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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Author’s response to reviews:

Reviewer 1

Comment 1: Thank you for revising your manuscript. There are a few further clarifications required.

Please clarify the sample size estimation. allowing 20% loss to follow-up would require 160 participants rather than the 154 quoted.

Reply 1: Thank you for your comment. We are aiming to recruit 20% over our sample size that was produced by our power calculation, rather than a 20% loss to follow-up. Our current follow-up rate for our primary outcome at one year is 93%. We therefore do not feel we have to increase our sample size to 160.

Action 1: The following text has been modified in the Methods section under ‘Sample size’ and also under ‘Missing Data’:

‘This assumes a standard deviation of 20. 26 The sample size has been increased by 20% to account for any loss to follow-up.’

‘The study sample size has been increased by 20% to account for loss to follow-up at the primary outcome point (12 months).’
Comment 2: You are stratifying on young/old assuming a 3:1 ratio, and using opaque envelopes for the randomisation. What will you do if the patients presenting are in a different ratio? Will you be adjusting for age in the primary outcome analysis?

Reply 2: Randomisation of treatment will be on a 1:1 ratio. Randomisation will be stratified according to age with a ‘young group’ (<65 years) and an ‘older group’ (≥65 years). Based on retrospective data reporting the epidemiology of ankle fractures at our centre we will stratify on a 3:1 ratio between the ‘young’ and ‘old’. This will be factored into the computer-generated randomisation schedule, which will utilise a block design of mixed block sizes and will be generated by an independent statistician employed through the local University research methodology department. Current recruitment is in line with the anticipated ratio.

The unadjusted t-test will be the analysis of the primary outcome, or a non-parametric alternative, dependant on the normality of the data. As suggested, a supplementary analysis of covariance adjusting for age and the baseline patient reported outcome measure (OMAS) will be performed.

Action 2: We have modified the wording regarding randomisation and stratification. Please see change in the manuscript in the Methods section, under ‘Randomisation and allocation’. Please also see changes made to Methods – Statistical analysis: ‘An analysis of covariance adjusting for age and the baseline patient reported outcome measure (OMAS) will be performed.’

Comment 3: OMAS is being collected at multiple time-points. It would therefore be beneficial to undertake a mixed effects regression model taking all of these into account. This method is reasonably robust to missing at random data. The 12 month time-point can be taken from the complete model and all available data is included. Looking at change over time by assessing the slope of the linear regression line assumes that recovery trajectory is linear. This is unlikely to be the case.

Reply 3: As stated in our paper, given that the OMAS is being collected at multiple time points we will also calculate the 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.

With regards to the change over time of the OMAS score, in this instance we will account for missing data through linear regression. Any patients that do not have data at the primary outcome point (12 months), will be excluded from the final analysis. Our current follow-up rate for our primary outcome at one year is 93%. We do not feel a mixed effects regression model is likely required.

Action 3: No changes currently made.
Comment 4: The primary outcome should also adjust for the stratifying factor of age group as well as the baseline OMAS score.

Reply 4: Many thanks for this comment. The unadjusted t-test will be the analysis of the primary outcome, or a non-parametric alternative, dependant on normality. A supplementary analysis of covariance adjusting for age and the baseline patient reported outcome measure (OMAS) will be performed.

Action 4: Please see changes made to Methods – Statistical analysis: ‘An analysis of covariance adjusting for age and the baseline patient reported outcome measure (OMAS) will be performed.’

Reviewer 2

Comment 1: The sample size calculation is incorrect. It allows for approximately 17% loss to follow-up, rather than the 20% stated. An overall sample size of 160 would be required to allow for 20% loss to follow-up. Please update accordingly, either by increasing the sample size or reflecting the true rate of loss to follow-up accounted for.

Reply 1: Thank you for your comment. We are aiming to recruit 20% over our sample size that was produced by our power calculation, rather than a 20% loss to follow-up. Our current follow-up rate for our primary outcome at one year is 93%. We therefore do not feel we have to increase our sample size to 160.

Action 1: The following text has been modified in the Methods section under ‘Sample size’ and also under ‘Missing Data’:

‘This assumes a standard deviation of 20. 26 The sample size has been increased by 20% to account for any loss to follow-up.’

‘The study sample size has been increased by 20% to account for loss to follow-up at the primary outcome point (12 months).’
Comment 2: The analysis population is not defined. Please clarify who will be included in the analysis of the primary outcome.

Reply 2: In the primary outcome intention-to-treat analysis we will include all patients who have completed their 12-month follow-up.

Action 2: The following text has been added at the start of the ‘Statistical analysis’ section in the Methods:

‘The analysis of primary outcome data will include participants who have completed their 12-month follow up and will be analysed on an intention-to-treat basis.’

Comment 3: The planned analysis methods for the primary outcome remain unclear. Will the unadjusted t-test be the primary analysis of the primary outcome, with ANCOVA as a supporting analysis? Given your assertion that a short-coming of a previous trial was the lack of baseline measures would it not be better to have an adjusted analysis as your primary analysis? In addition, will you present an analysis adjusted for your stratification factor (age group)?

Reply 3: Many thanks for this comment. The unadjusted t-test will be the analysis of the primary outcome, or a non-parametric alternative, dependant on normality. A supplementary analysis of covariance adjusting for age and the baseline patient reported outcome measure (OMAS) will be performed.

Action 3: Please see changes made to Methods – Statistical analysis: ‘An analysis of covariance adjusting for age and the baseline patient reported outcome measure (OMAS) will be performed.’
Comment 4: In response to a previous reviewer's comment you assert that the primary outcome (OMAS) is only being recorded once; however, it appears this is not the case since you assert the OMAS will also be collected at 'numerous other time points'. I believe the 12 months timepoint is your primary endpoint but you are also collecting the primary outcome at other time points. It is unclear why you do not wish to fit a repeated measures model to take account of all available OMAS data. The estimate provided by this model will be more robust to missing data than using available cases (as you have planned for the primary analysis of the primary outcome). Please consider this as a supporting analysis of the primary outcome, or clarify why this will not be possible.

Reply 4: As stated in our paper, given that the OMAS is being collected at multiple time points we will also calculate the 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. With regards the change over time of the OMAS score, in this instance we will account for missing data through linear regression. Any patients that do not have data at the primary outcome point (12 months), will be excluded from the final analysis. Our current follow-up rate for our primary outcome at one year is 93%. We do not feel a mixed effects regression model is likely required.

Action 4: No changes currently made.

Comment 5: You have included an additional author on this version of the manuscript, please include their contribution in the relevant section.

Reply 5: Yes, we have included our trial statistician (CG), after detailed consultation with them regarding the statistical analysis, which was advised to us in the first review.

Action 5: The following text is included under ‘Author contributions’:

‘CG assisted with design of the study and provided detailed statistical guidance. All authors have contributed to and approved the final submitted manuscript.’