Author’s response to reviews

Title: Efficacy of heel lifts versus calf muscle eccentric exercise for mid-portion Achilles tendinopathy (the HEALTHY trial): study protocol for a randomised trial

Authors:
Chantel Rabusin (c.rabusin@latrobe.edu.au)
Hylton Menz (h.menz@latrobe.edu.au)
Jodie McClelland (j.mcclelland@latrobe.edu.au)
Angela Evans (angela.evans@latrobe.edu.au)
Karl Landorf (k.landorf@latrobe.edu.au)
Peter Malliaras (peter.malliaras@monash.edu)
Sean Docking (s.docking@latrobe.edu.au)
Shannon Munteanu (s.munteanu@latrobe.edu.au)

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Author’s response to reviews:

Reviewer #1

1. I welcome the chance to review this protocol and thank the authors for submitting it to the journal. The protocol represents a thorough evaluation of two commonly used therapies in a clinical area of direct relevance to the readership.

I note that the trial is funded through competitive funding streams so would have undergone peer review during this process. It also underwent review as part of the ethical approval process and is registered on an appropriate trials registry. The trial opened to recruitment in Aug 2017 and is due to complete in Sept 2019. As such I have focussed my comments to the reporting of the protocol rather than the design of the trial as these would be superfluous.

The protocol is well reported and I believe provides enough information to replicate the trial. It is published in accordance with the SPIRIT guidance and the checklist is available as supplementary material
I have the following minor comments for the authors consideration:

Page 9 line 207 - the abbreviation (UTC) appears to be used incorrectly.

Authors’ response
We agree with the comment and have removed the abbreviation. The manuscript now reads (page 9, lines 207-9):
‘(iii) gray-scale musculoskeletal ultrasound of the Achilles tendon showing diffuse or local thickening with or without irregular fibre orientation and hypoechoic areas within the mid-portion of the Achilles tendon [44]’.

2. Page 11 to 12 - I assume that participants will be randomised in a 1:1 ratio but do not think I saw this confirmed in the manuscript. Unless I have missed it, could the authors please add this information to the manuscript

Authors’ response
We have carefully considered the reviewer’s comment and amended the manuscript to include detail regarding the 1:1 randomisation ratio. The manuscript now reads: (page 12, lines 276-7):
‘The random allocation sequence will be generated with a 1:1 allocation ratio using permuted blocks of random sizes.’

3. Page 12 line 277 - it is recommended not to report block sizes while the study is still in progress in order to reduce the predictability of the sequence (See SPIRIT Guidance).

Authors’ response
Thank you for raising this point. We have carefully considered the reviewer’s comment and amended the manuscript to remove detail regarding the block sizes. The manuscript now reads: (page 12, lines 276-7):
‘The random allocation sequence will be generated with a 1:1 allocation ratio using permuted blocks of random sizes.’

4. Page 20 line 487 - whilst I appreciate that the protocol would have been written prior to the publication of the DELTA2 guidance on reporting sample size calculations (2018). I would ask the authors to review this section in light of the recent guidance.

Authors’ response
Thank you for this suggestion. The protocol was developed prior to the publication of the DELTA2 guidance (November 2018). We have carefully reviewed (i) the DELTA2 guidance recommended reporting items for the sample size calculation of a randomised controlled (superiority) trial (1), as well as (ii) the SPIRIT 2013 guidance for protocols of clinical trials (2). We have amended this section of the manuscript to include additional information. It now reads (pages 20-21, lines 489-97):
‘The sample size has been determined a priori using the t-test for two independent groups with common variance function in SPSS Sample Power 3.0 (IBM Corporation, USA) based on the VISA–A questionnaire as the primary outcome. Using an allocation ratio of 1:1, a power of 80%, minimal important difference (MID) of 10 points [28], standard deviation of 16.9 [25] (standardised effect size =
0.59) and alpha set at 0.05, we estimate that a minimum of 92 participants (i.e. approximately 46 per group) will be required. We did not allow for participant loss to follow-up in our calculation as missing data will be imputed [67]. Further, we have conservatively ignored the extra precision provided by covariate analysis when estimating the sample size.’

5. I note that the SPIRIT guidance asks authors to provide details of a DMEC or an explanation of why a DMEC was not required. I assume that this function was performed by the PhD supervisory team and will leave it to the authors whether they wish to include a statement to this effect.

Authors’ response

Thank you for this suggestion. We did not deem that a Data Monitoring and Ethics Committee (DMEC) was necessary for this study for a number of reasons (3-4). First, the trial duration was considered to be relatively short. Second, the interventions that were used are commonly used in clinical practice and considered to be relatively safe (low risk of adverse events or adverse events likely to be minor). Third, the participants in the study were not considered to be vulnerable. Fourth, the research staff providing the interventions and the participants were not blinded to their intervention allocation. The senior study investigators (SEM, HBM, KBL, AME, JAM, PM) acted as the Trial Management Committee and provided oversight of the trial through regular meetings to review safety reports, data quality, protocol adherence and participant retention. We have amended the manuscript to include this information. It now reads (page 21, lines 500-5):

‘A Data Monitoring and Ethics Committee (DMEC) will not be required for this study. This study is relatively short and has included two safe and commonly used interventions for participants who are not considered to be vulnerable [68,69]. This study will have a Trial Management Committee that will comprise of senior study investigators (SEM, HBM, KBL, AME, JAM and PM). The Committee will meet every two weeks to review safety reports, data quality, protocol adherence and retention rates’.

Reviewer #2

1. The protocol investigates an area where evidence is lacking. As this protocol has been through previous review processes (funding, clinical trials registry and ethics I have no comments to make on the design.

I have only two comments.

Firstly, Relating to the use of UTC. Page 9 line 207: Will UTC be used to echotype the tendon in the initial diagnosis of tendinopathy?

Authors’ response

Thank you for bringing this to our attention. Gray-scale features of the UTC will be used to diagnose Achilles tendinopathy. UTC will not be used to echotype the tendon in the initial diagnosis. We have now made the following amendment to clarify how the UTC will be used to diagnose Achilles tendinopathy (page 9, lines 207-9):

‘(iii) gray-scale musculoskeletal ultrasound of the Achilles tendon showing diffuse or local thickening with or without irregular fibre orientation and hypoechoic areas within the mid-portion of the Achilles tendon [44]’.
2. Is there a data monitoring committee? (SPIRIT item 21a)

Authors’ response
Thank you for your question. This question was also raised by Reviewer 1 and has now been addressed. It now reads (page 21, lines 500-5):
‘A Data Monitoring and Ethics Committee (DMEC) will not be required for this study. This study is relatively short and has included two safe and commonly used interventions for participants who are not considered to be vulnerable [68,69]. This study will have a Trial Management Committee that will comprise of senior study investigators (SEM, HBM, KBL, AME, JAM and PM). The Committee will meet every two weeks to review safety reports, data quality, protocol adherence and retention rates’.

Additional amendments:
We have amended the title by removing the letter ‘a’. The title now reads ‘Efficacy of heel lifts versus calf muscle eccentric exercise for mid-portion Achilles tendinopathy (the HEALTHY trial): study protocol for a randomised trial’.

References:
4. National Health and Medical Research Council (2018), Data Safety Monitoring Boards (DSMBs)