Author’s response to reviews

Title: Medial Malleolus: Operative Or Non-operative (MOON) Trial Protocol

A prospective randomised controlled trial of operative versus non-operative management of associated medial malleolus fractures in unstable fracture dislocations of the ankle

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Dear Editorial Team at Trials

Manuscript ID: TRLS-D-18-00892

Title: Medial Malleolus: Operative Or Non-operative (MOON) Trial Protocol

'A prospective randomised controlled trial of operative versus non-operative management of associated medial malleolus fractures in unstable fracture dislocations of the ankle'

Many thanks for reviewing our manuscript. We have made revisions, summarised below, addressing each of the reviewer’s comments in turn. We have included the replies of our trial statistician for many of the comments, who is also a co-author for this manuscript. We now hope that it is now suitable for publication in your journal and is of interest to your wide readership.

Yours sincerely,
Reviewer 1

Comment 1: This is a well written and structured protocol paper.
Reply 1: Thank you for the positive feedback regarding our protocol paper.
Action 1: Nil required.

Comment 2: There is no mention of blinding in the article. As the primary outcome is a patient reported outcome it is important for this to be described If blinding is not possible, then please state this.
Reply 2: Thank you for your comment. It is extremely hard to blind either the surgeon or the patient in this study. Those treated with fixation of the medial malleolus will have an incision on the medial side of their ankle and those who are randomised to non-fixation, will not. The same is true for radiographs (presence or absence of medial sided metalwork). As the primary outcome measure was a patient reported outcome, the assessor at follow-up is not blinded.
Action 2: The following text has been added in ‘Methods’ section after ‘Interventions’ under the new sub-heading ‘Blinding’:
“Given the invasive nature of surgery those patients randomised to ‘FIXATION’ will have an additional surgical wound on the medial aspect of their ankle and those who are randomised to ‘NON-FIXATION’ will not. It is therefore not possible to blind either the surgical team or the patients in this trial.”

Comment 3: There is mention of the allocation sticker being added to the consent form on randomisation. Would the patient be aware of this?
Reply 3: The allocation sticker is contained within an opaque envelope and attached to the study consent form. The allocation of randomisation ‘fixation’ or ‘non-fixation’ is not revealed until during the operation when the surgeon has authorised the envelope to be opened by a member of theatre staff who is independent of the trial. There is no way the patient or surgeon would know the result of randomisation contained within this envelope before surgery.
Action 3: The following text has been added to the ‘Methods’ section under the ‘Randomisation and allocation’ sub-heading:
“The participant will not be aware of the result of randomisation at the point of study enrolment.”
Comment 4: As the primary outcome is a patient reported outcome it is important for this to be described.

Reply 4: The primary outcome measure, the OMAS is a validated lower limb outcome score that has been used in large HTA funded trials around the ankle including the Ankle Injury Management Trial (AIM) by Willett et al and is currently being used by the WARRIOR trial by Weil et al.

Action 4: The following text has been included in the Methods section under ‘Primary Outcome’ along with the corresponding references:

“The primary outcome measure will be the OMAS at one-year following surgery. [ref] This is a validated lower limb outcome score that has been used in large Health Technology Assessment (HTA) funded trials around the ankle. [refs]”

HTA has been added to the abbreviations section.

Comment 5: Sample size is appropriate. Statistical analysis outline: one of the criticisms you make of an earlier RCT is that the sample size was small and that baseline patient reported outcome scores were not recorded. Are you collecting these in your study, it is not clear from the description.

Reply 5: Yes, we are building on the results of the earlier RCT by including baseline patient reported outcome scores and a larger sample size. Apologies that this was not clear from the original submission.

Action 5: The following text has been added to the start of the final paragraph in the ‘Background’ section:

“Building on the current evidence and by including baseline patient reported outcomes and a larger sample size, the aim of the MOON……”

Comment 6: If you are collecting them the appropriate statistical analysis would be Analysis of covariance adjusting for the baseline PROM. Please could you clarify.

Reply 6: Yes, we are collecting baseline data in the form of the Olerud-Molander Ankle Score (OMAS). You are correct, the appropriate statistical analysis would be Analysis of covariance adjusting for baseline PROM. This is the statistical analysis we intend to perform.
Action 6: The following text has been included in the Methods section under ‘Statistical analysis’:

‘An analysis of covariance adjusting for the baseline patient reported outcome measure (OMAS) will be performed.’

Comment 7: Are you planning on adjusting for the stratification factors used in the randomisation?

Reply 7: Yes, we are stratifying randomisation based on patient age. We will include a ‘young’ group (<65 years) and an ‘older group’ (≥65 years).

Action 7: This information is included in the Methods section under ‘Randomisation and allocation’:

‘Randomisation will be stratified by age into a ‘young group’ (<65 years) and an ‘older group’ (≥65 years), calculated on a 3:1 ratio between ‘young’ and ‘old’.

Comment 8: There is no discussion about what you will do with missing data.

Reply 8: Thank you for your comment, which raises an important point that we had failed to include. To account for any potential missing data at the primary outcome point (12 months) we have increased our sample size by 20% to account for loss to follow up. We are collecting the outcome score at an outpatient clinic where participants are returning for their final radiographs and clinical review, which we anticipate will limit the loss to follow up considerably. We will report the number of participants that drop out of each arm and perform a direct comparison to assess if there is a significant difference between them. If the participant dropout rate at the primary outcome point is large we may perform a sensitivity analysis to account for this, but we feel this is very unlikely. Missing data at the intermediate data collection points is most likely to occur at the three- and six-month assessment points as data collection is via postal questionnaire. In this situation, missing data will be assessed by performing a linear regression model comparing the rate of change in the two treatment arms, considering the repeated measurements for each participant. We will not impute for missing data.
**Action 8:** The following paragraph has been included under ‘Missing data’ at the end of the methods section:

‘The study sample size has been calculated to account for up to 20% loss to follow-up at the primary outcome point (12 months). The primary outcome point will be collected at the final outpatient clinic appointment and as such it is anticipated that missing data for the primary outcome will be low. The participant dropout rate for each arm of the trial will be reported and compared. If the participant dropout rate at the primary outcome point is high, a sensitivity analysis may be performed. Missing data at the intermediate data collection points is most likely to occur at the three- and six-month assessment points as data collection is via postal questionnaire. However, by performing an analysis on change over time through fitting regression models the impact of missing data will be minimised.’

**Comment 9:** The primary outcome is being collected at multiple time points. Is all the available data going to be used in the analysis, such as using a mixed level model taking all time-points into account Please expand the statistical analysis section with more details about the primary and supporting analysis for the primary outcome as a minimum. I would recommend that you ask the statistician who will be analysing the data to review and update this section.

**Reply 9:** The primary outcome (OMAS) is only being recorded once, at 12 months post-randomisation. However, the OMAS score will be collected at numerous other time points in the trial as a method of monitoring progress of each participant. We will not take all the time points into account and do not plan to perform a mixed level model. However, we will measure the change in OMAS over the study period by fitting a linear regression model to OMAS responses from six-weeks to 12-months and by using the slope of the regression line we will compare the two treatment arms. This recommendation is on the advice of our trial statistician.

**Action 9:** The following text has been included under the ‘Statistical analysis’ section of the methods.

‘The OMAS will also be collected at multiple time points to calculate change in outcome over time. This will be determined by fitting a linear regression to the 6-week to 12-month values of each participant and comparing the slope of the regression line between treatment arms.’
Comment 10: Limitations: the authors describe the main limitations of the study: intra-operative randomisation. Have you thought how this can be mitigated in that the envelope/sticker could include the time that the envelope was opened and this could be compared to the timing of the operation to see if the envelope was open at the correct time.

Reply 10: Thank you for your comment. The intra-operative randomisation is one of the main difficulties in executing this trial. There are no concerns that the envelope would be opened at the incorrect time as all of the operating surgeons have been educated on the trial and at what point to authorise randomisation (opening of the envelope). One of the research co-ordinators will be present in theatre during surgery and when the decision of suitability for randomisation is made by the operating surgeon as per the trial protocol, the envelope will be opened by an independent member of staff, overseen by the research co-ordinator in theatre. This ensures that the allocation of randomisation is not executed until the correct stage in the surgical procedure.

Action 10: The following text has been modified at the end of the discussion to clarify this important point:

“Revealing the allocation of randomisation before the reduction has been assessed would create potential bias regarding the interpretation of reduction quality. It is crucial that the envelope is not opened until authorised to do so by the operating surgeon and this must be performed by an independent member of staff. A research co-ordinator will be present in theatre to ensure the result of randomisation is not revealed until the correct stage in the surgical procedure”

Comment 11: Single centre - although the authors have discussed this, I still think it is a potential quite a large limitation for this pragmatic trial in that the results may not be generalisable outside the centre. Expanding the study to more centres would provide a shorter time scale for completion and also improve the generalisability.

Reply 11: Thank you for your comment. This is a limitation, which we have acknowledged it in the discussion section and we would agree with your comment. However, the trial is already well into the recruitment phase from a large single centre (90 patients recruited to date). Due to cost and time constraints we would not be able to recruit further centres. However, we feel that the results of the trial will still be generalisable given the large volume of patients we surgically manage following ankle fractures and the high number of Orthopaedic trauma consultants (n=12) involved in patient care.

Action 11: Please see the final paragraph of discussion, in which we have addressed this limitation. We do not feel that there is anything we can change at this stage.
Comment 12: As the primary outcome is a patient reported outcome, I would recommend the authors to report following the relevant extension to the CONSORT statement for patient reported outcomes.

Reply 12: Thank you for drawing our attention to the CONSORT-PRO extension. We have modified our CONSORT diagram by adding a column to the right which highlights where we have acknowledged the extension. This will allow us to report our trial results in a similar manner. We have also acknowledged the PRO-specific extensions in the manuscript as detailed below.

Action 12: New CONSORT diagram attached to the revised submission (Figure.1)

The following PRO-specific extensions have been acknowledged in the manuscript:

1. The PRO should be identified in the abstract as a primary or secondary outcome.

The following text appears in the abstract to identify the PRO:

‘The primary outcome measure will be the Olerud Molander Ankle Score (OMAS) at one year following surgery.’

2. The PRO hypothesis should be stated and relevant domains identified, if applicable.

The following text appears in the ‘Primary Outcome’ section of the Methods:

‘Our primary null hypothesis is that there is no difference in outcome (primary outcome measure – OMAS) after one year between fixation of associated medial malleolus fractures AND non-fixation in patients undergoing surgery for an unstable fracture of the ankle.’

3. Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic, other).

The following text appears in the ‘Primary outcome’ section of the Methods, along with the additional supporting reference:
‘A recent study found that the OMAS had acceptable levels of internal consistency, test-retest validity and correlated strongly with other lower limb injury outcome scoring systems and measures of general health, including the EuroQol-5D.’ [ref]

4. How the sample size was determined, if the primary study outcome is a PRO.

The following text appears in the ‘Sample size’ section of the Methods:

‘The primary outcome measure will be the OMAS. In total, 154 patients (77 per arm) will be required with 80% power with 5% (2-sided) significance in order to detect a clinically meaningful difference of 10 points on the OMAS scale at 12 months between the two groups. [refs] This assumes a standard deviation of 20 and a 20% loss to follow-up. [ref]’

5. Statistical approaches for dealing with missing data are explicitly stated.

This point has now been addressed under Comment 8.

6. PRO-specific limitations and implications for generalizability and clinical practice should be included in the discussion.

The following text has been included at the end of the discussion section as part of limitations of the trial:

‘Patient reported outcome scores are being increasingly used in orthopaedic trials with clear benefits: the focus of outcome is centred on the patient and outcome scores can be collected remotely. The OMAS (primary outcome) may be limited as it focuses more on physical symptoms (pain, stiffness and swelling) and patient performance (running, jumping, squatting), whilst neglecting the impact on emotional/mental well-being. It is therefore important to collect data on general health outcome (EuroQol-5D) as part of the assessment in this prospective trial.’