Statistical Analysis Plan for Corticosteroid injection plus exercise versus exercise, beyond advice and a heel cup for patients with plantar fasciopathy: a randomised clinical superiority trial (the FIX-Heel trial)

Riel, Henrik; Vicenzino, Bill; Olesen, Jens Lykkegaard; Jensen, Martin Bach; Ehlers, Lars Holger; Rathleff, Michael Skovdal

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

Section 1: Administrative info

Statistical Analysis Plan for *Corticosteroid injection plus exercise versus exercise, beyond advice and a heel cup for patients with plantar fasciopathy: a randomised clinical superiority trial (the FIX-Heel trial)*

Henrik Riel[1]: hriel@dcm.aau.dk

Bill Vicenzino[2]: b.vicenzino@uq.edu.au

Jens Lykkegaard Olesen[1]: jlo@dcm.aau.dk

Martin Bach Jensen[1]: mbj@dcm.aau.dk

Lars Holger Ehlers[3]: lehlers@business.aau.dk

Michael Skovdal Rathleff[1,4,5]: misr@hst.aau.dk

[1]Center for General Practice at Aalborg University, Fyrkildevej 7, 9220 Aalborg East, Denmark

[2]The University of Queensland, School of Health and Rehabilitation Sciences: Physiotherapy: Sports Injury Rehabilitation and Prevention for Health, St. Lucia QLD 4072, Australia

[3]Danish Center for Healthcare Improvements (DCHI), Department of Business and Management, The Faculty of Social Sciences, Aalborg University, Fibigerstræde 11, 9220 Aalborg East, Denmark

[4]Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Fredrik Bajers Vej 7D, 9220 Aalborg East, Denmark

[5]Department of occupational therapy and physiotherapy, Aalborg University Hospital, Hobrovej 18-22, 9100 Aalborg, Denmark

Trial registration no.: NCT03804008
SAP version: 1.0

Principal investigator Henrik Riel

12-12-2020 

Study chair Michael Skovdal Rathleff

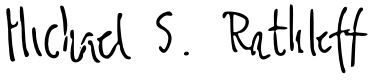

Table of contents

Section 1: Administrative info **1**

Section 2: Introduction and objectives **3**

Section 3: Study methods **3**

3.1: Ethical statement *3*

3.2: Study design *3*

3.3: Randomisation *3*

3.4: Sample size *4*

Section 4: Statistical principles **4**

Section 5: Study population **5**

5.1: Eligibility criteria *5*

5.2: Baseline characteristics *5*

Section 6: Analysis **6**

6.1: Experimental outcomes *6*

6.2: Statistical methods *7*

Primary analysis 7

Secondary analyses 8

Cost-effectiveness analysis 8

Exclusion cohort 9

6.3: Harms *9*

Section 7: Acknowledgements **10**

Section 8: References **11**

Section 2: Introduction and objectives

Plantar fasciopathy has a lifetime prevalence of 10%. Patients suffer from sharp pain under the heel, often for several months or years. Multiple treatments are available, but no single treatment appears superior to the others. A corticosteroid injection offers short-term pain relief but is no better than placebo in the longer term (>8 weeks). Heavy-slow resistance training has shown potentially positive effects on long-term outcomes (>3 months) and combining exercises with an injection may prove to be superior to exercises alone. However, the effect of heavy-slow resistance training compared with a simpler approach of patient advice (e.g. load management) and insoles is currently unknown. This trial compares the efficacy of patient advice (PA) versus patient advice plus heavy-slow resistance training (PAX) versus patient advice plus heavy-slow resistance training plus a corticosteroid injection (PAXI) in improving the Foot Health Status Questionnaire pain score after 12 weeks in patients with plantar fasciopathy.

Section 3: Study methods

3.1: Ethical statement

The trial is being conducted according to the Declaration of Helsinki III, and the protocol, template informed consent forms, and participant information were approved by the Ethics Committee of North Denmark Region (N- 20180066) prior to the inclusion of participants. All participants provide informed consent before enrolment. When participants sign the consent form, they agree that they have been adequately informed about the purpose, methods, advantages, and disadvantages of participation; they know that participation is voluntary; and they can withdraw from the trial without losing their current or future rights to receive treatment.

3.2: Study design

The FIX-Heel Trial is designed as a randomised, superiority trial with a 3-group parallel design. The preparation of the trial, including publishing this trial protocol, was done in accordance with the PREPARE Trial guide.(1)Before the inclusion of the first participant, the trial was registered on clinicaltrials.gov (NCT03804008).

3.3: Randomisation

Participants will be stratified by sex and block randomised in random concealed block sizes of 3 to 12 (1:1:1) into three parallel groups. A researcher not involved in the trial generated the allocation

sequence using a random number generator on www.sealedenvelope.com and is the only person who knows the block sizes. The researcher was trained by the project manager in generating allocation sequences and the process was piloted.

The randomisation is coded so that the project manager does not know which intervention is linked to which group number (Group 1, 2 or 3). The envelopes will be kept in a locked room at Aalborg University Hospital where only the two physiotherapists involved in baseline testing have access. The randomisation schedule was prepared at the Center for General Practice at Aalborg University by a person not involved in the actual trial. The notes in the envelopes state both group number and intervention and the physiotherapists responsible for assessing participants and delivering the interventions will not be aware of the coding before they open the first envelopes. In practice, after a participant has been enrolled, has filled out questionnaires and received initial patient advice and information regarding the practicalities of participation, the physiotherapist will take an envelope and assign the participant to the allocated treatment based on randomisation.

3.4: Sample size

The minimal important difference of the FHSQ pain domain has been found to be either 12.5 or 14.1 points in this patient population.(2,3) We have chosen the most conservative option (i.e. 14.1 points) to form the basis of the sample size calculation. Based on a standard deviation of 22 points, which is comparable to the overall standard deviations found in previous studies of this patient population (4–7), a two-sided 5% significance level and a power of 90%, a sample size of 53 participants in each group will be necessary. Taking into consideration possible drop-outs, we will include 60 participants in each group and, thus, a total sample size of 180 participants.

Section 4: Statistical principles

We will report two-sided 95% confidence intervals and P-values <0.05 are interpreted as statistically significant. We will use Q-Q plots and histograms to assess data normality and analyses are performed following the intention-to-treat principle such that randomised participants will be analysed according to the treatment group to which they were originally assigned, regardless of treatment received, crossover or non-adherence. The data analyst will be blinded to the interventions received in each group and remains unblinded until after the primary analysis has been performed. Data is collected and stored in REDCap (Vanderbilt University, Nashville, TN, USA). Data will be exported to Microsoft Excel (Microsoft Corporation, Washington, USA) where

it they will be prepared for analyses will be performed in SPSS (IBM Corporation, New York, United States).

Section 5: Study population

5.1: Eligibility criteria

The inclusion criteria are: history of inferior heel pain for at least three months before enrolment; pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia; thickness of the plantar fascia ≥4.0 mm and; mean heel pain of ≥30 mm on a 100 mm VAS during the previous week. The exclusion criteria are: below 18 years of age; diabetes; history of inflammatory systemic diseases (e.g. rheumatoid arthritis or spondyloarthritis)(4); prior heel surgery; pregnancy or breastfeeding; corticosteroid injection specifically for PF within the previous six months; pain or stiffness in the 1st metatarsophalangeal joint to an extent where the exercises cannot be performed; known hypersensitivity to corticosteroids or local anaesthetics; skin or soft tissue infection near the injection site; received any treatment by a healthcare professional for PF within the previous 12 weeks; or made any substantial changes to usual self-care of the condition in the last 4 weeks (e.g. started using insoles, started performing stretching, made a substantial decrease in physical activity level). These criteria are in line with those of similar studies in this patient population.(4,8,9) These criteria lead to a representative sample of patients with PF as previous studies include the majority of potentially eligible participants.(4,8,9)

5.2: Baseline characteristics

Characteristic	**Unit**	**Reporting**
Sex	Male/Female	Frequency
Height	Cm	Mean (Standard deviation)
Weight	Kg	Mean (Standard deviation)
Body mass index	Kg/m^2	Mean (Standard deviation)
Symptom duration	Months	Mean (Standard deviation)
Pain during past week	mmVAS	Mean (Standard deviation)
Bilateral pain	Yes/No	Frequency
Plantar fasciopathy incidents	Number of incidents	Frequency
Plantar fascia thickness	mm	Mean (Standard deviation)
Educational level	n/a	Frequency
Job situation	n/a	Frequency
Days of sick leave	Days	Mean (Standard deviation)

Contact to healthcare practitioners	n/a	Frequency
Previous treatment	n/a	Frequency
Comorbidities	n/a	Frequency

Section 6: Analysis

6.1: Experimental outcomes

The primary outcome is the pain domain of the Foot Health Status Questionnaire (FHSQ) at the 12-week follow-up. The FHSQ is a questionnaire ranging from 0 (worst possible score) to 100 (best possible score) with a high reliability (ICC=0.74-0.92) that assesses multiple dimensions of foot-related health and function and is recommended in this patient population.(10,11) The minimal important difference of the pain domain is 14.1 points.(2) We will use a Danish validated translation of the original questionnaire.(12)

Secondary outcomes include: i) the other domains of the FHSQ (function, footwear and general foot health domains), ii) Global Rating of Change (GROC), iii) PASS, iv) Pain Self-Efficacy Questionnaire (PSEQ), v) weekly light, moderate and vigorous physical activity level, and to perform a cost-effectiveness analysis vi) EQ-5D-5L, and vii) patients' co-payments and other condition-related expenses.

- We will use the GROC to measure participants' self-reported improvement on a 7-point Likert scale ranging from "much improved" to "much worse". Participants are dichotomised as improved if they rate themselves as "much improved" or "improved" (categories 6 and 7) and categorised as not improved if they rate themselves from "slightly improved" to "much worse" (categories 1 to 5).
- PASS (Yes/No) will be used as a measure of when participants achieve a self-evaluated satisfactory result and feel no need for further treatment. Therefore, this is not necessarily a measure of complete recovery as some may be satisfied despite still experiencing symptoms. PASS has been used to evaluate clinically relevant states in PF and in other musculoskeletal disorders and post-operative pain.(9,13–15) Participants will be asked to report to the physiotherapists as soon as they experience PASS and the date will be noted. Furthermore, participants will be asked about their PASS status during follow-ups. After the participant reports a PASS, they will be instructed to continue performing the exercise as prescribed for

at least four weeks and to report back if their PASS status changes (i.e. if the condition deteriorates and they would need treatment again).

- The PSEQ measures pain self-efficacy and provides a score ranging from 0 (not at all confident) to 60 (completely confident) with lower scores indicating lower self-efficacy.(16) The Danish version of the PSEQ has been validated in a Danish chronic pain population and has a high reliability (ICC=0.89).(17)
- To estimate weekly physical activity level expressed as Metabolic Equivalents (METs), we will use 3D accelerometry. Participants will be given a wrist-worn accelerometer (ActiGraph wGT3X-BT (ActiGraph LLC, Pensacola, FL, USA)) during baseline and will be asked to wear this during the first three weeks after baseline and then return the accelerometer in a postmarked envelope. During the 12-week follow-up, participants receive the accelerometer again and will be wearing it for an additional three weeks before returning it. Participants will be instructed to wear the accelerometer at all times. We will use data from the first valid week recorded during the first and second round of wearing the accelerometer (i.e. one week during weeks 1 to 3, and one week during weeks 13 to 15). A valid week is defined as ≥4 days of ≥10 hours of wear time.(18) Data will be extracted from the accelerometers using the ActiLife software and divided into light (<3 METs), moderate (3–6 METs), and vigorous (>6 METs) physical activity.(19)
- The Danish version of the EQ-5D-5L is a generic tool for measuring health-related quality in life and will be used to estimate QALYs and perform a cost-effectiveness analysis. It consists of five dimensions (mobility, self-care, usual activities, pain/ discomfort and anxiety/depression) that each have five ranked response options ranging from no problems or concerns to largest possible problems or concerns.
- Patients' co-payments and other condition-related expenses are estimated based on a questionnaire with questions about sick leave, loss of productivity due to PF, co-payments for treatments and/or equipment and medication.

6.2: Statistical methods

Primary analysis

The primary analysis will investigate the between-group difference in FHSQ pain. We will visually explore the trajectory of improvements before applying the statistical model to the data. This will ensure our choice of model match the specific trajectories. We will use a linear mixed effects model

with the participant as random effect. The baseline value, time (4, 12, 26 and 52 weeks), group allocation (PA or PAX or PAXI) and term for interaction between time and group will be treated as fixed-effect variables. Conclusions will only be drawn based on differences or the lack hereof at the primary endpoint (12 weeks).

Secondary analyses

We will also analyse the mean values of the secondary continuous outcomes (other domains of FHSQ, PSEQ and physical activity level (light, moderate, and vigorous)) using linear mixed models with participant as random effect. The baseline value, time (4, 12, 26 and 52 weeks), group allocation (PA or PAX or PAXI) and term for interaction between time and group will be treated as fixed-effect variables. The risk difference ($= \frac{Positive\ outcomes\ in\ one\ group}{Number\ of\ participants\ in\ group}$ - $\frac{Positive\ outcomes\ in\ another\ group}{Number\ of\ participants\ in\ group}$) will be calculated for the dichotomised GROC to determine the probability of being improved, for the PASS (Yes/No) to determine the probability of achieving a self-evaluated satisfactory result within the 12, 26 and 52 weeks of intervention We will also calculate risk differences to determine the probability of experiencing a deterioration of PF defined as a decrease in FHSQ pain of the minimal important difference (≥14.1 points) from one follow-up to another, or changing ones status from having achieved PASS to no longer having achieved PASS. We will calculate the number needed to treat for the primary outcome at the primary endpoint as 1/risk difference. We will use a Kaplan-Meier survival analysis and compare survival curves using logrank tests to investigate between-group differences in time to achieving PASS.(20,21) If a participant changes PASS multiple times (e.g. achieving PASS before 12 weeks, reporting not to have achieved PASS at 26 weeks and then having achieved PASS again at the 52-week follow-up), only time to the first PASS achieved is used in the analysis. To explore the association between exercise compliance and FHSQ pain-score we will use Pearson's correlation coefficient and we will use an unpaired t-test to explore between-group differences in exercise compliance between the PAX and PAXI groups.

Cost-effectiveness analysis

The reporting of the economic evaluation will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist for a more transparent and complete reporting of methods and findings.(22) For each intervention, mean values (and standard errors of the mean) will be reported for the main categories of estimated costs and QALYs, as well as mean differences

between the comparator groups. Probabilistic sensitivity analyses will be used to estimate the decision uncertainty and calculate incremental cost-effectiveness ratios.

Exclusion cohort

Potential participants who are excluded during the physical examination and eligible participants who decide to withdraw before randomisation will be asked to be part of a concurrent observational cohort. These participants receive the same questionnaires as the participants of The FIX-Heel Trial with the addition of a questionnaire about care-seeking behaviour and treatments received during the time between the last follow-up and the current. We will use the same follow-up times (4, 12, 26 and 52 weeks) as in The FIX-Heel Trial, however, all follow-ups will be conducted through e-mail. We will report the outcome data of the follow-ups descriptively with means and standard deviations for continuous outcomes and frequencies for categorical outcomes.

6.3: Harms

Participants will be asked to report any adverse events to the physiotherapists immediately after they occur by either telephone, SMS or e-mail. Expected adverse events due to the injection are plantar fascia rupture, signs of infection (e.g. fever and local swelling and redness), and local pain in the area of injection lasting more than 48 hours after injection. Adverse events after the palpation-guided injection are rare and two trials that used ultrasound-guided injections reported no adverse events occurred.(4,23,24) No stopping rules are planned. Expected adverse events due to the exercise are injuries to the musculoskeletal system such as muscle tears, muscle strains, a sprained joint, injury from falling or exacerbation of symptoms related to PF, delayed onset muscle soreness equal to or greater than 20 mm on a 0 to 100 mm VAS that lasts for more than 48 hours after performing the exercises or exacerbation of PF.

Adverse events will be graded 1 to 5 according to the Common Terminology Criteria for Adverse Events v4.03.(25) A medical doctor specialised in either rheumatology or general medicine will assess and grade the adverse event and ultimately have the decision whether the participant should be withdrawn from the trial due to the adverse event. If the adverse event is a grade 1 (mild), the participant may be allowed to skip one or two training sessions without any assessment. If the adverse event recurs after having skipped the exercise, the participant will have to be assessed by the medical doctor before participation in the trial is continued. If a participant experiences an

adverse event and requests withdrawal from the study, data until the last exercise activity before the adverse event occurred will be included in the analyses. The physiotherapists will report any incidents to the sponsor as quickly as possible and no later than 15 days after the participant reported the event. Sponsor will report any severe adverse events (grade 3-5) to the Ethics Committee of North Denmark Region no later than seven days after being informed. All adverse events will be reported in the future reporting of the trial. Any participants who suffer harm from trial participation will receive compensation by The Patient Compensation Association.

Section 7: Acknowledgements

We would like to thank Peter Enemark Lund, statistician at Unit of Epidemiology and Biostatistics at Aalborg University Hospital, and Alina Zalounina Falborg, biostatistician at Center for General Practice at Aalborg University, for their assistance and guidance in the development of the Statistical Analysis Plan.

Section 8: References

1. Bandholm T, Christensen R, Thorborg K, Treweek S, Henriksen M. Preparing for what the reporting checklists will not tell you: the PREPARE Trial guide for planning clinical research to avoid research waste. Br J Sports Med. 2017 Sep 7;bjsports-2017-097527.
2. Landorf KB, Radford JA. Minimal important difference: Values for the Foot Health Status Questionnaire, Foot Function Index and Visual Analogue Scale. Foot. 2008 Mar;18(1):15–9.
3. Landorf KB, Radford JA, Hudson S. Minimal Important Difference (MID) of two commonly used outcome measures for foot problems. J Foot Ankle Res. 2010 May 14;3:7.
4. McMillan AM, Landorf KB, Gilheany MF, Bird AR, Morrow AD, Menz HB. Ultrasound guided corticosteroid injection for plantar fasciitis: randomised controlled trial. BMJ. 2012;344(21):e3260.
5. Georgiou M, Ponte C. Introducing media, technology and the migrant family: Media uses, appropriations and articulations in a culturally diverse Europe. Vol. 94, Observatorio. Oxford University Press; 2013. p. 1–11.
6. Landorf KB, Keenan A-M, Herbert RD. Effectiveness of Foot Orthoses to Treat Plantar Fasciitis. Arch Intern Med. 2006 Jun 26;166(12):1305.
7. Radford JA, Landorf KB, Buchbinder R, Cook C. Effectiveness of low-Dye taping for the short-term treatment of plantar heel pain: a randomised trial. BMC Musculoskelet Disord. 2006 Aug 9;7:64.
8. Riel H, Vicenzino B, Jensen MB, Olesen JL, Holden S, Rathleff MS. The effect of isometric exercise on pain in individuals with plantar fasciopathy: A randomized crossover trial. Scand J Med Sci Sport. 2018 Sep 11;28(12):2643–50.
9. Riel H, Jensen MB, Olesen JL, Vicenzino B, Rathleff MS. Self-dosed and pre-determined progressive heavy-slow resistance training have similar effects in people with plantar fasciopathy: a randomised trial. J Physiother. 2019 Jun 13;65(3):144–51.
10. Bennett PJ, Patterson C, Wearing S, Baglioni T. Development and validation of a questionnaire designed to measure foot-health status. J Am Podiatr Med Assoc. 1998 Sep 1;88(9):419–28.
11. Riskowski JL, Hagedorn TJ, Hannan MT, 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 Questionnair. Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 1(SUPPL. 11):S229-39.
12. Riel H, Jensen MB, Olesen JL, Rathleff MS. Translation and cultural adaptation of a Danish version of the Foot Health Status Questionnaire for individuals with plantar heel pain. Foot. 2019 Mar 4;38:61–4.
13. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multina. Arthritis Care Res (Hoboken). 2012 Nov;64(11):1699–707.
14. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis. 2005 Jan;64(1):34–7.
15. Myles PS, Myles DB, Galagher W, Boyd D, Chew C, MacDonald N, et al. Measuring acute postoperative pain using the visual analog scale: The minimal clinically important difference and patient acceptable symptom state. Br J Anaesth. 2017 Mar;118(3):424–9.
16. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. Eur J Pain.

2007 Feb 1;11(2):153–63.
17. Rasmussen MU, Rydahl-Hansen S, Amris K, Samsøe BD, Mortensen EL, Mortensen EL. The adaptation of a Danish version of the Pain Self-Efficacy Questionnaire: reliability and construct validity in a population of patients with fibromyalgia in Denmark. Scand J Caring Sci. 2016 Mar;30(1):202–10.
18. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sport Med. 2017 Sep 16;47(9):1821–45.
19. Crouter SE, Churilla JR, Bassett DR. Estimating energy expenditure using accelerometers. Eur J Appl Physiol. 2006 Dec 21;98(6):601–12.
20. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). BMJ. 1998 Dec 5;317(7172):1572.
21. Bland JM, Altman DG. The logrank test. BMJ. 2004 May 1;328(7447):1073.
22. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013 Mar 25;346:f1049.
23. David JA, Sankarapandian V, Christopher PR, Chatterjee A, Macaden AS. Injected corticosteroids for treating plantar heel pain in adults. Cochrane database Syst Rev. 2017 Jun 11;6(6):CD009348.
24. Ball EMA, McKeeman HMA, Patterson C, Burns J, Yau WH, Moore OA, et al. Steroid injection for inferior heel pain: a randomised controlled trial. Ann Rheum Dis. 2013 Jun;72(6):996–1002.
25. Common Terminology Criteria for Adverse Events (v4.03). U.S.Department of Health and Human Services; 2010.