**Statistical Analysis Plan: Shoe-stiffening inserts for first metatarsophalangeal joint osteoarthritis (the SIMPLE trial): a randomised controlled trial**

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# Section 1: Administrative information

## 1.1a Title

Shoe-stiffening inserts for first metatarsophalangeal joint osteoarthritis (the SIMPLE trial): a randomised controlled trial

## 1.1b Trial registration number

Australian New Zealand Clinical Trials Registry (ACTRN12616000552482).

**1.2 SAP version**

Version 1. Date: 19.7.2016

## 1.3 Roles and responsibilities

A/Prof Shannon E. Munteanu and Prof Hylton B. Menz are chief investigators of the SIMPLE trial and designed the statistical analysis plan.

## 1.4 Signatures

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| A/Prof Shannon E. Munteanu | Prof Hylton B. Menz |

# Section 2: Introduction

## 2.1 Background and rationale

Osteoarthritis of the first metatarsophalangeal joint (first MTP joint OA) is the most common form of foot OA, affecting approximately 8% of people aged 50 years and over.1 Evidence for effective treatment of this condition is lacking. Our Cochrane review in 20102 found only one randomised trial of physical therapy,3 and since the publication of this review, only three additional trials have been undertaken: a placebo-controlled trial evaluating intra-articular hyaluronan,4 a comparison of prefabricated foot orthoses and rocker-soled footwear,5 and a non-inferiority surgical trial comparing arthrodesis to a synthetic cartilage implant.6

Shoe-stiffening inserts are semi-rigid insoles that are commonly recommended as an intervention for first MTP joint OA,2 and preliminary evidence suggests clinically worthwhile improvements in foot pain and foot-related disability after 12 weeks of wear.7 Whilst these findings are promising, there is a need to conduct a rigorous randomised controlled trial and economic analysis to evaluate whether this simple, non-invasive and relatively low cost intervention is effective.

## 2.2 Objectives

* To determine if shoe-stiffening inserts are more effective at reducing pain associated with first MTP joint compared to sham shoe inserts
* To determine if shoe-stiffening inserts are more effective at reducing first MTP joint motion when walking compared to sham shoe inserts
* To determine if shoe-stiffening inserts are more cost-effective compared to sham shoe inserts

# Section 3: Study methods

## 3.1 Trial design

Parallel group, participant- and assessor-blinded, randomised controlled trial.

## 3.2 Randomisation

Participants will be allocated to the intervention or control groups using minimisation8 incorporating stratifications by age (18 to 40, 41 to 60, > 61 years) and sex, using an interactive voice response telephone service provided by the NHMRC Clinical Trials Centre at the University of Sydney, Sydney, Australia.

## 3.3 Sample size

The sample size was determined *a priori* using SPSS Sample Power 3.0 (IBM Corporation, USA) based on the Foot Health Status Questionnaire (FHSQ) pain domain as the primary outcome measure. Using a power of 90%, minimal important difference of 12.5 points in the foot pain domain of the FHSQ,9 standard deviation of 16.8 (based on the 12 week time-point in our previous trial),5 assuming a 10% drop-out rate, and a significance level set at α < 0.05, we estimated that a total of 90 participants would be required.

## 3.4 Framework

Superiority trial.

## 3.5 Statistical interim analyses and stopping guidelines

None planned.

## 3.6 Timing of final analysis

All analyses will be undertaken once all participants have completed their 52 week follow-up.

## 3.7 Timing of outcome assessments

All outcomes will be assessed at baseline and at 4, 12, 24 and 52 weeks.

# Section 4: Statistical principles

## 4.1 Level of statistical significance

Level of significance is p<0.05.

## 4.2 Rationale for any adjustment for multiplicity

To avoid over-testing and to minimise the risk of Type I error associated with serial measurements, statistical analysis of the efficacy of the interventions specifically focused on the change in primary outcome measures between baseline and 12 weeks.10 11

## 4.3 Confidence intervals to be reported

95% confidence intervals will be reported.

## 4.4 Definition of adherence and how this is assessed

Adherence to the interventions in both groups will be assessed at monthly intervals up to 52 weeks via postal survey. For the shoe insert interventions, participants will provide information regarding the number of hours per day and number of days that they had worn their inserts during the previous 4 weeks. For the rehabilitation therapy intervention, participants will provide information regarding the average number of days per week that they performed their exercises during the previous 4 weeks.

## 4.5 How adherence to the intervention will be presented

Adherence to shoe inserts will be presented as total hours of wear over the 52 week period. Adherence to rehabilitation therapy will be presented as the total number of days participants performed their therapy over the 52 week period.

## 4.6 Definition of protocol deviations

Receiving the following treatments during the 52 week period will be considered protocol deviations: (i) surgery for the first MTP joint, (ii) intra-articular injections into the first MTP joint.

## 4.7 Definition of analysis populations

Analysis will adhere to the intention-to-treat principle for all randomised participants.

# Section 5: Trial population

## 5.1 Eligibility criteria

To be included in the trial, participants must: (i) be aged at least 18 years, (ii) report pain in the first MTP joint on most days for at least 12 weeks, (iii) report pain rated at least 30 mm on a 100 mm visual analogue scale (VAS), (iv) have pain upon palpation of the dorsal aspect of the first MTP joint, (v) be able to walk household distances (>50 metres) without the aid of a walker, crutches or cane, (vi) be willing to have their foot x-rayed, (vii) agree to attempt to not receive additional interventions (such as shoe modifications, physiotherapy, foot orthoses, intra-articular injections, or surgery) for the first MTP joint pain during the course of the trial, (viii) be able to reach their feet to perform rehabilitation therapy of the first MTP joint, and (ix) be willing to attempt to discontinue consuming any pain relieving medications for first MTP joint OA (except paracetamol [up to 4 grams per day] as rescue medication) for at least 14 days prior to the baseline assessment and during the trial period.

Exclusion criteria include: (i) previous first MTP joint surgery, (ii) currently pregnant, (iii) significant first MTP joint deformity including hallux valgus (defined as a score of 2 or 3 using the Manchester scale),12 13 (iv) presence of one or more conditions within the foot or ankle that could confound pain and functional assessments of the first MTP joint, such as forefoot pain that is not first MTP joint OA, (v) presence of any systemic inflammatory condition such as gout or rheumatoid arthritis, (vi) any medical condition that, in the opinion of the investigators, made the participant unsuitable for inclusion (e.g. clinically important pain in the musculoskeletal system other than the first MTP joint), (vii) an inability to speak and read English, (viii) cognitive impairment (ix) intra-articular injections (such as corticosteroids) of the first MTP joint in the previous 3 months, (x) unwilling to discontinue use of any foot orthotic devices if currently wearing them (xi) currently wearing shoe-stiffening inserts, and (xii) regularly wear shoes not able to accommodate the shoe-stiffening inserts.

## 5.2 Information to be included in CONSORT flow diagram

CONSORT flow diagram will include: (i) number of participants assessed for eligibility by telephone (and number excluded, including reasons), (ii) number of participants assessed for eligibility by clinical assessment (and number excluded, including reasons), (iii) number of participants randomised, (iv) number of participants allocated to each group, (v) number of participants who received their allocated intervention, (vi) number of participants who completed 4, 12, 24 and 52 week follow-up (and reasons for non-completion) and (vii) number of participants analysed.

## 5.3 Withdrawal / follow-up

All withdrawals will be reported and reasons given.

## 5.4 List of baseline characteristics to be summarised

Baseline characteristics to be summarised will include: age, sex, height, weight, body mass index, Short Form 1214 physical and mental summary scores, total hours of physical activity per week (from International Physical Activity Questionnaire15), pain duration in months, Foot Posture Index scores, Maximum 1st MTPJ dorsiflexion, proportion of participants who have pain on palpation, palpable dorsal exostosis, pain on motion of 1st MTP joint, hard-end feel of joint when dorsiflexed, crepitus, radiographic features (including dorsal osteophytes, joint space narrowing, lateral osteophytes, lateral joint space narrowing, radiographic case definition using the La Trobe Radiographic Atlas.16

## 5.5 How baseline characteristics will be summarised

Baseline chacateristics will be reported as n (%) for dichotomous variables, and mean (standard deviation) for continuous variables.

# Section 6: Analysis

## 6.1 Outcomes – timing and units of measurement

The primary outcome measure is the Foot Health Status Questionnaire (FHSQ) pain domain.16 The FHSQ consists of 13 questions that assess foot health in four domains: ‘foot pain’, ‘foot function’, ‘footwear’, and ‘general foot health’. There are a total of four questions under the ‘foot pain’ domain. Questions are scored using a Likert response format and the participants’ responses are transformed into a score ranging from 0 to 100 for each domain (0 = worst foot health and 100 = optimal foot health).16 Participants will be instructed to specifically focus on their big toe joint when answering the questions. The FHSQ has been subjected to an extensive validation process, with each domain being shown to demonstrate high internal consistency, good reproducibility and discriminant validity,16 as well as good responsiveness.17 Further, the FHSQ is rated as one of the highest quality foot health status measures currently available18 19 and has been used previously in clinical trials of interventions for first MTP joint OA.4 5

Secondary outcome measures include: (i) foot-related disability (using the FHSQ function domain),16 (ii) severity of pain at the first MTP joint while walking over a flat surface and during rest over the past week (each via a 100 mm VAS), (iii) self-reported magnitude of symptom change (using a 15-point Likert scale where the responses range from “A very great deal better” to “A very great deal worse”). This variable will then be dichotomised into the categories of ‘effective’ (‘a very great deal better’, ‘a great deal better’, ‘a good deal better’, ‘moderately better’, ‘somewhat better’) and ‘ineffective’ (‘a little better’, ‘about the same, hardly any better at all’, ‘no change’, about the same, hardly any worse at all’, ‘a little worse’, ‘somewhat worse’, ‘moderately worse’, ‘a good deal worse’, ‘a great deal worse’, ‘a very great deal worse’),9 (iv) level of physical activity (using the using the Incidental and Planned Activity [IPAQ] Questionnaire),15 (v) health status (using the Short-Form-12 Version 2 [SF-12®] questionnaire14 and EuroQol [EQ-5D-5L™] questionnaire),20 (vi) use of paracetamol rescue medication (number of participants and mean consumption) and co-interventions to relieve pain at the first MTP joint, documented with a monthly diary throughout the 52 week follow-up period.4 5

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| *Outcome* | *Timing* | *Unit* |
| FHSQ – pain | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 points |
| FHSQ – function | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 points |
| Pain severity while walking | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 mm |
| Pain severity at rest | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 mm |
| Physical activity | Baseline, 4, 12, 24 and 52 weeks | Hours |
| SF12 – physical | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 points |
| SF12 – mental | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 points |
| EQ-5D-5L | Baseline, 4, 12, 24 and 52 weeks | 0 – 100 points |
| Global improvement | 12 weeks | n (%) reporting as at least moderate improvement (score ≥ 4) on 15-point Likert scale |

## 6.2 Analysis method

Continuously-scored outcome measures will be analysed using analysis of covariance (ANCOVA) with the intervention group and baseline scores entered as independent variables. Ordinal scaled data will be analysed using non-parametric tests. Dichotomous-scaled outcome measures will be compared using relative risk, risk difference, and number needed to treat (NNT).

## 6.3 Adjustment for covariates

No adjustment for covariates will be performed.

## 6.4 Sensitivity analyses

None planned.

## 6.5 Subgroup analyses

None planned.

## 6.6 Missing data

Data will be explored to determine whether it is missing at random. Multiple imputation21 will then be used to replace any missing data using five iterations, with sex, age, baseline scores, and group allocation as predictors. No data substitution will be applied for self-reported magnitude of symptom change, adherence, use of co-interventions, or adverse events.

## 6.7 Harms

Adverse events will be assessed at monthly intervals up to 52 weeks via postal survey. Participants will be asked to document the type of adverse event, the body location, the frequency and/or severity of the effect. Serious adverse events will be defined as events that were life-threatening, required hospitalisation, or resulted in persistent or significant disability or incapacity.22

## 6.8 Statistical software

All analyses will be performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA).

## 6.9 References

1. Roddy E, Thomas MJ, Marshall M, et al. The population prevalence of symptomatic radiographic foot osteoarthritis in community-dwelling older adults: the Clinical Assessment Study of the Foot. *Ann Rheum Dis* 2015;74:156-63.

2. Zammit GV, Menz HB, Munteanu SE, et al. Interventions for treating osteoarthritis of the big toe joint. *Cochrane Database Syst Rev* 2010(9):CD007809.

3. Shamus J, Shamus E, Gugel RN, et al. The effect of sesamoid mobilization, flexor hallucis strengthening, and gait training on reducing pain and restoring function in individuals with hallux limitus: a clinical trial. *J Orthop Sports Phys Ther* 2004;34:368-76.

4. Munteanu SE, Zammit GV, Menz HB, et al. Effectiveness of intra-articular hyaluronan (Synvisc, hylan G-F 20) for the treatment of first metatarsophalangeal joint osteoarthritis: a randomised placebo-controlled trial. *Ann Rheum Dis* 2011;70:1838-41.

5. Menz HB, Auhl M, Tan JM, et al. Effectiveness of Foot Orthoses Versus Rocker-Sole Footwear for First Metatarsophalangeal Joint Osteoarthritis: Randomized Trial. *Arthritis Care Res* 2016;68(5):581-9.

6. Baumhauer JF, Singh D, Glazebrook M, et al. Prospective, Randomized, Multi-centered Clinical Trial Assessing Safety and Efficacy of a Synthetic Cartilage Implant Versus First Metatarsophalangeal Arthrodesis in Advanced Hallux Rigidus. *Foot Ankle Int* 2016;37(5):457-69.

7. Jerilyn TX, Menz HB, Murley GS, et al. Effectiveness of Shoe Stiffening Inserts for First Metatarsophalangeal Joint Osteoarthritis: A Proof-of-Concept Study. *Am J Phys Med Rehabil* 2016;95(2):103-11.

8. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31(1):103-15.

9. Landorf KB, Radford JA, Hudson S. Minimal Important Difference (MID) of two commonly used outcome measures for foot problems. *J Foot Ankle Res* 2010;3:7.

10. Matthews JN, Altman DG, Campbell MJ, et al. Analysis of serial measurements in medical research. *BMJ* 1990;300:230-35.

11. Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol* 2001;54:343-49.

12. Garrow AP, Papageorgiou A, Silman AJ, et al. The grading of hallux valgus. The Manchester Scale. *J Am Podiatr Med Assoc* 2001;91:74-78.

13. Menz HB, Munteanu SE. Radiographic validation of the Manchester scale for the classification of hallux valgus deformity. *Rheumatology* 2005;44:1061-66.

14. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.

15. Delbaere K, Hauer K, Lord SR. Evaluation of the incidental and planned activity questionnaire for older people. *Br J Sports Med* 2010;44:1029-34.

16. Bennett PJ, Patterson C, Wearing S, et al. Development and validation of a questionnaire designed to measure foot-health status. *J Am Podiatr Med Assoc* 1998;88:419-28.

17. Menz HB, Auhl M, Ristevski S, et al. Comparison of the responsiveness of the Foot Health Status Questionnaire and the Manchester Foot Pain and Disability Index in older people. *Health Qual Life Outcomes* 2014;12(1):158.

18. Martin RL, Irrgang JJ. A survey of self-reported outcome instruments for the foot and ankle. *J Orthop Sports Phys Ther* 2007;37:72-84.

19. Riskowski JL, Hagedorn TJ, Hannan MT. Measures of foot function, foot health, and foot pain: American Academy of Orthopedic Surgeons Lower Limb Outcomes Assessment: Foot and Ankle Module (AAOS‐FAM), Bristol Foot Score (BFS), Revised Foot Function Index (FFI‐R), Foot Health Status Questionnaire (FHSQ), Manchester Foot Pain and Disability Index (MFPDI), Podiatric Health Questionnaire (PHQ), and Rowan Foot Pain Assessment (ROFPAQ). *Arthritis Care Res* 2011;63:S229-39.

20. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43.

21. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.

22. Keech AC, Wonders SM, Cook DI, et al. Balancing the outcomes: reporting adverse events. *Med J Aust* 2004;181(4):215-8.