Author’s response to reviews

Title: A comparison of customised and prefabricated insoles to reduce risk factors for neuropathic diabetic foot ulceration: a participant-blinded randomised controlled trial.

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Author’s response to reviews: see over
Dear Dr Landorf

We thank you for the review of our paper and have resubmitted it, dealing with reviewers points below. Although you had said that, as it arrived late, we did not need to address Professor Edmonds review, we have taken advantage of his useful review and have addressed those points as well.

We hope that you will now find the paper suitable for publication. As Professor Edmonds said, this article is of importance and no such study has been completed in the UK. We hope that you will now find it suitable to publish.

Yours sincerely
Ray Jones on behalf of Dr Paton and colleagues.

Reviewer 1: Dr Bijan Najafi

Major Compulsory Revisions

1. It is unfortunate that Dr Najafi concluded incorrectly from our manuscript that our study excluded all patients with foot deformity. As reported in Table 1, 50% of our sample presented with lesser toe deformity, a common structural complication of the diabetic neuropathic foot associated with increased plantar pressure. The entry criteria for the study only excluded those patients with severe fixed midfoot or rearfoot deformity (specifically Charcot foot deformity). We are sorry if this was not made clear in our original manuscript and have added this additional information for greater clarity (page 5). We agree with the reviewer that many severe and asymmetric deformities may only benefit from custom made insoles and footwear, it was not our intention to suggest otherwise.

The study recruitment criteria were designed to recruit a sample representative of the general diabetic neuropathic population. The mean and SD FPI of our diabetic neuropathic population was 2.42 (SD 2.955) which compared well with Redmond et al (Redmond, Crane et al 2008) whose study of normative values for the FPI found that means and SD for the diabetic neuropathic population were 2.14 (SD 2.96). It is our experience that the foot type presented by the subjects recruited for our RCT and described by Redmond et al 2008 were representative of that found in the general neuropathic diabetic population.

This reviewer selected the Burns et al RCT for comparison; however this trial has a number of key differences from our RCT, which in our view, prevents the useful comparison of findings. For example the sham insole used within the Burns et al trial was ‘made from flat non supportive 3mm latex foam, a material shown to be least effective at reducing pressure’. In contrast our prefabricated insole was a ‘prefabricated full length 3mm medium EVA contoured shell covered in 6mm poron’ designed to reduce pressure.

2. When designing the data collection protocol for our RCT we incorporated a number of precautions to improve the accuracy and reliability of the kinetic data collected. We can therefore assure the reviewer that each subject run was timed over a set distance and the velocity calculated at every data collection session for consistency. In the event that variation was found the data was discarded and the test repeated. We can also confirm that before each data collection session each patient was weighed and each pair of insoles calibrated against body weight following the manufacturer’s instructions. This information has been added to page 7 of the manuscript.

3. We clearly acknowledge and accept within our study limitations (pg 17) that ‘the implication that peak pressure is symbolic of ulceration risk is too simplistic and should be approached with caution’. However the literature suggests that increased peak pressure in patients with diabetes results in increased ulceration risk (Lavery, Armstrong et al 2003, Crawford, Inkster et al 2007). Thus it is also common practice in the preventative management of the diabetic neuropathic foot to design insoles aimed at
reducing peak pressure (Spencer 2007). As alluded to by the reviewer, what is undetermined is the most effective mode of action by which insoles achieve that aim i.e. by modifying biomechanical gait abnormalities or simply increasing plantar surface area. It was this interesting debate that lead to the undertaking of our RCT.

Discretionary Revisions
1. We do not really understand Dr Najafi’s request, but note that this is a discretionary revision.
2. Added page 7 and 8: The first and last step of each trial was excluded to allow for gait acceleration and deceleration. A minimum of six steps were averaged for the final results.
3. Added page 8. Participants wore the standardised therapeutic footwear provided during the collection of pressure data.
4. Added page 8: The following detail has been added regarding the process of masking;

   Duration of load at the site of highest peak pressure. Extracted using TAM analysis software (TEKSCAN Ltd), the data is presented for the masked area as the duration and variation of load as a percentage of stance. The seven TAM analysis boxes were manually positioned to overlie seven anatomical regions of one movie display. The seven regions represented; the hallux, first metatarsal, second metatarsal, third and fourth metatarsal, fifth metatarsal, midfoot and heel. To ensure constituency, the box positions were saved to the system and then downloaded onto subsequent trials.
5. Added page 10: statistical values added.
6. We remain unaware of any other randomised controlled trial to indicate that custom-made functional insoles are significantly more effective in reducing forefoot pressure time integral than prefabricated insoles when used to reduce ulcer risk in neuropathic diabetic feet.

References

Reviewer 2: Professor David Torgerson
The team included a member (RJ) who is qualified in statistics and had carried out a number of RCTs. We also had advice from Plymouth University Statistics Department.
1. Professor Torgerson argues that ‘carry forward’ analysis has problems and that we should present complete case analysis. In the doctoral thesis, from which this paper is drawn, three types of analysis were pre-specified and carried out: (i) intention to treat analysis of all 119 patients with ‘carry forward’ data for 23 (19%) patients that did not complete follow-up, (ii) complete case analysis for the 96 who completed kinetic data follow-up, and (iii) ‘as-treated’ analysis for the 39 who followed the treatment protocol. We are aware that both the ‘carry forward’ and the ‘complete case’ methods have their limitations and critics, and for that reason we planned to take both approaches from the beginning of the study. We were of the view that statistical opinion now favoured the ‘carry forward’ approach. (The corresponding author has published another study in the BMJ with this as the main analysis and complete cases as supplementary information).
When we first presented this paper to the journal we included ‘intention to treat (with carry forward) and ‘as treated’. In his review of 23rd December Dr Landorf had suggested that we should only present the ITT. However, given Professor Torgerson’s criticism of this we have amended the paper to include all three analyses as Additional File 2 as was done originally by Dr Paton in her PhD thesis (examined by Professor Edmonds).

2. We accept Professor Torgerson’s argument that a baseline comparison is not essential if the randomisation has not been compromised in any way. Our randomisation process was robust so we have deleted the sentence about comparing the two groups at baseline.

3. We think that Professor Torgerson has misread our analysis section – our apologies therefore if it was not clear. The primary analysis comparing the insoles was by ANOVA (“therefore split plot ANOVAs using data collected at issue and 6-month follow-up were used to compare the custom-made functional and prefabricated insoles.”). The paired t-test was a WITHIN group analysis looking at the impact of the insoles on pressures (“Paired-samples t-tests were conducted to determine a treatment effect within groups at issue and 6-months”). We have just deleted this last sentence as it obviously detracts from reading the main analysis.

4. Professor Torgerson was not clear if it was the patient or the clinical assessor who was blinded. It was the patient. We are unable to think how to make this clearer. In the section on randomisation and blinding we have said “single blind to accommodate unavoidable ethical and practical concerns regarding potential adverse effect. Participants remained blind to the intervention group assignment.” And in the title of the paper we describe it as “participant blinded”.

5. Professor Torgerson suggests that ANCOVA would be better than the split plot ANOVA in the analysis of the change scores. We had been advised by a statistician at Plymouth University to use split plot. The majority of previous work into the effect of insoles on kinetic measures reports on mean levels of change pre and post intervention rather than looking at the difference between mean levels in the groups post intervention adjusted for baseline scores. In addition, the threshold below which insoles must maintain peak pressure to prevent ulceration is as yet unknown, instead the evidence suggests that the lower peak pressure the lower the ulceration risk. We do not think that using an ANCOVA would actually make any difference to our conclusions and thought that our approach would be better understood by clinicians reading this article. So we have persisted with the split plot ANOVA on mean levels of change. We have acknowledged the alternatives preferred by Professor Torgerson in the discussion.

6. We regret that we have not been able to add confidence intervals at this time and have noted that deficiency in the CONSORT statement. The output given by SPSS for split plot ANOVA does not provide confidence intervals. We have therefore just presented p-values and standard deviation.

7. We have added the comparison of the number with adverse events in each insole group, to the results.