter quote is from a single review that is currently not peer-reviewed.

   a. Thank you, this paragraph did not clearly state the reasons for excluding other outcome measures so we have expanded on it significantly. The paper which was also previously referenced as an unpublished review has now been accepted for publication and therefore properly referenced. (Page 10)

   “Only studies that used a validated and reliable outcome measure of pain and function in mid-portion Achilles tendinopathy will be included. A recent consensus statement recognised the VISA-A as a valid and reliable tool for assessing AT. The VISA-A is a self-reported outcome
measure which includes a variety of questions about both pain and function. The VISA-A has also been identified as the only reliable and valid measure of pain and function in the mid-portion Achilles. Trials which used the visual analogue scale (VAS) or numerical rating scale of pain will not be included. The VAS at rest has been shown to have a test-retest reliability of $r=0.45$ in mid-portion Achilles tendinopathy. The relationship between pain and function is also intricately linked in tendinopathy given symptoms are load dependant. Therefore, including a measure of pain without linking it to function may introduce bias.”

5. There is insufficient information regarding the data synthesis.

a. If the only outcome measure is VISA-A, then mean difference is appropriate. If, however, there is more than one outcome measure (which is also continuous), then you will likely need to consider standardised mean differences. If so, please add details to the data synthesis section. This query relates to point 3 that it is not clear if VISA-A will definitely be the only outcome measure.

i. Thank you had we included other measures we would have had to look at SMD instead. However, given we have included further rationale into why we chose to use only the VISA-A this will remain unchanged.

b. The author states (line 221) that "data will be analysed at every reported time point". How will the authors deal with differing time points across studies?

i. This is a good point and difficult to do in the event study numbers are small. We have therefore decided to amend this and only analyse the data at the final time point in which the rehabilitation protocol was being completed. (Page 15)

“Data will be analysed at the final time point while the patient is undergoing the loading intervention.”

c. Will the authors differentiate between the types of calf training interventions and make several comparisons, or assume that all calf training interventions are equally effective?
i. We have added further detail to discuss that heterogeneity will be incorporated as a component of the sensitivity analysis. (Page 16)

“Where substantial heterogeneity (P ≤ 0.10 or $I^2 \geq 40\%$) is found a subgroup analysis investigating the possible impact of the a study will be determined by completing a sensitivity analysis.”

d. What methods of meta-analysis will the authors employ? For example, a fixed-effect or random-effects meta-analysis, what estimation method, what software.

i. Thank you, we have included the software we plan to use for the meta-analysis. (Page 17)

“Meta-analysis will be performed using an inverse variance statistical method and random effects analysis model in Review Manager version 5.3 (Review Manager [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) to calculate the mean difference.”

e. The authors state that they will group data into the duration of follow-up. It is unclear what purpose this grouping has. Will the authors conduct subgroup analyses in which only studies of short-term follow-up, for example, are synthesised?

i. Thank you for this query. Based on the feedback we have removed this section of the manuscript.

f. The authors have made information regarding intended subgroup / sensitivity analyses, so I do not fully agree with reviewer 1. However, some of my earlier comments relate to subgroup analyses, so addressing these should cover the subgroup aspect more fully.

i. We agree this section did not contain sufficient detail and we have included more information on the planned sub-groups for analysis. (Page 17)

“Sensitivity analysis will be conducted by allocated a weight of 0% to different subgroups in order to assess their influence on the overall effect size and measures of heterogeneity. A sensitivity analysis will be conducted on the following subgroups:

• Studies in which the standard deviation was inputted as per the methods section above.
• Studies in which the adherence was not reported.
• Studies which used different exercise protocols were used as the comparator to heavy eccentric calf training.
• Studies in which both heavy eccentric calf training and the exercise intervention used as the comparator both received placebo interventions.
• Studies in which there was a high-risk of bias as assessed by the RoB 2.0 tool.”

Reviewer One

1. Insert the prosperous registry

   a. Thank you we have included the PROSPERO registration number both below the abstract and in the methods section. (Page 3 and 17)

2. Assessment of methodological quality

   a. We have expanded the section on quality of the evidence in order to more clearly state the sections which will be assessed to determine the quality of the literature. (Page 16)

   “Assessment of the quality of the body of evidence was assessed using the GRADE approach as recommended in Part 2, Section 12.2.1 of the Cochrane Handbook for Systematic Reviews of Interventions. The GRADE approach involves making an overall judgement on the quality of the body of evidence based on the overall risk of bias, consistency of results, directness of the evidence and publication bias.”

3. Strategy for data synthesis

   a. Thank you for this feedback you will see our amendments to data synthesis in answer to the associate editor in question 5.d.

4. Analysis of subgroups or subsets
a. Thank you, we have included further information on the analysis of sub-groups and how we plan to complete this with a sensitivity analysis in response to the associate editor in question 5.c and 5.f.

5. Summary of Evidence

a. Thank you we will be included a summary of the quality of the evidence will be included as per the GRADE approach. (Page 16)

6. Discussion.

a. Thank you as suggested we have included a short discussion to the end of the manuscript. (Page 18)

“Heavy eccentric calf training is currently advocated for as the gold standard for treatment of mid-portion Achilles tendinopathy. However, to date no systematic has compared this intervention to wait-and-see, sham rehabilitation, traditional physiotherapy or different exercise rehabilitation protocols. This systematic review aims to complete a comprehensive systematic review and meta-analysis of the current gold standard of treatment in mid-portion Achilles tendinopathy to determine if it really is the gold standard of management for mid-portion Achilles tendinopathy.”

Reviewer Two

1. PROSPERO registration number should be given.

b. Thank you we have included the PROSPERO registration number both below the abstract and in the methods section. (Page 3 and 17)

Additional Changes

In addition to the changes detailed above we have also chosen to include “traditional physiotherapy” as a comparator to heavy eccentric calf training and therefore both the title and
the methods section have changed to reflect this. The inclusion in the manuscript has been placed below. (Page 9)

“Types of traditional physiotherapy

Traditional physiotherapy groups will be included if the participants had no exercise intervention, either a real or sham exercise intervention, but had some form of traditional physiotherapy intervention. The traditional physiotherapeutic interventions included will be:

- Deep friction massage to the tendon, and/ or
- Other forms of manual physical therapy to local tissues, and/ or
- Ultrasound, and/ or
- Kinesiotape

Given the lack of robust evidence confirming that these interventions are not effective, and that there is also a lack of robust evidence saying these interventions may not interfere with an exercise rehabilitation protocol these interventions were not classified as sham.”

We have also included the dates of the search strategy into the manuscript. (Page 10)