Author’s response to reviews

Title: The effects of low-intensity blood flow restricted exercise compared with conventional resistance training on the clinical outcomes of active UK military personnel following a 3-week in-patient rehabilitation programme: protocol for a randomized controlled feasibility study

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Author’s response to reviews:

We did not receive a "View Decision Letter" Link that had any comments by the reviewer or editor. Instead we sent an email to the Journal editorial office where we received the following review comments on our manuscript. We have also attached this information as a separate file titled "Itemised response to reviewers comments.

1) Lines 269-283 and lines 334-350 the verb tense is either present or future.

2) Page 10: line 195 - how is this study a factorial design - this is not clear to me?

3) Page 11- line 237 :what is the block for the randomization. Also, it would be better to have strata, as the sample size is small and there is likely to be variations.

4) Is there any way manual sing the therapy - which would assist in the main trial?

5) What are targets which would enable you to decide that a main study can work - need some objective criteria within the feasibility study

6) Page 22: line 536: independent sample t-test - the sample is too small for this - no statistically testing to be carried out, but rather summarize using confidence intervals
7) Similarly not need for p-value

Our response to these comments are as follows:

1) We have amended these extracts to ensure the correct verb tense is used.

2) We agree that the use of the term ‘factorial design’ is potentially confusing as we are using a limited (x2) number of experimental conditions / “arms” in our RCT, and our objective is to compare the individual experimental conditions to each other directly. We recognise this is not the case in factorial designs/experiments where the objective is generally not to compare individual conditions to each other. We originally employed the term ‘factorial’ in our design simply to reflect our use of multiple outcomes/measures on more than one level1. However, we agree with the reviewer that a distinction should be made between a true ‘factorial’ experiment and a randomized controlled trial. We have therefore removed the term factorial from our design methodology.

3) We will employ x2 blocks of 10 (x5 per arm of the study in each block), and x1 block of 8 (x4 per arm of the study in this block). After patient eligibility and informed consent have been confirmed, an envelope will be opened to reveal group allocation by an independent administrator not involved in the recruitment, treatment or assessment of study outcomes. Our blocks are small and balanced with pre-determined group assignments, which keeps the numbers of participants in each group similar at all times, whilst ensuring there is a 1:1 likelihood of participants being allocated to either group. This block randomisation method will be used to randomise participants into groups that result in equal sample sizes.

We considered at length the potential usefulness of employing stratified randomisation. We acknowledge and accept the reviewers comment that this form of randomization is particularly important for small clinical trials, where known clinical factors (gender, age, disease stage) are thought to affect treatment outcomes, and the use of strata may avoid a Type I error. With our participants the known clinical and personal factors shown to have a large effect on prognosis are already controlled for and standardised by the routine admission criteria into the rehabilitation centre (stage of treatment, injury type, occupation, age and gender etc). Moreover, the maximum desirable number of strata is unknown and once a decision to stratify is made the chosen factors must be accounted for in the analysis2. Therefore, our decision to employ a simple form of Block randomisation is because (a) we want to ensure an equal number of participants are assigned to each group during a finite, time-limited period for data collection, (b) we already have a homogenous participant group with standardised prognostic factors, and (c) we will not be undertaking formal statistical testing.

We have made a minor amendment to our manuscript with further clarification at lines 238-242.

4) We are not familiar with the term ‘manual sing the therapy’. Moreover, to our knowledge the term is not used in the scientific or clinical literature. We are of course familiar with the theory and practice of manual therapy, delivered by a physiotherapist, with each manual therapy technique selected and tailored to the individual needs of each patient and determined by results
of clinical assessment’s and patient response to treatment. The Consultant led multi-disciplinary, residential treatment intervention employed in our study describes an accepted and widely used broad bio, psycho, social approach to physical rehabilitation. Manual therapy will form an integral part of this holistic approach as a common core-element of treatment for participants in both arms of our RCT.

5) We have provided details of several objective physical and functional outcome measures we will collect during the conduct of this study. These include muscle volume, muscle strength assessment, functional performance tests’ and pain perception. These standardised clinician-rated and patient self-reported clinical outcomes have demonstrated good reliability and validity for use in people with lower-limb musculoskeletal injuries and will enable some comparison between studies that will inform the viability of a main RCT. As it is inappropriate to use feasibility trial data to formally test for between-group treatment effects, the analyses will primarily be of a descriptive nature. The descriptive statistics of the clinical outcome data will be produced for all objective outcomes for each study arm. Interval estimates of the potential intervention effects, relative to usual care only, will be produced in the form of 95% confidence intervals, to ensure that the effect size subsequently chosen for powering the definitive trial is plausible, but no formal hypothesis testing will be undertaken. We shall progress to a full trial application if minimum success criteria are achieved in key feasibility aims and objectives, or if we can identify solutions to overcome any identified issue. These criteria will be finalised in discussion with the Trial Steering Committee, but are likely to include:

• A minimum of 80% recruitment of the intended 28 participants within the 6-month recruitment window

• A minimum of 80% completion rate of key outcome measures

We have inserted some further clarification at lines 541-545.

6) We agree that as a feasibility study that has not been subject to a formal power calculation it is not necessary (or usual) to conduct statistical testing. We are interested as a form of local service evaluation to assess and quantify the between-group differences in our selected physical and functional outcome measures to see if this is suggestive of any differences in adaptation between groups, though we acknowledge this will not constitute a statistically significant difference provide evidence of a different response to treatment. We will therefore implement the reviewer recommendations and remove the reference to statistical analysis and agree to report our results using confidence intervals.

We have amended this extract in the section headed ‘Statistical Analyses’, lines 530-545. The amendment also refers to previous extract and text we have deleted (i.e. use of the independent t-test).

7) We will remove the reference to reporting p-values.