Statistical Analysis Plan (SAP)

Trial: Foot ORthoses for big Toe joint osteoarthritis: the FORT randomised controlled trial

Contents

Section 1. Administrative Information

1. Title

Foot ORthoses for big Toe joint osteoarthritis: the FORT Randomised Controlled Triall

2. Trial registration

Prospectively registered (Australian New Zealand Clinical Trials Registry Trial Id: ACTRN12619000926134, 03/07/2019)

3. SAP version

Version: 1.0 Date: 06/05/2021

4. Protocol Version

This document has been written based on information contained in the FORT study protocol version 1.0 dated 02/02/20. The protocol was published as follows:

Paterson KL, Hinman RS, Metcalf BR, Jones SE, Menz HB, Munteanu SE, et al. Foot orthoses for first metatarsophalangeal joint osteoarthritis: study protocol for the FORT randomised controlled trial. BMC Musculoskeletal Disorders 2020; 21: 830. Published 2020 Dec 10. doi:10.1186/s12891-020-03809-x

5. SAP Revisions

Not applicable

6. Names and affiliations

Document prepared by Dr Kade Paterson, Prof Rana Hinman, Ms Fiona McManus, Prof Hylton Menz, Assoc Prof Shannon Munteanu, Mr Ben Metcalf, Dr Sarah Jones and Professor Kim Bennell, University of Melbourne.

Emails: KL Paterson kade.paterson@unimelb.edu.au; RS Hinman ranash@unimelb.edu.au; F McManus fmcmanus@unimelb.edu.au; HB Menz H.Menz@latrobe.edu.au; SE Munteanu S.Munteanu@latrobe.edu.au; BR Metcalf b.metcalf@unimelb.edu.au; SE Jones jones.s@unimelb.edu.au; KL Bennell k.bennell@unimelb.edu.au;

Signatures:

Signature of senior statistician responsible (Ms Fiona McManus): *Date: 04/05/2021*

Signature of chief investigator (Dr Kade Paterson): *Date: 04/05/2021*

Section 2: Introduction

7. Background and rationale

Osteoarthritis (OA) of the foot is as prevalent as knee OA, and the most commonly affected foot site is the first metatarsophalangeal (MTP) joint.[1] First MTP joint OA is highly debilitating with most (72%) sufferers reporting pain described as disabling.[1] The condition causes dorsal osteophytes and joint space narrowing which impair range of motion, and in turn, lead to substantial problems performing functional weight bearing activities and impaired quality of life.[2] Non-drug, non-surgical strategies are recommended as first line treatments in international clinical OA guidelines,[3-6] however there have only ever been three randomised controlled trials evaluating non-drug, non-surgical treatments for first MTP joint OA. Accordingly, foot OA has been highlighted as an under-researched problem and identified as a research priority by OA experts and by all leading international OA clinical bodies.[3, 7, 8]

Unlike for hip and knee OA, there are no "joint-specific" clinical guidelines for managing patients with first MTP joint OA, and scant research is available to guide clinical practice. In the absence of clinical trial evidence, we conducted an international survey of podiatrists and physiotherapists who currently treat people with first MTP joint OA, to see how the condition was managed in clinical practice. The results showed that foot orthoses, which are purported to work by changing the biomechanical function of the foot, were one of the most commonly used treatment strategies.[9] However, it is unknown whether these devices are effective in improving the symptoms associated with first MTP joint OA. The need for such research has also been highlighted by OA stakeholders and patients, who have rated non-surgical treatment and biomechanical strategies within their top 10 OA research priorities.[10]

8. Objectives

Research hypothesis:

Primary alternative hypothesis: That contoured foot orthoses will lead to significantly greater reductions in first MTP joint pain on walking compared to sham flat insoles when worn daily over 12 weeks, in people with painful first MTP joint OA.

Secondary alternative hypothesis: That contoured foot orthoses will have significantly greater benefits on overall first MTP joint pain, and on other clinical outcomes (physical function, other measures of foot pain, global ratings of change, health-related quality of life, physical activity levels), compared to sham flat insoles, at 12 weeks.

Study objective:

Primary objective: To determine if contoured foot orthoses lead to significantly greater reductions in first MTP joint pain on walking compared to sham flat insoles when worn daily over 12 weeks, in people with painful first MTP joint OA.

Secondary objective: To determine if contoured foot orthoses will have significantly greater benefits on overall first MTP joint pain, and on other clinical outcomes (physical function, other measures of foot pain, global ratings of change, health-related quality of life, physical activity levels), compared to sham flat insoles, at 12 weeks.

Section 3: Trial Methods

9. Trial design

The FORT trial is two-arm, superiority, participant- and assessor-blinded randomised controlled trial. Treatment allocation is a 1:1 ratio. Participants are randomized to either contoured foot orthoses or sham flat insoles.

10. Randomisation

Participants will be randomly allocated to the contoured foot orthoses group or the sham flat insoles group using a randomization schedule prepared by the study biostatistician. Randomization will occur according to a 1: 1 allocation (permuted block sizes 6 to 12) with varying sizes of 6 to 12, stratified by podiatrist. The schedule will be stored on a password-protected website (REDCap) maintained by a researcher not involved in either participant recruitment or administration of primary/secondary outcome measures. Group allocation will be revealed by this same researcher after baseline primary/secondary outcomes have been completed.

11. Sample size

We aim to detect the MCID on the primary outcome between groups (1.8 out of 10 units on change in NRS for walking pain). We conservatively assume a between-participant SD of 2.5 and a baseline to 12-week correlation of 0.3 based on our pilot RCT data. Using ANCOVA adjusted for baseline score, we need 37 per arm to achieve 90% power to detect the MCID in pain. Allowing for 15% attrition, we will recruit 44 people per arm in total (n=88).

12. Framework

This trial uses a superiority hypothesis testing framework between groups for all outcomes.

13. Statistical Interim analyses and stopping guidance

Nil

14. Timing of final analysis

Final analysis will be performed after all (n=88) participants have reached the 12 week timepoint and completed assessments.

15. Timing of outcome assessments

Table 4.6 in the study protocol details the timing of outcome assessments, the majority of which occur at baseline and at 12 weeks.

Section 4: Statistical Principles

16. Level of statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

17. Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

We have one primary outcome (first MTP joint pain on walking). We have several secondary outcomes (overall first MTP joint pain, physical function, other measures of foot pain, global ratings of change, health-related quality of life, physical activity levels). All secondary outcomes are exploratory and not powered for. We will therefore not adjust for multiple secondary outcomes but instead report all effect sizes, confidence intervals, and p values in order to let readers use their own judgment about the relative weight of the conclusions on the effect of contoured foot orthoses for painful first MTP joint OA. This approach aligns with the usage of p-values favoured by the American Statistical Association.[11]

18. Confidence intervals to be reported

All confidence intervals will be 95% confidence intervals.

19. Adherence and Protocol Deviations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally assigned, regardless of their adherence to their assigned treatments. Any protocol deviations (if they occur), including errors applying inclusion/exclusion criteria and/or administration of the wrong intervention will be summarised in trial results (patient flow diagram/text) by treatment group. Randomisation errors resulting from these errors will be handled according to recommendations. [12]

Multiple measures of adherence are used in this trial (described in Table 4.6 of the protocol) and data from all measures will be reported using means, standard deviations and proportions (number and percentage) as appropriate for each treatment group.

Participants record the hours/day they wore their orthoses/insoles and footwear daily for the final 7 consecutive days of weeks 4, 8 and 12 in log books. Adherence will be calculated as the average percentage of time spent wearing the study orthoses/insoles when wearing shoes. Participants will be classified as adherent if they wear their insoles for an average of at least 70% of the time spent wearing shoes.

If a participant does not provide all log books, average daily allocated insole wear will be calculated using the available log books. If a participant does not provide any log books, non-adherence will be assumed.

20. Analysis Populations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally randomised, regardless of their adherence to their assigned treatments.

Section 5: Trial Population

21. Screening Data

Screening data will be collected and summarized. A CONSORT flow diagram will be used.[13] The following summaries will be presented in text and/or flow diagram: time frame for recruitment, the number of patients screened, the number of patients recruited, the number of screened patients not recruited, and the reasons for non-recruitment.

22. Eligibility

Trial inclusion and exclusion criteria are described in section 5.2 of the trial protocol. Reasons for exclusion will be summarized in the CONSORT [13] flow diagram.

23. Recruitment

A CONSORT flow diagram [13] will be used to describe the number of people enrolled, randomised, allocated to each treatment group, lost to follow up (including reasons) and analysed.

24. Withdrawal/follow-up

If a participant withdraws from the study, the nature, timing of and reasons for withdrawal will be described (provided the participant responds to contact made by the research team). Any data provided up to the point of withdrawal will be analysed in accordance with intention to treat analyses, unless the participant specifically requests to withdraw their data from the study. Losses to follow-up (including reasons) will be summarised in the CONSORT flow diagram by treatment group.

25. Baseline characteristics

Baseline characteristics will be summarised by treatment group and presented in a table:

- Age
- Gender
- Height, body mass, body mass index
- Radiographic disease severity using the La Trobe Foot Atlas
- Duration of first MTP joint OA symptoms
- Current employment status
- Hallux valgus severity
- Expectation of treatment outcome
- Credibility/Expectancy Questionnaire
- Co-intervention use
- Foot posture index

Baseline characteristics will be summarised as appropriate (means and standard deviations for continuous variables that appear to be distributed approximately symmetrically, medians and interquartile ranges for other continuous variables, counts and percentages for categorical variables). Tests of statistical significance will not be undertaken for comparing baseline characteristics of treatment groups; rather the clinical importance of any imbalance will be noted.

Section 6: Analysis

26. Outcome definitions

Primary outcome:

- Change in severity of first MTP joint pain during walking: overall average pain intensity on walking in the last week is assessed at baseline and 12-weeks using an 11-point numerical rating scale (NRS) with terminal descriptors of 'no pain' (score = 0) and 'worst pain possible' (score = 10). Change score at 12 weeks will be calculated as baseline minus follow-up.

Secondary outcomes:

- Change in foot pain: foot pain over the past week is measured using the pain subscale of the Foot Health Status Questionnaire (FHSQ), a foot-specific tool with high internal consistency and test-retest reliability. This subscale contains 4 questions related to overall foot pain, each rated on a 5-point Likert scale from 0 (none) to 4 (severe). Responses are recoded to provide a score between 0 (worst foot health) to 100 (optimal foot health). Change in FHSQ foot pain at 12 weeks will be calculated as baseline minus follow-up.

- Change in physical function: the function subscale of the FHSQ is used to assess physical function over the previous week. This subscale contains 4 questions related to how much foot pain interferes with specific activities, each rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely). Responses are recoded to provide a score between 0 (worst foot function) to 100 (best foot function). Change scores at 12 weeks will be calculated as baseline minus follow-up.

- Change in average overall first MTP joint pain: overall average pain intensity in the last week is scored on an 11-point NRS, with terminal descriptors 'no pain' (score = 0) and 'worst pain possible' (score = 10). Change scores at 12 weeks will be calculated as baseline minus follow-up.

- Global improvement at 12 weeks: Global improvement overall, and in pain and physical function will be scored using a 7-point global rating of change Likert scale with response options ranging from "much worse" to "much better" when compared to baseline. Participants indicating they are "moderately better" or "much better" will be classified as improved. All other respondents will be classified as not improved.

- Change in health-related quality of life: The AQoL questionnaire (version AQoL-6D) measures health-related quality of life. This is a 20-item questionnaire and scores range from -0.04 to 1.00 with 1.00 indicating full health-related quality of life. Change scores at 12 weeks will be calculated as baseline minus follow-up.

- Change in physical activity: The Physical Activity Scale for the Elderly is being used to assess physical activity over the previous week. This is a 10-item questionnaire which collects responses for the frequency, duration and intensity level of a range of activities typically chosen by older adults. Scores range 0 to >400 with higher scores indicating greater levels of physical activity. Change scores at 12 weeks will be calculated as baseline minus follow-up.

27. Analysis methods

Primary outcome:

Main comparative analyses between groups will be performed using intention-to-treat. If more than 5% of primary outcomes are missing, multiple imputation will be applied. For the primary hypothesis, differences in mean change in pain (baseline minus follow-up) will be compared between groups using linear regression modelling adjusted for baseline values and the stratifying variable of podiatrist. Results will be presented as mean differences between groups with 95% confidence intervals, and p-values will also be reported. Complete-

case analyses will also be conducted.

Secondary outcomes:
Analyses between groups will be performed using intention-to-treat. For continuous outcomes, analyses will be similar to those for the primary outcomes. Improvement based on global change scores will be compared between groups using log-binomial regression, adjusting for the stratifying variable of podiatrist, with results reported as risk ratios and risk differences. Counts and percentages of participants experiencing improvements will be reported in each treatment group. Should the log-binomial regression models fail to converge, logistic regression models adjusting for the stratifying variable will be fit, with results reported as odds ratios, risk ratios and risk differences, calculated from fitted logistic regression models. For all between-group comparisons, 95% confidence intervals for comparisons and p-values will be reported.

28. Statistical Methods – adjustment for covariates

For the primary hypothesis, differences in mean change in severity of first MTP joint pain during walking (baseline minus follow-up) will be compared between groups using linear regression modelling adjusted for baseline values and the stratifying variable of podiatrist. For continuous secondary outcomes, linear regression models will also be adjusted for baseline values and the stratifying variable of podiatrist. For the binary outcomes, regression models will be adjusted for the stratifying variable of podiatrist.

29. Statistical Methods – sensitivity analyses

A sensitivity analysis will estimate treatment effects on the primary outcome assuming full adherence, where full adherence is as defined in Section 19. That is, complier average causal effects will be estimated using an instrumental variables approach (where randomisation is the instrument for adherence). Two-stage least squares models will be fit [14] with complier average causal effects reported with 95% confidence intervals and p-values. A secondary sensitivity analysis will estimate treatment effects on the primary outcome adjusted for insoles density (blue medium versus red firm density insoles) in addition to baseline values of the primary outcome and the stratifying variable of podiatrist.

30. Statistical Methods – subgroup analyses

To assess whether the effect of insole group on the primary outcome of pain is moderated by any of the variables of BMI, a composite score for osteophyte or joint space narrowing, or first MTP joint range of motion, appropriate interaction terms between randomised group and each of these variables will be included in regression models for the primary outcome, and for each potential effect modifier separately. For the continuous moderators, fractional polynomials will be explored to determine whether a more complex functional form than linear is appropriate, following the approach of Royston & Sauerbrei.[15]

The rationale for the choice of *a priori* moderators is:

- BMI- we hypothesise that pain reduction with the foot orthoses will be lower in those with a higher BMI compared to sham, based on the likelihood that a greater mass will compress the arch support and heel contour properties of the foot orthoses that are believed to contribute to symptomatic benefits.
- Composite osteophyte or joint space narrowing score- we hypothesize that either greater or lesser radiographic OA severity may moderate pain reduction with orthoses. Pain reductions in those with more severe osteophytes and/or joint space narrowing may be lower with the foot orthoses compared to sham due to dorsal compression and pain caused by the first ray cut out. Alternatively, pain reductions in those with more severe osteophytes and/or joint space narrowing may be greater as the cut out may allow the first metatarsal to plantarflex and the proximal phalanx to dorsally glide, reducing sagittal plane rotation and preventing dorsal compression.

- First MTP joint range of motion- we hypothesise that pain reduction with the foot orthoses will be lower compared to sham in those with reduced range of motion due to increased joint and hallux loading from the orthoses cut out.

A secondary subgroup analysis will estimate and compare treatment effects on the primary outcome separately for those participants who received blue medium density insoles and those who received red firm density insoles using linear regression modelling with an interaction term between treatment group and insoles density, adjusted for baseline values of the primary outcome and the stratifying variable of podiatrist.

31. Missing data reporting and assumptions/statistical methods to handle missing data

Baseline characteristics of participants with the primary outcome missing at 12 weeks will be compared to those of participants with primary outcomes, as outlined in Section 25. If more than 5% of participants have primary outcomes missing at 12 weeks, multiple imputation will be applied. The number of imputed datasets will be approximately equal to the proportion of participants with missing primary outcomes. Missing baseline characteristics will be imputed using single mean imputation. Missing outcome values will be imputed separately by treatment group, using chained equations and predictive mean matching, using the five nearest neighbours. Imputation models will include baseline levels of outcomes and baseline characteristics that appear to be different between participants who provide complete follow up data and participants who do not. Initially imputation models for all outcomes will be chained together, with outcomes broken into subsets if imputation models do not converge. Imputed datasets will be compared to complete data using density plots for continuous outcomes and plots of proportions for binary outcomes.

To assess the potential impact of the violation of the missing-at-random assumption on conclusions for the primary outcomes, a pattern-mixture approach (as in White et al [16]) will be applied. We will explore the impact of the violation of the missing-at-random assumption if the assumption was violated in both groups, or in one group only.

32. Additional Analyses

Nil

33. Harms

The number (and percentage) of patients experiencing any adverse events will be presented for each treatment group and the nature of the event(s) described. An adverse event is defined as any problem experienced in the study foot or elsewhere in the body as a result of wearing the study insoles.

34. Statistical Software

Stata v16.1 will be used (StataCorp. 2020. *Stata Statistical Software: Release 16.1*. College Station, TX: StataCorp LLC)

35. References

1. Roddy E, Thomas MJ, Marshall M, Rathod T, Myers H, Menz HB, Thomas E, Peat G. The population prevalence of symptomatic radiographic foot osteoarthritis in community-dwelling older adults: cross-sectional findings from the clinical assessment study of the foot. Ann Rheum Dis. 2015; 74:156-163.
2. Bergin SM, Munteanu SE, Zammit GV, Nikolopoulos N, Menz HB. Impact of first metatarsophalangeal joint osteoarthritis on health-related quality of life. Arthritis Care & Research. 2012; 64:1691-1698.
3. National Clinical Guideline Centre. Osteoarthritis: Care and management in adults. Clinical guideline CG177. Methods, evidence and recommendations. London; National Institute for Health and Care

Excellence. 2014.
4. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H *et al*. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage. 2014; 22:363-388.
5. The Royal Australian College of General Practitioners. Guideline for the management of knee and hip osteoarthritis, 2nd ed: East Melbourne, Vic: RACGP; 2018.
6. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, Doherty M, Geenen R, Hammond A, Kjeken I *et al*. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Annals of the Rheumatic Diseases. 2013; 72:1125-1135.
7. Conaghan PG, Kloppenburg M, Schett G, Bijlsma JWJ. Osteoarthritis research priorities: a report from a EULAR ad hoc expert committee. Annals of the Rheumatic Diseases. 2014; 73:1442-1445.
8. Sharma L. Osteoarthritis year in review 2015: clinical. Osteoarthritis and Cartilage. 2016; 24:36-48.
9. Paterson KL, Hinman RS, Menz HB, Bennell KL. The ABC foot study: an international, multi-phase, mixed methods study of the assessment of beliefs and clinical practice for managing first metatarsophalangeal joint osteoarthritis. Osteoarthritis and Cartilage. 2018; 26:S320.
10. Gierisch JM, Myers ER, Schmit KM, McCrory DC, Coeytaux RR, Crowley MJ, Chatterjee R, Kendrick AS, Sanders GD. Prioritization of patient-centered comparative effectiveness research for osteoarthritis. Annals of internal medicine. 2014; 160:836-841.
11. Wasserstein RL, Schirm AL, Lazar NA. Moving to a world beyond "p < 0.05". The American Statistician. 2019; 73:1-19.
12. Yelland LN, Sullivan TR, Voysey M, Lee KJ, Cook JA, Forbes AB. Applying the intention-to-treat principle in practice: Guidance on handling randomisation errors. Clin Trials. 2015; 12:418-423.
13. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340:c869.
14. Maracy M, Dunn G. Estimating dose-response effects in psychological treatment trials: the role of instrumental variables. Statistical Methods in Medical Research. 2008; 20:191-215.
15. Royston P, & Sauerbrei, W. Two Techniques for Investigating Interactions between Treatment and Continuous Covariates in Clinical Trials. The Stata Journal. 2009; 9:230-251.
16. White IR, Kalaitzaki E, Thompson SG. Allowing for missing outcome data and incomplete uptake of randomised interventions, with application to an Internet-based alcohol trial. Stat Med. 2011; 30:3192-3207.