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Foot orthoses versus hip exercises and the effect of greater foot mobility in the management of patellofemoral pain

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Abstract

The patellofemoral joint comprises of an articulation of the patella with the trochlear groove of the femur. The patella is tethered distally via the patella tendon, proximally via the quadriceps tendon and multiple local structures such as medial and lateral patellofemoral ligaments retinaculum. When the knee flexes and extends, the patella engages and translates through the groove, often under high stress, during complex multidirectional motion. Patellofemoral pain (PFP) is a prevalent and recalcitrant knee pain condition that can have a significant impact upon a person's quality of life. Patellofemoral pain is defined as anterior, retro and/or periarticular pain around the patellofemoral joint that is typically aggravated by weight bearing activities with a flexed knee. Patellofemoral pain is considered to be a multifactorial condition with various biomechanical, neurological and/or psychological contributors proposed in its aetiology. Due to its multifactorial nature, PFP can be an enigmatic condition for clinicians to treat. Various approaches targeting structures and areas local, distal and proximal to the patellofemoral joint have been proposed. As such, clinicians can become confused about what interventions are most effective for particular patient. Two evidence-based recommended treatment approaches for PFP are foot orthoses and hip exercises. Foot orthoses and hip exercises have been investigated in clinical trials with each treatment having a proposed biomechanical mechanism of effect at the patellofemoral joint. However, these two treatments have not been compared head to head, to determine if either treatment is superior. Whilst the treatments have been shown to be effective, they are not a one-size-fits-all approach with results from clinical trials suggesting the presence of subgroups that reported a more favourable outcome to a particular treatment. Clinical guidelines recommend using evidence-based treatments that are tailored to the individual patient, however there is a dearth of guidance on how to tailor the treatments. Furthermore, there is a paucity of evidence on how to identify the unique subgroups that might benefit most from a specific treatment. There was a need for further research to (i) determine if and what patient characteristics identify those with PFP who would benefit most from a specific treatment, and (ii) compare the clinical superiority of foot orthoses versus hip exercises.

The chapters within this thesis explore the evidence and describe the design, implementation and results of a randomized clinical trial. Study one was a systematic review of the literature. Preliminary evidence suggested greater midfoot width mobility (at least 11mm change in the width of the midfoot moving from non-weight bearing to weight bearing) was associated with greater global improvements with foot orthoses treatment. Crucially, the evidence was limited by studies lacking a comparator treatment and over-fitting of variables for the statistical models. Review indicated that further research was needed to explore the potential treatment effect modification midfoot width mobility may have with regards to foot orthoses.

Based on this preliminary evidence, study two was the design of a two-arm parallel; superiority randomised clinical trial in Australia and Denmark to address two aims. The aims were to test (i) the potential treatment effect modification of greater midfoot width mobility for foot orthoses treatment over hip exercises, and (ii) the clinical superiority of foot orthoses versus hip exercise treatments for managing PFP. The trial required the recruitment of 220 participants (18-40years) who reported an insidious onset of knee pain (≥6 weeks duration); that was aggravated by activities (e.g. stairs, squatting, running), and at least three out of ten pain on the numerical rating scale (ten being worst imaginable pain). Participants were stratified by their midfoot width mobility (*high* ≥11mm change in midfoot width) and site, and then randomised to foot orthoses or hip exercises. The primary outcome was a patient-perceived global rating of improvement at 12 weeks.

Study three was the implementation of the randomised clinical trial. Of the 218 participants recruited and enrolled from June 2014 to April 2017, 192 completed follow up at 12 weeks. We found no difference in success rates between foot orthoses versus hip exercises in those with *high* midfoot width mobility (6/21 v 9/20; 29% v 45% respectively) or *low* midfoot width mobility (42/79 v 37/72; 53% v 51%). There was no association between midfoot width mobility and treatment outcome (Interaction effect P=0.19). This study found no difference in success rate between foot orthoses versus hip exercises

(48/100 v 46/92; 48% v 50% respectively). The discovery that those with patellofemoral pain and greater foot mobility did not have superior benefits using foot orthoses, compared to hip exercises contradict common clinical assumptions. We found that foot orthoses and hip exercises offer similar global outcomes in the management of patellofemoral pain. These results suggest that clinicians should not use midfoot width mobility to decide which patients would benefit from foot orthoses, versus hip exercises. Given both foot orthoses and hip exercises offer similar global benefits, clinicians and patients can consider either in managing patellofemoral pain.

Study four highlights a clinical case of a person with PFP. The person met the exclusion criteria for the trial as she had done briefly hip exercises as part of a fitness program in the last 12months. The case provides a clinical exemplar of the evidence, and reasoning, in the management of someone with PFP which may be clinically useful for similar case presentations. The case demonstrates the research in action and explores one avenue of tailoring treatment to the individual. Whilst the limitations of a case study are acknowledged, it offers hypotheses about relationships between physical, psychological, social and behavioural variables which remain to be investigated for PFP. Overall, the research in this thesis, and published studies, adds to the evolution of knowledge and clinical management of PFP. A potent outcome from this study showed both foot orthoses and hip exercises offer comparable benefits and needn’t select patient characteristics for one or the other on current evidence. This research opens path for foundations on future research on the beneficial effects of combining foot orthoses and hip exercises, cost-benefit analysis of interventions for PFP, and consideration for a stepped-approach to the management of PFP that includes an educational and activity modification aspect.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, financial support and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my higher degree by research candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications included in this thesis

Matthews, M., Rathleff, M. S., Claus, A., McPoil, T., Nee, R., Crossley, K., & Vicenzino, B. (2017). Can we predict the outcome for people with patellofemoral pain? A systematic review on prognostic factors and treatment effect modifiers. *Br J Sports Med*, *51*(23), 1650-1660.

Matthews, M., Rathleff, M.S., Claus, A., McPoil, T., Nee, R., Crossley, K., Kasza, J., Paul, S., Mellor, R. and Vicenzino, B. (2017). The Foot Orthoses versus Hip eXercises (FOHX) trial for patellofemoral pain: a protocol for a randomized clinical trial to determine if foot mobility is associated with better outcomes from foot orthoses. *Journal of foot and ankle research*, *10*(1), 5.

Matthews, M., Vicenzino, B., Rivett, D. (2019) Targeting treatment distally at the foot for bilateral persistent patellofemoral pain in a 23-year-old: a new answer to an old problem. *Clinical Reasoning in Musculoskeletal Practice 2ed.* Chapter 10, 164-178 Elsevier Health Sciences.

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Larsen P, Nielsen HB, Lund C, Sørensen DS, Larsen BT, Matthews M, Vicenzino B, Elsoe R. (2016). A novel tool for measuring ankle dorsiflexion: a study of its reliability in patients following ankle fractures. Foot and Ankle Surgery. Dec 1;22(4):274-7

Maclachlan LR, Collins NJ, Matthews ML, Hodges PW, Vicenzino B. (2017) The psychological features of patellofemoral pain: a systematic review. *British Journal of Sports Medicine* 1;51(9):732-42.

Riel, H., Matthews, M., Vicenzino, B., Bandholm, T., Thorborg, K. and Rathleff, M.S., (2018). Feedback Leads to Better Exercise Quality in Adolescents with Patellofemoral Pain. *Medicine and science in sports and exercise*, *50*(1), pp.28-35

Rathleff, M.S., Rathleff, C.R., Stephenson, A., Mellor, R., Matthews, M., Crossley, K. and Vicenzino, B., (2017). Adults with patellofemoral pain do not exhibit manifestations of peripheral and central sensitization when compared to healthy pain-free age and sex matched controls–An assessor blinded cross-sectional study. *PloS one*, *12*(12), p.e0188930.

Matthews, M., Rathleff, M.S., Vicenzino, B. and Boudreau, S.A., 2018. Capturing patient-reported area of knee pain: a concurrent validity study using digital technology in patients with patellofemoral pain. *PeerJ*, *6*, p.e4406.

Maclachlan, L.R., Matthews, M., Hodges, P.W., Collins, N.J. and Vicenzino, B., (2018). The psychological features of patellofemoral pain: a cross-sectional study. *Scandinavian Journal of Pain*, *18*(2), pp.261-271.

Boudreau, S.A., Royo, A.C., Matthews, M., Graven-Nielsen, T., Kamavuako, E.N., Slabaugh, G., Thorborg, K., Vicenzino, B. and Rathleff, M.S., (2018). Distinct patterns of variation in the distribution of knee pain. *Scientific reports*, *8*(1), p.16522.

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Dr Michelle Smith sat as an independent committee member for the confirmation, mid-candidature and thesis review milestones of this PhD. Her review and guidance helped shape the final content of this thesis.

Statement of parts of the thesis submitted to qualify for the award of another degree

No works submitted towards another degree have been included in this thesis.

Research Involving Human or Animal Subjects

Ethical approval was granted by the University of Queensland Medical Research Ethics Committee (2013000981). Ethical approval in Denmark was granted by the local ethics committee in the North Denmark Region (N-20140022).

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"Medicine is a science of uncertainty and an art of probability" - Sir William Osler*

(*I often wonder if life, is much the same; *a balance of science and art;* of varying amounts depending on the context)

"A PhD is like the Tour de France bike race. It is a revered event. At the start, there are easier moments, which are bit of a mad chaotic sprint for the enthused (in-experienced) ones, whilst the seasoned pros settle in. There is a team ethos to support a leading rider, to help out over the rough and daunting sections. There are some individual races against the clock. Each day everyone is trying to make the (time) cut for the next day of racing. Then you hit the mountains, the 'Hors Cat' which sorts out the contenders and the 'also-rans'. Eventually you end up grinding away at your own pace, chewing on the handle bars, trying not to let anyone down, doing your best. It is an emotional experience; a roller coaster. Take the chance to look up; you'll see hundreds of supporters all cheering you on, willing you to make the next pedal turn, push a little harder, to keep going. If you're patient and persevere, you'll be greeted at the finish line by an overly enthusiastic crowd. With time, you'll have the fondest of memories of the journey you took, and a new perspective of the road you still ride."
M.L.G Matthews October 2013 – email conversation

I blame the curse of curiosity for this prolonged endeavour. Undertaking the research and the frivolous adventures has been some experience. Undertaking this entire project has been an exercise of sustained persistence and perseverance. A casual reader may not fully comprehend the complexities involved, and endured, to have reached this point. For those of you who have played the larger role in this process, this exploration and evolution of knowledge, this path along the road of life, you know who you all are, without your guidance, encouragement and support, for all that you offered, gave or imparted, big or small, I will forever be truly indebted to you.

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Fizzing - Like a cold stone and wood pacific ale, *gin'n'tonic, pint of plain,* or whiskey, ginger and lime on a warm summers evening.

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Keywords

Clinical, treatment effect modification, patellofemoral, pain, prediction, midfoot width mobility, foot orthoses, hip exercises, management, randomised clinical trial

Australian and New Zealand Standard Research Classifications (ANZSRC)

Provide data that links your thesis to the disciplines and discipline clusters in the Federal Government's Excellence in Research for Australia (ERA) initiative.

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ANZSRC code: 110317, Physiotherapy (100%)

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FoR code: 1103, Clinical sciences (100%)

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List of Figures & Tables

List of Abbreviations used in the thesis

ACTRN …… Australian New Zealand Clinical Trial Registry
BMI ……... Body mass index
CINAHL …… Cumulative index to nursing and allied health literature
CONSORT .. Consolidated standards of reporting trials
DiffMFW ..… Difference in midfoot width
EAI …… Epidemiological appraisal instrument
EQ-5D ..…... Euroquol - 5 dimensions
FPI-6 …… Foot posture index
FOHX ……... Foot orthoses versus hip exercises
GROC …….. Global rating of change
HADS ……... Hospital anxiety and depression scale
IR …….. Internal rotation
KOOS …….. Knee injury and osteoarthritis outcomes score
KOOS-PF … Knee injury and osteoarthritis outcome score - patellofemoral
LAD .....…… Lunge ankle device
LR ……..….. Likelihood ratios
MFW ……... Midfoot width
MVIC ……... Maximal voluntary isometric contraction
NRS ……. Numerical rating scale
N ……...…… Newtons
NWB …….. Non-weight bearing
OR ..…….. Odds ratio
PASS ……... Patient acceptable symptom state
PCS ……... Pain catastrophising scale
PFP …….. Patellofemoral pain
PSFS ……... Patient specific functional scale
QUADCPR .. Checklist for prescriptive, derivation-based clinical prediction rules
PRISMA …... Preferred reporting items for systematic reviews and meta-analyses
PPT …….. Pressure pain threshold
PTA-d ……... Patellar tilt angle difference

RM …… Repetition maximum

RR …… Risk ratio

SD …… Standard deviation

SANE ……. Single assessment numeric evaluation

SIRPH …….. Sports Injury Rehabilitation and Prevention for Health

SPIRIT ……. Standard Protocol Items: Recommendations for Interventional Trials

TDT …….. Treatment direction test

TIDieR ……. Template for intervention description and replication checklist

TRIPOD ….. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis

TSK …….. Tampa scale for kinesiophobia

VAS …….. Visual analogue scale

VM …… Vastus Medialis Obliquus

WB …… Weight bearing

Chapter 1. Introduction

The knee is the largest, and one of the most complex joints in the human body. The knee must withstand high multidirectional forces all the while performing complex tasks to move the lower limb, transmit forces, absorb shock and maintain an upright body position during physical activity. The knee is the most commonly injured joint with an estimated 2.5 million sports-related injuries presenting to emergency departments in the United States annually [1]. Adolescent athletes (15-24 years) had the highest injury rate (3.43 per 1,000), with most injuries occurring during sports and recreational activities (49.3%) [1]. The knee has a complex interplay between the tibiofemoral joint and patellofemoral joint that allow for flexion, extension and rotation motions of the lower limb whilst generating and transmitting large forces [2]. The patellofemoral joint plays a vital role in allowing large forces to transmit across the anterior aspect of the knee, through a large range of motion. It does this via complex and dynamic interplay between articulation of the patella bone within the trochlear groove of the femur, ligamentous attachments and muscular tissues [3]. Due to the high multidirectional forces exerted across the knee, and the complex interplay of biomechanical and psychosocial factors, insidious conditions such patellofemoral pain (PFP) are prevalent [4].

Patellofemoral pain is a common musculoskeletal condition of the knee that presents to health practitioners [5, 6]. Studies on adolescents and young active adults have investigated the incidence of PFP [7-10]. In a prospective study of 145 adolescent female basketball players, 14 (11%) players developed PFP during the season [7]. In a 2 year prospective study of 282 students aged 17-21years (mean age 18.6) enrolled in physical education classes, 24 (9%) were diagnosed with PFP. [9] In military cohorts of new infantry recruits undertaking basic training, incidence has been reported to range from 3 to 32% [8, 10-12]. Current evidence indicates that the incidence of PFP in young active adults are around 10-15%, while in military population, the rates are more varied (range 3-32%).

Evidence is indicating PFP is not self-limiting for a substantial proportion of people with PFP [13, 14]. A recent prognostic study reported 40% of 310 PFP participants involved in treatment trials reported an unfavourable recovery at 12 months follow-up [15]. Factors such as duration of symptoms greater than 2 months, higher age [16] and greater pain severity at baseline have been associated with a poor outcome. Moreover, PFP has been suggested as a precursor in the cascade of degenerative changes in the patellofemoral joint . In summary, for a substantial proportion of those with prolonged PFP symptoms, the prognosis is poor with possible degenerative longer-term consequences.

Chapter 2. Background

This chapter covers the broad aspects of patellofemoral pain aetiology and the local, proximal and distant contributing factors. It highlights broad considerations towards the management of patellofemoral pain and a appreciation of the biopsychosocial aspects of patellofemoral pain.

Patellofemoral pain is described as a pain originating in the anterior, retro or peri-patellar region of the knee. [17] It is theorised to be an overuse tissue-stress injury around the patellofemoral joint related to local, proximal and/or distal factors [5, 18, 19]. Diagnosis of PFP is based on around the clinical presentation, and the exclusion of other structural pathologies that may manifest similar anterior knee pain symptoms. [20, 21] Characteristic symptoms of PFP arise from activities that load the patellofemoral joint in the flexed knee position, such as running, squatting, climbing or descending stairs or sitting for a prolonged period of time. [22]

Recent studies have investigated the quality of life impact of PFP. Adolescents with PFP reported lower quality of life scores and higher pain catastrophizing scores compared to pain free controls and that their symptoms had a significant impact on their quality of life (P<0.0001) [23, 24] Fear-avoidance beliefs about physical activity were identified as a strong predictor of function and pain outcome in those with PFP. [25] This growing

body of evidence from studies of adolescent participants has identified the profound detrimental impact of PFP on psychological and physical wellbeing. There is a need for more research in adolescent and adult populations to determine i) the impact of PFP on the quality of life, ii) longitudinal follow-up and iii) intervention studies to minimise the persistence of symptoms and optimise the person's quality of life.

2.1 Aetiology of Patellofemoral Pain

The aetiology of PFP, its causes and contributing factors are an area of ongoing research [26]. There are conceptual theories that PFP symptoms are a result of elevated stresses on the patellofemoral joint and surrounding tissues [26, 27]. One theory is that PFP results from mal-tracking of the patella; that is, the patella laterally deviates in the trochlea groove of the femur, resulting in elevated contact pressure between the lateral facet of the patella and the lateral femoral condyle elevating patellofemoral joint stress [28]. Theories have been proposed that patella mal-tracking may adversely stress the lateral patellofemoral structures, contributing to processes such as ischemia, inflammation of the synovial lining, stress patella retinaculum and fat pad tissues, overload of the sub-chondral bone and increase osseous metabolic activity [29-31]. Studies have reported a decrease in patellofemoral joint contact area and subsequent increased lateral patellofemoral joint stress during fast walking [32] and squatting activities [33] in individuals with PFP when compared to pain-free controls. However, these are studies on small samples with methodological limitations such as the unknown limits in accuracy of surface tracking measures to infer dynamic changes in relative position of the patella and femoral condyles. Whilst evidence has suggested an association between elevated patellofemoral joint stress and incidence of PFP, it is also possible that people with PFP may modify their movement strategies to normalise the magnitude of force at the patellofemoral joint [32]. Additionally, cross-sectional studies are unable to draw conclusions on the causality of elevated patellofemoral joint stresses and PFP. It is hoped that methodological limitations for calculations of joint contact pressures can be overcome in the future, and the relationship of this variable to patient

symptoms and disability better understood. It would be ideal if prospective studies could investigate longitudinal changes in motion of the patella and patellofemoral joint stresses in the development of PFP, to infer directions of causality between changes in mechanics and symptoms.

Extensive research has focused into biomechanical and physiological aetiology of PFP. In particular, abnormalities of the retro-patellar structures and overload of subchondral structures may play a role in the pathogenesis of PFP [2]. These structural abnormalities are proposed to be a precursor to the cascade of developing patellofemoral joint osteoarthritis [34]. As such, research has investigated patellofemoral cartilage composition and surrounding structures to gain a better understanding in the pathogenesis of PFP. Despite the recent advancement of high-resolution magnetic resonance imaging, structural abnormalities of the patellofemoral joint and diminished patellofemoral cartilage composition are not associated with PFP [35, 36]. Thus, research and clinicians alike are warranted in considering other possible causes for pain and disability, aside from just tissue injury models.

Pain is the predominate symptom reported by those with PFP. The processing of information to create the perception of pain results from interplay of factors ranging from peripheral tissue pathology to the mind and immune system. Biological, psychological and social contextual factors can each profoundly modulate symptoms and motivate behaviour [37]. Some factors are modifiable, such as tissue robustness, beliefs and behaviours. Others are non-modifiable with health interventions, such as genetics, age, socioeconomic [38]. The neurophysiological processing of information to create pain perception has been described as a neuromatrix, that encompasses the peripheral nociceptive input that informs about location of physical or chemical danger to the tissues. Thoughts and feelings based on past experiences and current interpretation of the environment modulate pain [39]. An example of the plasticity between stimulus and perception is that people with PFP demonstrate lower mechanical pressure pain thresholds than those without PFP [40]. A decrease in mechanical threshold for pain perception has been associated with a poor outcome. [41-43] A recent review

reported linear correlations with pain and physical function with mental health and cognitive factors such as anxiety and depression, pain catastrophizing and fear-avoidance beliefs. [44] Thus, although the behaviour of patient's pain may appear to follow the magnitude of mechanical load at the knee, the complexity of interacting factors at the nervous system, with ascending and descending modulation must be acknowledged. Onset or persistence of PFP can be modulated by neurophysiological, psychological and social factors. This project focusses on specific, modifiable biological interventions, but if an effect is observed with these, it should still be considered that the mechanism(s) for any individual participant might have involved a wide range biological, psychological and social factors in combination.

A recent concept of neurotags suggests the brain is an complex array and interaction of neural representations whose output act on particular systems, such as motor system to create movement or consciousness to create a pain output [45]. This highly complex matrix of factors is suggested to subserve a regulatory i.e. control and protection purpose for the body on both a physiological and perceptual level [45]. It is plausible clinical interventions for PFP may address this complex neuromatrix indirectly through altering physiological processes, with neuro-motor techniques and appropriate activity management, and perceptual through patient education and behaviours. In summary whilst extensive research has gone into investigating anthropometric, anatomic and neuromuscular factors in PFP, any improvement in pain symptoms to clinical interventions with a biomechanical and pathoanatomical approach may only be one component of the recovery process. [39, 45-48]

2.2 Local factors for Patellofemoral Pain aetiology

A variety of anthropometric measurements locally at the knee have been investigated in relation to mal-tracking of the patella in people with PFP. The Q-angle is the angle formed at the knee by a line connecting three points on the lower limb; the anterior superior iliac spine at the pelvis, the patella, and the tibial tubercle. It has been reported that more patients with PFP had a Q-

angle > 20° (73%) in static stance compared to control participants (46%) [49]. Other radiographical studies have reported a shallow trochlear groove (sulcus angle) as a predictor of patellar displacement at 0-9 degrees of knee flexion [50], with greater lateral patella displacement and patella tilt being demonstrated in those with PFP when compared to a control group [51]. However, two radiographic studies of sulcus angle and patella tilt failed to identify any difference in these parameters between people with PFP and pain free control groups [52, 53]. A point worth consideration is that the multi-planar motion of patella during physical activity may not be well represented by any morphological measure in a single plane. The role of these morphological measures in contributing to PFP remains unclear.

A potential cause of patellofemoral mal-tracking is deficits of neuromuscular functioning of the quadriceps muscles [54, 55]. Deficits in neuromuscular control may alter coordination of the medial and lateral quadricep muscles that insert on the patella, exposing the patellofemoral joint to elevated stresses. Deficits reported include delays in onset timing of vastus medialis obliquus (VMO), delayed co-ordination of VMO relative to vastus lateralis and an overall reduced strength of the quadriceps muscle group [55, 56]. Delays in the timing of muscle activation onset of VMO relative to vastus lateralis has been reported as a risk factor in development of PFP [11]. Additionally results suggest that timing of VMO onset of activation is delayed in participants with PFP, compared to control participants [57, 58]. However there is conflicting evidence from one prospective study, which reported that a delay in onset timing of VMO, relative to vastus lateralis, was not a significant risk factor for development of PFP [9]. Contrasting results from prospective studies could be due to the differences in study cohorts, with military personnel undergoing greater rigorous physical activity [11] than student cohorts [9]. In conclusion, while deficits have been identified in neuromuscular function of VMO, results from cross-sectional study design are unable to determine whether these deficits are causative factors for PFP, or an effect of PFP symptoms. The role of VMO timing in PFP symptoms should be investigated with prospective studies of adult cohorts that are representative of the wider population.

Patellofemoral pain has historically been viewed as a local problem at the knee, however research and clinical trials focused on PFP have investigated regions outside of the knee. The lower limb comprises of multiple multi-axial joints to form an interdependent kinetic chain. Studies have recently shifted focus to investigate and report on a myriad of proximal and distal factors to the knee to propose hypotheses that may influence PFP and identify potential predictors of onset and resolution of symptoms.

2.3 Proximal factors for Patellofemoral Pain aetiology

A pathomechanical model has been suggested of a proximal influence on patellofemoral joint stress. The model proposes that aberrant deviation of the femur into hip adduction and internal rotation during weight bearing activity would medially deviate the femur under the patella, resulting in patella mal-tracking and place excessive stress on the patellofemoral joint [28, 59, 60]. A prospective study of 400 female runners reported that those who developed PFP (*n*=15) exhibited greater hip adduction during running [61]. In a cross-sectional study of 32 female runners (16 with PFP, 16 healthy controls), it was reported those with PFP had greater peak hip adduction, hip internal rotation and shank internal rotation than healthy controls [62]. Aberrant hip adduction and internal rotation during weight bearing tasks has also been associated with strength deficits of the gluteal muscles, particularly the hip abductors and external rotators [61, 63, 64]. When compared to pain-free controls, those with PFP exhibit 15-20% less isometric strength for hip abduction and external rotation (expressed as percentage of body weight) [65]. Conflicting this hypothesis, a prospective military cohort of 1597 new recruits found increased hip external rotation strength as a risk factor in those that develop PFP [63]. So too, a prospective trial reported no differences in isometric strength of any hip muscle groups (flexors, extensors, abductors, adductors, external and internal rotators) between the runners who did or did not develop PFP [66]. A case-control study reported no differences in the isometric muscle strength of the hip abductors or external rotators in those with PFP compared to gender matched controls [67]. In a kinematic analysis, females with PFP exhibited similar hip and knee kinematics during a step-down task to matched pain free control participants, despite the fact that participants with PFP had a

significant hip muscle weakness [68]. The pathomechanical model suggests a biomechanical relationship between neuromuscular systems and hip kinematics, however there is conflicting evidence. The variation in results for gluteal muscle function and kinematics in people with PFP could be due to the specific cohort variables or methodological differences in challenging the neuromuscular system. These conflicting results could suggest that people with PFP recruit compensatory strategies during activity to normalise the load on the patellofemoral joint.

Research has investigated the effect of loading and the neuromuscular system in those with PFP. In a cross-sectional study, subjects with PFP have demonstrated a deficiency in neuromuscular control with delay in activation of both anterior and posterior fibres of gluteus medius, when compared to asymptomatic controls [69, 70]. Delayed activation in gluteus medius could impair control of the hip position in weight bearing, and contribute to hip adduction and internal rotation, predisposing individuals to patellofemoral joint stress and subsequent development of PFP. In a military cohort, increased hip internal rotation during a drop jump landing task was identified as a risk factor for the development of PFP [63]. The drop jump landing task required participants to drop down from a box set at 50% of their body height, land on a force platform and jump vertically for maximum height [63], challenging the neuromuscular system much more than a step-down task [68]. In a study of running and PFP, the PFP group exhibiting decreased hip abduction and external rotation strength ($P<0.0125$) but no changes to hip internal rotation or adduction kinematics ($p>0.05$)[71] relative to pain free control participants. In another running kinematic study, the PFP cohort demonstrated three distinct kinematic strategies, and all three of the strategies demonstrated less overall motion compared to healthy controls [72]. Whilst both studies were designed to push participants to the point of exhaustion, PFP cohorts in both studies experienced pain during testing. Therefore, it cannot be determined whether pain and/or exhaustion induced the group differences that were observed. These findings from more demanding activities suggest that people with PFP could have insufficient neuromuscular capacity to tolerate the loading demands upon the lower limb during a pre-selected physical activity.

Prospective and cross-sectional studies are required that look at the activation timing of the gluteal muscles and the effects of loading on a spectrum of PFP and pain-free populations to test these hypotheses. Additionally, interventional studies need to examine whether neuromuscular training of the hip muscles, such as strength, movement retaining and endurance capacity, can have an effect on PFP symptoms.

2.4 Hypothesised Distal factors for Patellofemoral Pain aetiology

A distal model to bottom-to-top lower limb biomechanics has proposed that excessive foot pronation or prolonged phases of foot pronation during gait could indirectly increase patellofemoral joint stress [73]. This dynamic coupling model hypothesized that aberrant foot pronation induced greater tibial internal rotation during the mid-stance phase of gait, restricting tibiofemoral joint extension (normal gait mechanics would require the tibia to externally rotate as the tibiofemoral joint extends). Due to the foot being grounded, a proposed compensatory mechanism is for the femur to internally rotate on the tibia, to achieve full extension of the tibiofemoral joint. This compensatory mechanism results in lateral displacement of the patella relative to the femur, and is hypothesised to elevate stress at the patellofemoral joint [73].

Studies have investigated the distal pathomechanical model of excessive or prolonged foot pronation during gait proposed. [73] Various anthropometric measurements and scales have been developed to quantify the degree of foot pronation, or to define excessive motion in the foot. The navicular drop was described as a sagittal plane representation of foot pronation, calculating the change in the navicular tuberosity height off the ground, from a weight-bearing subtalar joint neutral position to a relaxed foot posture. Normative values for navicular drop have been reported as 10-15mm [74]. The foot posture index is a 6-item scale assessment tool that evaluates multiple segment and multiple plane static foot posture [75]. Another published measure of foot mobility at the midfoot calculated the difference in mediolateral midfoot width (midfoot defined as 50% of total foot length), between a non-weight bearing to weight

bearing posture (Figure 2.1) [76]. In a normative study of 345 participants (left and right feet of asymptomatic individuals), average midfoot width mobility was reported to be of 9.6 mm on the left and 9.3 mm on the right [76].

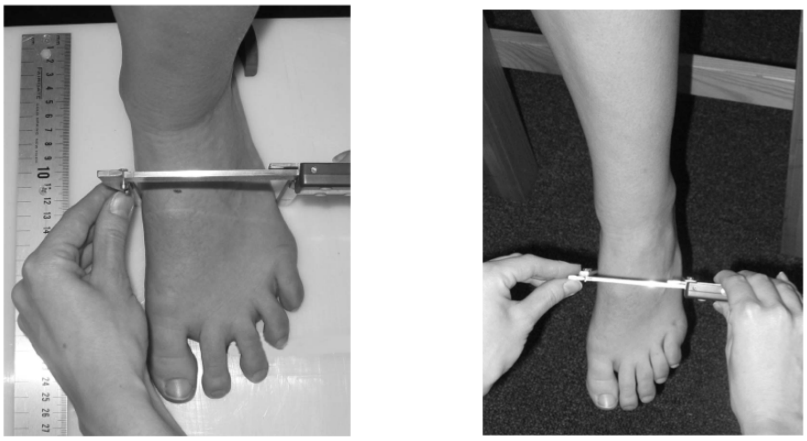

Figure 2.1. Measurement of midfoot width
in weight bearing (left image) and non-weight bearing (right image) (from McPoil et al. [76]).

One point of contention has been the use of static measurements and scales to represent motions of the foot that are implicated in PFP. A recent development of dynamic foot kinematics analysis has investigated rearfoot eversion with three-dimensional motion-analysis system, to quantify foot pronation (Figure 2.2) [77].

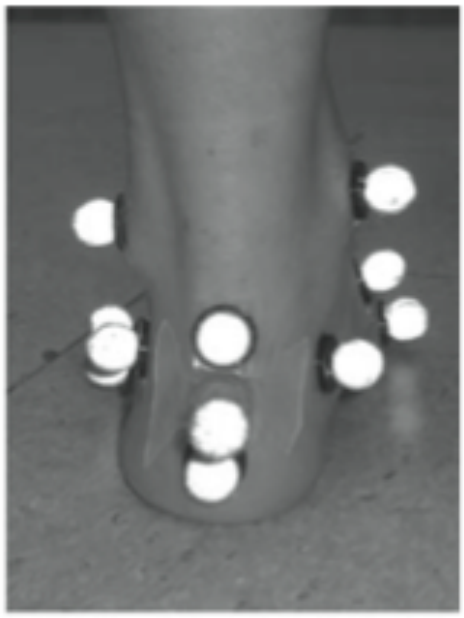

Figure 2.2. Reflective marker placement to measure dynamic rearfoot motion (from Barton et al. [77]).

Studies have reported excessive foot pronation, measured statically by the foot posture index [78] and greater peak rearfoot eversion within PFP cohorts [77] . In a prospective study of a military cohort, an increased navicular drop was reported as a risk factor for developing PFP [63]. Those who displayed a navicular drop of 10.67 mm or more (90^{th} percentile) were reported to be 3.4 times more likely to develop PFP than those who had a navicular drop measurement of 4 mm or less (10^{th} percentile) [63]. In a kinematic gait study, the PFP group demonstrated peak rearfoot eversion, relative to the tibia, to occur 7% later in stance compared to the control group indicating a prolonged foot pronation phase associated with PFP [79]. However prospective evidence from three studies has contradicted a model of excessive or prolonged pronation in stance phase. In a study of 400 female runners, there was no statistically significant difference in rearfoot eversion between those who developed PFP and those who didn't [61]. Likewise, in a study of military recruits who were initially pain free, those who developed PFP demonstrated significantly more laterally directed pressure distribution; with the authors suggesting this indicating a less pronated foot posture [80]. Lastly, in a study of novice runners, there was no association between an excessively pronated or supinated foot posture and the development of PFP [81]. Furthermore, cross-sectional studies have also reported no difference in peak rearfoot eversion between PFP and control groups during physical activities. [82-84]. Reports suggest that the PFP group may have a more rigid landing, thus higher impact forces, which could contribute more to PFP development than foot posture [81, 85]. A contributor to these conflicting results could be the methodological challenges of motion analysis. It is questionable if foot pressure distribution can accurately determine foot motion. Likewise, it is debateable whether reflective surface markers can truly represent motion of the underlying bones during motion analysis of foot and lower limb during gait. Overall, evidence is inconclusive about the relevance of a distal pathomechanical model causing PFP, with a need for prospective and cross-sectional studies using robust motion analysis on a wider population.

Most current evidence on aetiology has been drawn from retrospective studies with research paradigms isolated to a biomechanical and physiological focus. A key focus needs to be to determine where correlation and associations may actually represent causality. A strong focus needs to consider co-existence of multiple mechanisms around PFP. Current theories representing a strong biomechanical paradigm to PFP and do not consider the influence on central and peripheral pain processes. It is plausible altered pain processing mechanisms may have a stronger influence on the aetiology and persistence of PFP in some individuals than others with PFP. Overall there is a need for prospective designs that consider co-existence of multiple mechanisms behind PFP symptoms for higher levels of evidence and to support theorised aetiologies.

In summary, the local, proximal and distal theories to aetiology of PFP have supporting evidence from specific cohorts, demonstrating that PFP is indeed multifactorial. Contradictory results between studies highlight the heterogeneity of the aetiology of PFP and indicate the need further investigations on a for a variety of cohorts need to be undertaken before solid conclusions can be drawn. Notwithstanding these limitations, it is plausible that the aetiology of PFP arises from an individual-dependent combination of local, proximal and distal factors combined with extrinsic factors, such as loading forces from activity, may have an overloading influence on the patella kinematics and results in PFP symptoms. It is highly probable that a biomechanical approach to managing PFP will have vectors of effect on the nervous system functioning, whether sensory or motor and the central pain processing mechanisms. This area of research is outside the scope of this thesis, but also warrants consideration.

Chapter 3. Non-surgical management of patellofemoral pain

This chapter broadly explores the evidence behind the management of patellofemoral pain. In particular, it draws on considerations for tailoring treatment towards the individual and potential treatment effect modification.

The multifactorial nature of PFP and various identified associated local, proximal and distal factors involved is reflected in the broad options of management strategies proposed for PFP. Various options regarding conservative (non-surgical) and surgical methods have been proposed [86] [87]. Conservative interventions are regarded as the cornerstone of PFP management over surgical interventions in the management of PFP. Surgical intervention is rarely indicated for PFP and is reserved only when a clearly defined abnormality that the operation can specifically target is present (e.g., identifiable lesion or structural instability) [88, 89] Surgical options usually considered are patellar realignment, resurfacing, patellofemoral trochleoplasty and arthroplasty. [87] The benefits gained from surgery remain inconclusive though as most surgical studies have been single arm in design. One randomised controlled trial has compared arthroscopic surgery plus an 8-week exercise programme to an exercise program alone [90]. At nine month, 24 month and 5 year follow-up both intervention groups showed equally marked improvement across all outcome measures [90, 91] suggesting arthroscopy gave no added benefit to a home exercise program. These findings strengthen the evidence that conservative interventions as the forefront mainstay initial management of PFP.

3.1 Evidence for conservative interventions for patellofemoral pain

Research into managing patients with conservative interventions has been an evolution of knowledge with wide variability and controversial approaches. Intervention options have historically included wait-and-see, bracing, electrotherapy, manual therapy, foot orthoses, taping, open and/or closed chain exercises, strength training, flexibility training and acupuncture. This multitude of therapy options adds to heterogeneity of managing a multifactorial condition.

Current best practice guidelines for optimising management of PFP propose four key over-arching principles to ensure effective management of this multifactorial condition, including (1) individually tailored approach with treatment, (2) focusing on an immediate pain relief to gain patient trust, (3) a strong emphasis on active over passive interventions to empower the patient and (4) thorough patient education and relative activity modification. [86]

Randomised controlled trials investigating conservative interventions for PFP have reported heterogeneity in patient outcomes to specific interventions, from successful to worsening. [92-94] This spectrum of results is difficult to interpret in part due to the nature of PFP, the outcome measures used and the potential effect an intervention has to alter, or modify, the prognosis of the condition. Studies have looked to compare an intervention against a control group. Previous clinical trials have shown foot orthoses to be effective compared to a wait-and-see (9/19 versus 1/20; p = 0.008, relative risk reduction = 8.47%, numbers needed to treat = 2) or flat inserts (relative risk reduction 0.66, 99% confidence interval 0.05 to 1.17; NNT 4 (99% confidence interval 2 to 51). [92] In another trial comparing hip exercises to a usual-care approach, at 3 months the hip exercise group showed better outcomes than the usual care group with regard to pain at rest (adjusted difference −1.07, 95% confidence interval −1.92 to −0.22; effect size 0.47), pain on activity (−1.00, −1.91 to −0.08; 0.45), and function (4.92, 0.14 to 9.72; 0.34).[93] Whilst evidence indicates a difference in response rate, differences in outcome alone (i.e. successful to worsening) do not automatically suggest the direct effect of an intervention response and should be interpreted with a degree of caution.

Research has suggested the presence of more homogenous subgroups within the PFP population who have a favourable outcome to a specific intervention [77, 95]. Patient outcome could be optimised if clinicians could identify the homogeneous treatment and target the treatment to their presenting local, proximal and/or distal presenting characteristics. Whilst PFP is acknowledged as a local condition to the knee and patellofemoral joint, the knee is only part of an integral kinetic chain of the lower limb. During daily

activities, the lower limb is exposed regularly to cyclic load bearing tasks, such as walk, up very high load tasks, such as running, squatting with weights. The lower limb must have sufficient compliance and capacity to absorb these loads and optimally transfer the forces without overloading certain tissues. In those with PFP, evidence from clinical trials addressing these deficits (i.e. proximally at the hip with exercises, and distally with foot orthoses) is highlight the significant improvement in symptoms. While the mechanism of effect of these treatments remains inconclusive with different theories proposed [96], the ultimate mechanisms of effect may still be local at the patellofemoral joint. The importance of addressing proximal factors at the hip, and distal at the foot still remains pertinent.

One limitation of the guidelines is advice on how to individually tailor treatment to the patient. In summary, whilst these results from interventional studies highlight the benefits that prefabricated foot orthoses can have on reducing PFP, not all patients reported a successful outcome. Whilst exercise is now considered an efficacious approach for most with PFP [4], considerable debate continues on in regards to the type of specific exercises (i.e., strength, endurance, motor-patterning), target muscles, and duration of an ideal exercise program for patients with PFP.

3.2 Evidence for targeting interventions proximal to the knee

Studies have investigated interventions for hip muscle strength for treatment of PFP. Hip muscle weakness, particularly the hip abductors and external rotators, is a modifiable factor in those with PFP [26, 62, 97]. Clinical trials investigated the outcomes of hip strengthening treatment for PFP, with many participants showing improvement [98-101]. In one trial, a 4-week isolated open-chain hip strengthening protocol was compared to a 4-week quadriceps strengthening protocol, prior to weight-bearing exercises. Results indicated the initial hip strengthening protocol was more effective in reducing PFP symptoms than quadriceps strengthening [102]. Trials also investigated the comparison of a knee strength and stretching program versus a knee strength and stretching program, supplemented with hip strengthening exercises [101, 103]. The hip exercises targeted the hip abductor, external rotator and

extensor muscle groups. Results reported improved single leg hop, stair tasks and reduced pain in the supplemented programme compared to the program for knee strength / flexibility [101, 103]. Additional clinical trials have targeted hip abductor and external rotator muscle groups in those with PFP, reporting significantly reduced pain, increasing hip strength and improved health status over control groups [104, 105]. Furthermore, improvements in hip abductor and external rotator strength can change lower extremity kinematics [106]. This growing body of evidence from randomised clinical trials has highlighted the efficacy of hip strengthening programmes in the PFP population. However, a substantial proportion of clinical trials have been conducted on only female cohorts [99-101, 103]. While these results are promising, it is unknown whether hip strength for males is as important a factor as it is for females with PFP. Further clinical trials are required that investigate the effects of hip strengthening on a mixed cohort, that is generalizable to the wider clinical population.

3.3 Evidence for targeting interventions distal to the knee

Another form treatment alternative for PFP is foot orthoses. Foot orthoses are specially designed shoe inserts. Notable features of therapeutic orthoses include contouring and intrinsic medial posting, a variety sizes, shapes and hardness, that are either custom-made or prefabricated, and fitted based on patient comfort and performance improvement [107]. Foot orthoses are fundamentally designed to realign and correct an aberrant motion of the foot [108]; however this traditional notion of skeletal realignment is questionable [109]. Foot orthoses have also been proposed to enhanced activation of the quadriceps and gluteal musculature and reduced lower limb muscle activity and joint moments by enhancing footwear comfort and [110, 111]. A recent systematic review and meta-analysis on the mechanisms of foot orthoses reported that foot orthoses could cause a reduction in rearfoot eversion and tibial internal rotation in non-injured cohorts [96]. A significant finding reported was the shock attenuating effect of a posted molded orthosis compared with a posted non-molded orthosis in uninjured participants [96]. These findings infer that the benefit of foot orthoses results from the modification of loading rate

and force through the foot and lower limb. However, this is based off evidence with small effect size from non-injured cohorts. There is a need for further studies investigating the exact mechanism of foot orthoses, particularly in injured cohorts. A greater understanding of this mechanism could influence the management of PFP with foot orthoses and help to optimize treatment outcomes.

Whilst there is a paucity of mechanistic evidence of foot orthoses, interventional studies have investigated clinical outcomes from foot orthoses treatment for PFP. Evidence has highlighted the efficacy of prefabricated foot orthoses in those with PFP [92, 112, 113]. A case-series reported foot orthoses had an immediate impact to reduce pain and improve function in step-down, single leg raise and squat tasks for people with PFP [113]. Foot orthoses provide greater improvements in patient-specific function and patient perceived global improvement in a 6 and 12 week intervention period compared with flat shoe inserts [92]. A high quality clinical trial randomly allocated 179 participants with PFP to four treatment arms, comparing the treatment efficacy of flat inserts, foot orthoses, a proven multimodal physiotherapy program [114], and combination of foot orthoses plus physiotherapy [92]. No significant difference was reported on global improvement between foot orthoses and physiotherapy, or between physiotherapy and foot orthoses plus physiotherapy, whether considered at 6, 12 or 52 weeks follow-up [92]. Collins et al. (2008) identified that the number needed to treat with orthoses for PFP was 4 [92]. However, the 99% confidence interval ranged from 2 to 51, and should be interpreted with caution.

Chapter 4 is adapted from a publication:

Matthews, M., Rathleff, M. S., Claus, A., McPoil, T., Nee, R., Crossley, K., & Vicenzino, B. (2017). Can we predict the outcome for people with patellofemoral pain? A systematic review on prognostic factors and treatment effect modifiers. *Br J Sports Med*, *51*(23), 1650-1660.

Contributor	**Statement of contribution**
M. Matthews (Candidate)	Research question design (35%), literature search (80%), data extraction and analysis (45%), quality appraisal (40%), tables and figures (40%), manuscript preparation (30%)
M. Rathleff	Research question design (20%), literature search (20%), data extraction and analysis (10%), quality appraisal (30%), tables and figures (10%), manuscript preparation (10%)
A. Claus	Research question design (5%), data extraction and analysis (10%), quality appraisal (10%), tables and figures (10%), manuscript preparation (10%)
T. McPoil	Research question design (5%), data extraction and analysis (5%), manuscript preparation (10%)
K. Crossley	Research question design (5%), data extraction and analysis (5%), manuscript preparation (10%)
R. Nee	Research question design (10%), %), data extraction and analysis (5%), tables and figures (10%), manuscript preparation (10%)
B. Vicenzino	Research question design (20%), data extraction and analysis (20%), quality appraisal (20%), tables and figures (30%), manuscript preparation (20%)

Chapter 4. Can we predict the outcome for people with patellofemoral pain? A systematic review on prognostic factors and treatment effect modifiers.

This chapter is a systematic review of the literature for patient characteristics that provide prognostic benefit or modified treatment effect. In summary, the review identified a number of studies that had report prognostic findings or clinical prediction rules, however the lack of a comparator treatment, and over-fitting statistical models, greatly restricted the findings.

4.1 Introduction

Patellofemoral pain is a prevalent and persistent knee condition [115, 116] that affects approximately 1 in 20 teenagers and 1 in 10 adult women. [6, 117-120] Despite receiving evidence-based treatments that are initially effective, more than one third of patients' still report persistent symptoms 12 months later [116] with approximately 25% reporting symptoms up to 20 years later.[121] It might be helpful clinically to know whether certain prognostic factors can identify patients with PFP who are at risk for a poor outcome. [122] A review identified a number of prognostic factors for outcomes in those with PFP (e.g., age, pain severity, foot posture/motion), [121] only presented differences between groups at baseline, which are not helpful to the clinician wanting to determine the prognosis of a specific patient.

The complex and multifactorial nature of PFP leads to a heterogeneous clinical presentation.[48] A recent best practice guide recommended that treatment be tailored to each patient's presentation, but it did not provide direction for the clinician on how to individually tailor treatment.[86] Prognostic factors are patient characteristics that help to determine a clinical outcome, positive or negative, within a certain time period. [123, 124] Treatment effect

modifiers are patient characteristics that predict a response or clinical outcome, or lack of response, from a specific treatment. An evidence-based approach to individually tailor treatment requires the identification of treatment effect modifiers, because although prognostic factors help predict the likelihood of an outcome within a certain time period, they cannot predict the likelihood of an outcome after a specific treatment. [125]

To inform clinical practice and research related to PFP, the purpose of this systematic review was to determine which baseline patient characteristics were: (i) associated with a poor outcome (prognostic factors); or (ii) associated with a successful outcome after a specific treatment (treatment effect modifiers).

4.2 Methods

4.2.1 Search Strategy

The systematic review was conducted following the PRISMA guideline. [126] Electronic databases (Medline, Scopus, Embase, CINAHL, SPORTDiscus and Web of Science) were searched up to July 2016 for studies investigating conservative (non-surgical) treatments for PFP. Key search terms relating to PFP and other such synonyms used in all databases were adapted from similar search strategies. [48, 127, 128] Keywords used to narrow the search to the aim of the review were success*, factor*, predict*, charact*, prognos*. Searches were limited to human studies with no language restrictions (appendix 1). The protocol for the systematic review was not registered.

4.2.2 Eligibility

Studies were included if they had investigated: (a) participants diagnosed with PFP determined by clinicians based on the report of retro or peripatellar pain that was provoked by either a partial squat, stair ascent or descent and pain reported during palpation of peri-articular structures, and (b) an association between patient characteristics that were measured at the outset of the study and the outcome (status of the condition) at a later time (minimum period of 1

week). If an included study had used an intervention, only conservative (non-surgical) interventions were included. Studies were excluded if they included pain from structures other than the patellofemoral joint, and other knee pathologies such as internal derangement, knee ligament insufficiency or patellar tendinopathy. Case reports or reviews of the literature were also excluded.

4.2.3 Review process

All identified studies were imported into Endnote X6 (Thomson Reuters, Carlsbad, California, USA) and duplicates removed. Two reviewers (MM & MSR) independently assessed study titles and abstracts for eligibility with a third reviewer (BV) available if necessary, to resolve discrepancies. Where there was duplication or pooling of data from different trials, only the primary publication (the study of the highest relevancy to the purposes of this review as determined by all three reviewers) was included. Reference lists of all publications considered for inclusion were hand-searched recursively until no additional eligible publications were identified.

4.2.4 Quality assessment

Two reviewers (MM and MSR) independently assessed papers for quality. Any discrepancies were discussed to reach consensus, and if discrepancies remained, a third reviewer was consulted (BV). Study quality of all included studies was assessed using the Epidemiological Appraisal Instrument (EAI) [129] in a method used in previous reviews. [130, 131] Items were scored as Yes (score = 2), Partial (score = 1), No (score = 0), Unable to determine (score = 0) of the applicable items. An average score was then calculated across all applicable items for each study (range 0-2). The EAI is a valid and reliable appraisal instrument for systematic reviews [132]

Studies that aimed to investigate predictors of outcome after a specific treatment were further evaluated for quality using a checklist for prescriptive, derivation-based clinical prediction rules (QUADCPR). [133] The QUADCPR was designed and developed using a 3-round Delphi process involving physicians, epidemiologists and physical therapists. It includes 23 items across 4 sections – (i) sample and participants (ii) outcome measure (iii)

quality of tests and measures and (iv) statistical assumptions. Each item is scored yes, no, or unclear without generating a quantitative score. Two modifications were made to the QUADCPR for the purposes of this review. First, in accordance with the statement on Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) [134], an adequately powered study required at least 10 participants in the limiting sample size (group with least frequent outcome) for each variable analyzed as a potential predictor (Question 18). Second, in discussion with the corresponding author of the QUADCPR, a fifth section was added to assess whether outcomes are treatment effect modifiers - (v) quality of treatment approach. This section addressed the quality of the treatment approach using published recommendations on the preferred study methods for identifying treatment effect modifiers and subgroup effects.[125, 135, 136] An additional 4 questions were inserted into the checklist (Questions 24 -27) that addressed treatment explanation and implementation of the target treatment and comparator treatment.

4.2.5 Data Extraction and Analysis

Study details were extracted by MM and checked by MSR. Details extracted were: publication details, sample characteristics, participant demographics, study methods including study design, outcome measures, any intervention(s), and the baseline factors studied. Study results were extracted by following the definitions for a successful outcome or poor outcome applied by each individual study. Outcome measures used per study are detailed in Table 4.2 (col. 4) and Table 4.3 (col. 3). Relationships between baseline predictors and a poor outcome (i.e., prognosis) were expressed as R^2, whereas baseline predictors and a successful outcome after a specific treatment were quantified by extracting positive likelihood ratios (LR+) and odds ratios (OR). Positive likelihood ratios indicate the change in probability of a successful outcome if the identified predictor is present. Shifts in probability of a successful outcome are categorized as small and rarely important (LR+ 1-2), small but sometimes important (LR+ 2-5), moderate shift (LR+ 5-10) or large and often conclusive (LR+ >10). [137] Odds ratios measure the association between the exposure and an outcome (OR >1 higher odds; OR

<1 lower odds). For studies that did not report OR, LR+ or post-test probability scores, authors were contacted, and those indices were calculated from available data. Meta-analyses were performed where appropriate.

4.3 Results

4.3.1 Search results and critical appraisal of methods

The search retrieved 11629 citations, of which 7339 unique titles and abstracts were reviewed, with 59 papers identified for full text examination. Twenty-four studies met the eligibility criteria for quality assessment and data extraction, (figure 4.1) which evaluated 180 participant characteristics (appendix 2). The most frequently evaluated characteristics were age and sex (n=14 studies), knee pain duration (n=13), Q angle, body mass index, weight and height (n=8), sports participation (n=6) and navicular drop (n=5 studies). Twelve studies investigated patient characteristics associated with a poor outcome, and the remaining 12 studies investigated patient characteristics associated with successful outcome after a specific treatment.

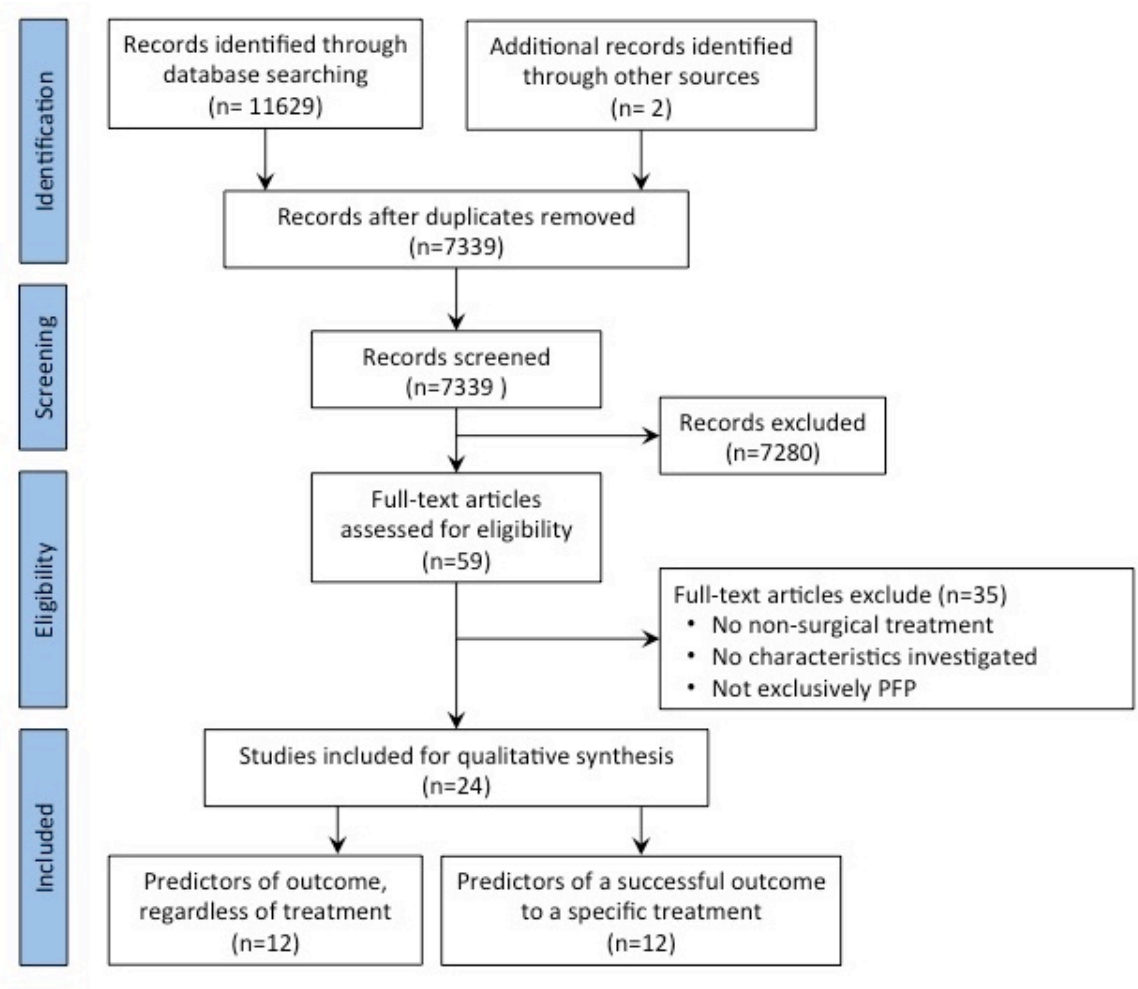

Figure 4.1 PRISMA flow diagram

4.3.2 Quality assessment

Overall across all 24 studies, there was good conformity of the study aims, treatments, assessments and main findings on the EAI checklist. Very few studies reported adequate adjustment for covariates in the statistical analyses, blinding of observers or reporting of adverse events. There was also a lack of reporting reliability and validity of the main outcome measures used (appendix 3). Twelve studies investigated prognostic factors for a poor outcome (three randomized controlled trials, eight case series and one had no treatment), only one of the randomized trials [138] adjusted for treatment and reported it was not a confounder.

In addition to being evaluated for quality on the EAI, studies that investigated patient characteristics associated with successful outcome after a specific

treatment were appraised under the QUADCPR checklist (n=12). Overall on the QUADCPR quality checklist, significant methodological limitations were identified with only one study using a control group. Only one study [139] had adequate statistical power with at least 10 participants in the limiting sample size (group with least frequent outcome) for each potential predictor included in the statistical analysis. Even if a lower threshold of 5 participants in the limiting sample size for each potential predictor is used, [140] this was still the only study that had adequate statistical power. An issue with potential reporting bias was identified with only four [95, 139, 141, 142] of the twelve studies administered outcome measures in a blinded fashion and in only three studies were the examining [95, 139, 143] or treating [95, 142, 144] clinicians blind to the outcome measures (appendix 4).

4.3.3 Patient characteristics associated with a poor outcome (prognosis)

Sixteen patient-reported and anatomical characteristics were associated with a poor outcome, with degree of association (e.g., R^2) ranging from 27 to 46% (appendix 5). The patient-reported characteristics were duration of PFP symptoms [138, 145, 146] bilateral symptoms, [147] higher frequency of pain occurrence, [148] older age, [149] female gender, [146] lower baseline Kujala knee pain score and function (Kujala scale and functional index questionnaire in [138]), poor health and low/middle education level. [147]
Anatomical characteristics associated with a poor outcome were swelling of the knee (self-reported by the participant in [147]), patellar hypermobility, [146] slower vastus medialis obliquus reflex response, [145] larger side to side differences in isometric quadriceps muscle strength, [150] smaller quadriceps cross sectional area on MRI and lower eccentric knee strength, [148] evidence of chondromalacia patella on MRI and a tibial tubercle lateral deviation > 14.6 mm relative to the trochlear groove. [151]

4.3.4 Patient characteristics associated with a successful outcome after a specific treatment

Six different specific treatments were investigated; foot orthoses, [77, 95, 142, 143, 152, 153] lumbopelvic manipulation, [144, 154] patellar taping, [141] femoral nerve mobilization, [155] leg press exercise and stretching [139] and exercise therapy (consisting of static and dynamic exercises for the quadriceps muscles, flexibility and balance exercises) [156] (appendix 6). Twenty-two patient characteristics were reported to be associated with a successful outcome after a specific treatment. Studies defined a successful outcome using a predetermined amount of improvement in pain scores, questionnaire and/or a rating on a global rating of changes scale to stratify respondents into successful or unsuccessful outcomes.

4.4.1 Foot orthoses

Fourteen predictors were univariately associated with a successful outcome after foot orthoses treatment across six studies. [77, 95, 142, 143, 152, 153] Four predictors were static measures of the foot; these were 2° or more of valgus forefoot alignment, 78° or less great toe extension, 3mm or less navicular drop [152] and two studies reporting a mid-foot width difference between weight bearing and non-weight bearing greater than 10.96mm. [95, 142] Two studies investigated foot movements during functional tasks. One study used 3-D kinematic analysis during gait to show those who had a successful outcome had a mean difference of 2.3° greater rearfoot eversion relative to the ground than those who reported an unsuccessful outcome. [77] The other study of a drop jump task reported those who had an immediate decrease in the medial-to-lateral peak foot loading went on to report improvements in pain and function after wearing foot orthoses for 12 weeks.[153] Two studies found baseline pain scores of usual pain less than 22.0 mm [143] and worst pain less than 53.25 mm [95] on a 100mm visual analogue scale predicted a successful outcome. One functional performance predictor was reduced pain during a single leg squat whilst wearing foot orthoses. [143] Ankle dorsiflexion range less than 41.3°, relative to the vertical, (measured as tibial inclination using a digital inclinometer placed anteriorly mid-tibia) during weight bearing ankle dorsiflexion with a bent knee also predicted a positive outcome. [143] Other demographic predictors reported were height less than 165 cm and age over 25 years. [95] In addition

to the patient centric factors, those participants who wore footwear with reduced motion control properties, assessed using a footwear assessment tool, [157] were more likely to report a successful outcome when wearing an orthosis. [143] Three predictors (height, forefoot valgus alignment, great toe extension) had a reported LR+ range of 4.0 - 4.9 [95, 152] but the 95% confidence intervals for these predictors were large raising greater uncertainty on the precision of these relationships. Three predictors of success had LR+ range between 2.5 to 3.9 and narrow confidence intervals; with two studies identifying midfoot width difference from weight bearing to non-weight bearing foot posture of >10.96mm [95] and >11.26mm, [142] reduced pain during single leg squat while wearing a foot orthosis and usual pain <22/100mm visual analogue scale.

Two studies used multivariate analysis to evaluate a combination of predictors for clinical prediction rules for success after treatment by foot orthoses (appendix 7). Each study reported a different combination of four predictors, with a LR+ of 8.8 (95%CI 1.2-66.9) [95] and 11.1 (95%CI 2.7-46.9) [143] when three or more predictors were present, raising post-test probability of success to 85.4% and 78% respectively. These LR+ suggest a moderate to large and often conclusive shifts in probability of a successful outcome after foot orthoses treatment. No participants in either of the two studies presented with all four of the respective predictors (appendix 7).

4.4.2 Lumbopelvic manipulation

Five predictors were identified using multivariate analysis and reported to be associated with a successful outcome after lumbopelvic manipulation. [154] A follow up study [144] on a different but similar sized PFP cohort failed to replicate the same five predictors reported by Iverson et al. [154]

4.4.3 Patellar taping

One study [141] reported three predictors of a successful outcome with patellar taping as described by McConnell. [158] After multivariate analysis, smaller lateral patellofemoral angle (an angle formed by the line between the femoral condyles and another line between the margins of the lateral facet of

the patella) measured with radiographs in 30° of knee flexion, larger Q angle and a lower body mass index [141] were reported to be associated with a successful outcome. Larger Q angle was the only one of three reported predictors have an OR >1 (OR 1.14 95%CI 1.03-1.26).

4.4.4 Femoral nerve mobilization

One study [155] reported two predictors to be associated with a successful outcome after six sessions of femoral nerve mobilization. After multivariate analysis, significant immediate improvement after a femoral nerve mobilization and a bilateral difference of at least 3° in hip extension angle of the femoral slump test, which had a LR+ 5.1 (1.3-20.3), suggests a moderate shift in probability of successful outcome after femoral nerve mobilization.

4.4.5 Exercise

Two studies investigated predictors of successful outcome after exercise. One study compared exercise therapy to usual care and found no significant predictors of a successful outcome to exercise therapy. [156] One study evaluated a leg press training and lower limb muscle stretching exercise program. [139] Patellar tilt angle difference (PTA-d), which is the difference in patellar tilt angle in a quadriceps contracted (Qc) and a quadriceps relaxed (Qr) position measured on axial computed tomography, was associated with a successful outcome after a leg press strengthening and lower limb stretching program. [139] Those who had greater PTA-d (i.e greater realignment of the patella with quadriceps contraction) before beginning exercise treatment had greater reductions in pain after treatment. [139] The optimal cut-off value was −1.5° PTA-d (Qc−Qr) for the clinical discrimination of treatment success based on a minimum pain reduction of 1.5-cm on the VAS (sensitivity = 0.74, specificity = 0.71, LR+ 2.5).

4.5 Discussion

Our systematic review on PFP investigated baseline patient characteristics that were associated with a: (a) poor outcome (prognosis), or (b) successful

outcome after a specific treatment after more than one week. The review highlighted a large amount of non-significant association with a total of 180 patient characteristics being investigated by 24 studies. Twelve prognosis studies investigated 104 characteristics and identified 16 prognostic factors associated with a poor outcome. Twelve studies reported that only 22 out of 100 potential treatment effect modifiers were associated with a successful outcome after a specific treatment. However, the review identified significant methodological limitations in all studies appraised with the EAI and modified QUADCPR tools. Of the 12 studies that investigated prognostic factors, only one study, a randomized controlled trial, [34] controlled for treatment and showed it was not a confounder. Of the 12 studies that investigated potential treatment effect modifiers, 11 did not have a control condition or a comparator treatment. Due to this methodological limitation, it is unclear whether the 22 baseline patient characteristics identified in these studies actually predict success following a specific treatment or are just non-specific prognostic factors. As a result of these limitations, pooling and meta-analyses of the data were not warranted. Although definitive conclusions cannot be drawn until these methodological limitations are addressed, in order to make the best use of available evidence, our discussion will focus first on studies investigating prognostic factors for a poor outcome followed by studies that investigated potential treatment effect modifiers.

Prognostic factors are important in the decision making process and managing patient expectations. [159] Persistent PFP symptoms could have a negative impact on the physiological and psychological well-being of an individual with PFP. [115, 160, 161] Of the 12 studies that evaluated prognostic factors for a poor outcome, 16 characteristics were reported, but only five were investigated by more than three studies. Longer duration of knee pain, [138, 145, 146] older age, [149] greater usual pain severity and lower baseline anterior knee pain score [138] were factors of an unsuccessful outcome (appendix 8). Three of the five studies that evaluated duration of knee pain, one a large prospective study, reported a consistent finding of longer duration of pain (>4 months [35]) as an indicator of a poor outcome. Longer duration of symptoms as a poor prognostic indicator seems to be

consistent across musculoskeletal conditions, [162] even in adolescents with knee pain.[115] It is important to consider that all identified prognostic factors were collected once a baseline, a final score. It is possible that a change in score, or lack of change, (i.e. collecting a score again after a certain time period) may prove to be a stronger prognostic factor (e.g. minimal change in reported worst pain or anterior knee pain score over 6-week period). It would appear prudent for clinicians to keep duration of symptoms in mind when consulting a patient with PFP. This prognostic factor should also be considered in guidelines and future research for the effective management/prevention of persistent PFP.

Twelve studies evaluated potential treatment effect modifiers associated with a successful outcome after a specific treatment with four conducting multivariate analyses to report clinical prediction rules for either foot orthoses, [95, 143] or lumbopelvic manipulation. [144, 154] A limitation of these single group studies identified in the QUADCPR appraisal was (a) the absence of an appropriate comparator intervention, [163] and (b) inadequate statistical power because limiting sample sizes were too small. Of the 12 studies that investigated potential treatment effect modifiers, 11 did not have a control condition or a comparator treatment. Lack of a control condition or a comparator treatment means there is no way to know that the outcome was necessarily due to the specific treatment. It is unclear whether the baseline patient characteristics identified in these studies actually predict success following a specific treatment or are just non-specific prognostic factors. The risk of spurious findings when overfitting or underfitting data to the limiting sample size was highlighted in a replication study of lumbopelvic manipulation for PFP [144] which used the same methods as the original study [154] but achieved contrasting results. Replication studies play an important role in predictive performance in a second, independent sample, especially when there are concerns about overfitting/underfitting data in the original study because of a relatively small limiting sample size. These studies need careful consideration in design that allow for an analysis of the interaction between treatment group and status on the prediction rule.

Foot orthoses were the most common treatment in studies that attempted to identify potential treatment effect modifiers (6 studies). One factor that was identified by two studies [95, 142] and formed part of a multivariate clinical prediction rule, was midfoot width difference of greater than 11mm, reported by Mills et al. [142] This study was the only one of the 13 studies looking at treatment effect modifiers to use a control group (wait-and-see approach). [142] Mills et al [142] provide preliminary evidence that midfoot width difference might be useful at identifying those who might benefit from a foot orthosis, beyond natural history of the condition in the short term. This provides the clinician some useful information/evidence beyond any prognostic value of this foot characteristic.

Whilst single group studies cannot distinguish between treatment effect modifiers and non-specific prognostic factors, they can identify prognostic factors that could potentially be treatment effect modifiers. Rather appropriately the bulk of identified factors that might predict success with foot orthoses, were based at or around the foot. The two studies reporting clinical prediction rules for prescribing foot orthoses reported likelihood ratios that could signify a moderate to large and often conclusive shift in probability of a successful treatment. [137] The factors that are most likely to be clinically modifiable are ankle dorsiflexion (tibial inclination <41.3° from the vertical),[143] mid-foot width difference (>11mm) [95, 142] and footwear motion control properties (weighted mean >5). [143] An interesting clinical examination finding that contributed to one of these clinical prediction rules was a positive treatment direction test, [164] which is essentially the immediate reduction in pain with a single leg squat on initial wearing of a foot orthosis. [143] Somewhat consistent with the report of a positive treatment direction test [143] is the finding of an immediate decrease in medial-to-lateral peak foot force with fitting a foot orthosis being associated with a successful outcome. [153] In another laboratory study, kinematic analysis found those with greater rearfoot eversion relative to the floor, would also successfully respond to foot orthoses. [77] Taking the findings collectively, there appears to be a body of exploratory results from single group studies that suggests the ability of the reported clinically measurable and modifiable prognostic factors

to be potential treatment effect modifiers to identify those who would be successful with foot orthoses (appendix 8). Further research is necessary to investigate clinically relevant and plausible prognostic factors from single group studies in appropriately designed clinical trials to test for their ability to be treatment effect modifiers. In particular, midfoot width difference should be further explored as a treatment effect modifier for foot orthoses compared to other treatments because it has been shown to predict success with foot orthoses when compared to no intervention.

In clinical practice, a positive finding of reproduction of symptoms with a femoral slump test, that reduced with neck extension, would reasonably direct the clinician to consider using femoral nerve mobilisations in patients who have PFP. Only one study reported clinical features that predicted success after femoral nerve mobilization treatment. [155]. In addition to the limitations of the single-group design, the authors used a modified testing protocol for the femoral slump test that is not easy to replicate in a timely manner in clinical practice. It is questionable the degree of confidence with which a clinician could determine a 3° difference from side to side as the authors did not report the error of this test measurement, so it is difficult to know if 3° exceeds measurement error. Nevertheless, further investigation of this treatment approach is warranted.

Patellar taping, strengthening and stretching exercises of the thigh and lower limb muscles are often recommended to treat PFP. [158] A study by Lan et al [141] reported that success following patellar taping was associated with lateral patellofemoral angle and Q angle. Peng et al [139] measured the difference in patellar tilt angle between relaxed and contracted states of the quadriceps, noting a greater difference i.e., greater realignment of the patella with a contracted quads with treatment success. Notably though, all these measures from single studies of patellar position were made with radiological imaging, which is not readily accessible in a typical clinical setting (appendix 8).

A series of important methodological issues were identified in the reviewed studies. Prognostic studies should ideally be prospective in design, [123] but

in order to review all available studies that reported prognostic factors, weaker-designed retrospective studies were also included in this in review. Studies investigating predictors of a successful outcome after a specific treatment usually analyzed too many potential predictors for the limiting sample size. This increases the risk of over-fitting (or under-fitting) the data which can lead to the identification of predictors that are implausible and likely to perform poorly in new samples of patients [140] The absence of comparator interventions in studies investigating outcomes after a specific treatment make it difficult to differentiate between treatment effect modifiers and non-specific prognostic factors. Future studies should determine a sufficient limiting sample size to order to guide recruitment of an appropriate sample size. [136] Lastly, studies need to apply appropriate blinding where possible for participants and treating clinicians, but it is critical to blind investigators assessing the outcome to minimize false positives, or negatives, and potential biases.

4.6 Conclusion

This review of relationships between patient characteristics and treatment outcomes for PFP identified that methodological limitations such as the absence of a control/comparator group, or too many predictors for the limiting sample size, make it unclear whether the predictors reported actually modify treatment effects. Despite the limitations inherent in current research evidence we identified modifiable and measurable factors that have been studied so as inform hypotheses that may help in the clinical decision-making process (appendix 8). Three prognostic studies of patient characteristics identified that persistence of PFP beyond 4 months should alert clinicians to increased risk of a poor outcome. Greater change in midfoot width from non-weight bearing to weight bearing was the only characteristic that had sufficient evidence for being a potential treatment effect modifier for a successful outcome after foot orthoses treatment. The LR+ suggested a small but sometimes important shift in probability of a successful outcome, and this characteristic did not predict short-term improvement in a control group who received no intervention. Adequately powered randomized trials that compare relevant treatments are needed so that treatment can be tailored to the individual patient.

Chapter 5 is adapted from a publication:

Matthews, M., Rathleff, M.S., Claus, A., McPoil, T., Nee, R., Crossley, K., Kasza, J., Paul, S., Mellor, R. and Vicenzino, B. (2017). The Foot Orthoses versus Hip eXercises (FOHX) trial for patellofemoral pain: a protocol for a randomized clinical trial to determine if foot mobility is associated with better outcomes from foot orthoses. *Journal of foot and ankle research*, *10*(1), 5.

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Chapter 5. The Foot Orthoses versus Hip eXercises (FOHX) trial for patellofemoral pain: A protocol for a randomized clinical trial to determine if foot mobility is associated with better outcomes from foot orthoses

Preliminary findings from the systematic review suggested midfoot width mobility as a potential treatment effect modifier for foot orthoses. Limitations in the methodology of the identified studies, primarily the lack of a comparator treatment, restrict the clinical utility of reported findings. This chapter outlines the protocol for a randomsied controlled trial with two aims; to determine: (i) if greater midfoot width mobility will be associated with greater success with foot orthoses, when compared to hip exercises, and (ii) the superiorty of hip exercises versus foot orthoses, irrespective foot mobility.

5.1 Background

Patellofemoral pain (PFP) is a prevalent knee condition throughout the lifespan [7, 119, 165, 166], with a propensity to become persistent. [116, 121] Patellofemoral pain classically presents as anterior knee pain aggravated by activities that load the patellofemoral joint, such as climbing or descending stairs, running, squatting or sitting for prolonged periods. [4] Diagnosis is based on the clinical presentation of PFP, in the absence of other pathologies that might manifest as anterior knee pain. [4]

Patellofemoral pain is also a multifactorial condition with guidelines suggesting optimal treatment should confer early pain relief and be targeted to the individual. [4, 86] Physical and exercise interventions for PFP are often targeted at the foot, knee and hip joints, or combinations thereof, with combined interventions proving superior. [167] Combined interventions for PFP often involve both active (e.g., progressive resistance exercise) and passive (e.g., orthoses, manual therapy, tape) therapies applied to the knee as well as the foot, thigh and hip regions. Selecting a tailored treatment plan for an individual patient from this range of interventions will potentially

enhance treatment outcomes and minimise exposing patients to non-essential treatments.

Clinical trials have shown that exercising the hip muscles or using foot orthoses are efficacious in managing PFP, [92, 142, 168] but no studies have compared which is superior. Kinematic data suggests that the position and movement of the femoral bone, which is largely governed by hip joint movement under control of hip muscles, is the main contributor to patellofemoral joint loads [169, 170]. Exercise of the hip muscles would then plausibly have more effect on PFP through reduction of patellofemoral joint load, when compared to interventions targeting the foot (e.g., foot orthoses). We propose undertaking a comparison between hip exercise and foot orthoses, as it will address a common point of contention regarding whether proximal or distal approaches to PFP are more beneficial. [171]

The recommendation to target treatments to the individual [86] has not been researched. One method of matching treatments to individual patients is to identify patient characteristics that can predict success after a specific treatment, known as treatment effect modifiers. [125] There are currently no valid treatment effect modifiers for treatment of PFP, but preliminary data suggest that further investigation of midfoot width mobility is warranted. Two studies have reported that greater midfoot width mobility [76] (defined as a change of 11mm or more moving from a weight bearing to non-weight bearing posture) was present in greater proportions of participants reporting improvement in their condition when treated with foot orthoses. [95, 142] These preliminary studies are limited in terms of the methods required to prove treatment effect modification. [172] Such limitations include failure to compare the specific intervention of interest against another relevant treatment and testing too many potential predictor variables for the sample size studied.

We will undertake a randomized clinical trial that will investigate the role of midfoot width mobility as a treatment effect modifier for treatment of PFP with foot orthoses. It will also evaluate the clinical efficacy of foot orthoses against

progressive resisted hip exercises. The prospective trial will stratify participants based on their midfoot width mobility and randomly allocate them to be treated with foot orthoses or hip exercises.

5.1.1 Objective

The objective of this trial is to determine if those individuals with PFP and greater midfoot width mobility will report better outcomes from foot orthoses when compared to hip exercises. The trial will also conduct a direct comparison between foot orthoses and hip exercises in the treatment of PFP.

5.1.2.Hypotheses

1. High midfoot width mobility is a treatment effect modifier for foot orthoses compared to progressive resisted hip exercises at 12 weeks. This means that beneficial effects of foot orthoses compared to hip exercises will be greater for patients with PFP who have high midfoot width mobility than in those who have low midfoot width mobility.
2. Hip exercises will be associated with better outcomes after 12 weeks, when compared to treatment with foot orthoses

5.2 Method

This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. [173] The study report will follow the CONSORT guidelines for randomized trials [174] with the extension for non-pharmacological treatments and TIDieR for intervention description. [175, 176]

5.2.1 Trial design

A two-arm prospective randomised superiority clinical trial in a multicentre setting with stratification on midfoot width mobility will evaluate if midfoot width mobility is a treatment effect modifier for foot orthoses compared to

progressive resisted hip exercises. An independent off-site body will generate a randomisation schedule for all participants for both trial sites. Participants will be allocated into either foot orthoses or progressive resisted hip exercises in a 1: 1 ratio using permuted block randomisation stratified by site and by the mid foot mobility measure. The primary end point will be 12 weeks.

5.2.2. Study setting

The trial will be conducted in Brisbane, Australia and Aalborg, Denmark. To reflect the common treatment settings in these countries, participants in Brisbane will attend private physiotherapy practices in the community while those is Aalborg will attend physiotherapy sessions in a hospital musculoskeletal outpatient department. [177]

5.2.3 Ethics

This study has been granted ethical approval by the University of Queensland Medical Research Ethics Committee (2013000981) and by the local ethics committee in the North Denmark Region (N-20140022). All participants will provide informed consent prior to being enrolled in the study.

5.2.4 Eligibility criteria

Volunteers will range from 18 – 40 years of age, report a history of anterior, retro or peri-patellar knee pain of non-traumatic origin that has persisted for more than six weeks. Self-reported worst pain over the previous week will be required to be greater than 3/10 on a numerical pain scale (0 = no pain, 10 = worst pain imaginable) with symptoms provoked by at least two or more of the following activities: squatting, running, prolonged sitting, stair ascending or descending. On physical examination, pain should be provoked by clinical palpation of the patellar borders, stepping down from a 25 cm step, during a double-leg squat and present on clinical compression of the patella into the trochlear groove. Eligible participants will be required to have basic comprehension of written and spoken English (Brisbane, Australia) or Danish

(Aalborg, Denmark) because of the descriptive nature of pain and behavioral outcome measures applied in this study.

Volunteers will be excluded if they have any of the following: concomitant injuries or pathologies affecting other knee structures (e.g. ligament, meniscal, tendon, iliotibial band, pes anserinus), a history of knee or other significant lower limb surgery, patellofemoral dislocation or subluxation, Osgood-Schlatter's disease, Siding-Larsen-Johanssen syndrome, a positive patellar apprehension test or evidence of knee joint effusion. Volunteers will be excluded if they present with any foot condition that may preclude the use of foot orthoses, pain in and/or referred from the hip, pelvis or lumbar spine, current use of anti-inflammatory or corticosteroid medication including injections, or any previous treatment for PFP or other conditions that included hip exercises or foot orthoses.

5.2.5 Stratification criterion

An investigator at each trial site, different to the investigator responsible for enrolment, baseline and follow up outcome measures and blind to those outcome measures, will measure each participant's midfoot width prior to treatment allocation. Midfoot width mobility is calculated as the difference in midfoot width between weight bearing and non-weight bearing postures and shown to be reliable. [76] The investigators taking the midfoot width mobility measurement will be trained to ensure they can reliably measure midfoot mobility. To test for midfoot width mobility as a treatment effect modifier for foot orthoses, we determined prior to the study that the stratification cutoff for midfoot width mobility will be 11 mm. [95, 142] Those who present with ≥11 mm midfoot width mobility will be defined as being *'high mobility'* and those with <11 mm as *'low mobility'*.

5.2.6 Interventions

Eligible participants will be randomly assigned to one of two interventions; (a) foot orthoses intervention or (b) a progressive resisted hip exercise

intervention. Registered/licenced physiotherapists who regularly treat musculoskeletal conditions will deliver both interventions. Treating physiotherapists at both sites will be trained by the same investigators (BV, MM & MSR) in the intervention protocols for both foot orthoses fitting and hip exercises prior to trial commencement to ensure consistent implementation of the interventions. Although the treatments are standard physiotherapy interventions, to ensure fidelity of treatment application all clinicians will be provided with extensive documentation including images of treatments, have an option to attend a refresher workshop, and access to a senior investigator for any queries or issues that arise during the trial. Treating physiotherapists will be blind to the participant's midfoot width mobility measurements and baseline and follow-up outcome measurements. At the start of the study all participants will receive education to facilitate a basic understanding of their PFP condition and advice on physical activity. Participants will be encouraged to remain physically active provided that their chosen activities do not provoke pain that persists after ceasing their activities, and there is no general deterioration of symptoms during or after the cessation of activity.

5.2.6.1 Foot orthoses

Prescription of foot orthoses will follow the protocol utilised in a previous randomised control trial. [92] Physiotherapists will be provided with a range of commercially available prefabricated foot orthoses (Vasyli International, Labrador, Australia) (Figure 5.1). The orthoses are manufactured and designed from ethylene-vinyl acetate with an inbuilt arch support and a manufacturer specified 6° varus wedge. The orthoses are constructed in 3 different levels of hardness [high (Shore A 75°), medium (Shore A 60°) or low (Shore A 52°)]. Prior to fitting the orthoses, the participant will perform a nominated aggravating task (e.g., step-ups). Physiotherapists will then follow a standardised fitting procedure (Figure 5.2). The physiotherapist has the scope within the fitting procedure to review the size, length, and hardness of the orthoses, that prioritises comfort as this is a key determinant of participant compliance. [178] To maximise comfort of the orthoses, physiotherapists can make modifications including heat molding and/or trialing various medial

wedges to the rear foot (2° or 4° inclination) and/or forefoot (4° or 6° inclination) and/or heel raise (4, 6 or 8 mm in height). Once the participant is satisfied with the comfort of the orthoses, the participant will perform the previously nominated aggravating task. An improved performance will be determined by the participant reporting a reduction in pain score or improved performance (e.g. more repetitions of an aggravating activity) before the onset of their pain.

Figure 5.1 Orthoses types

(*From front)* Full length, three-quarter length, easy fit & contoured sandal

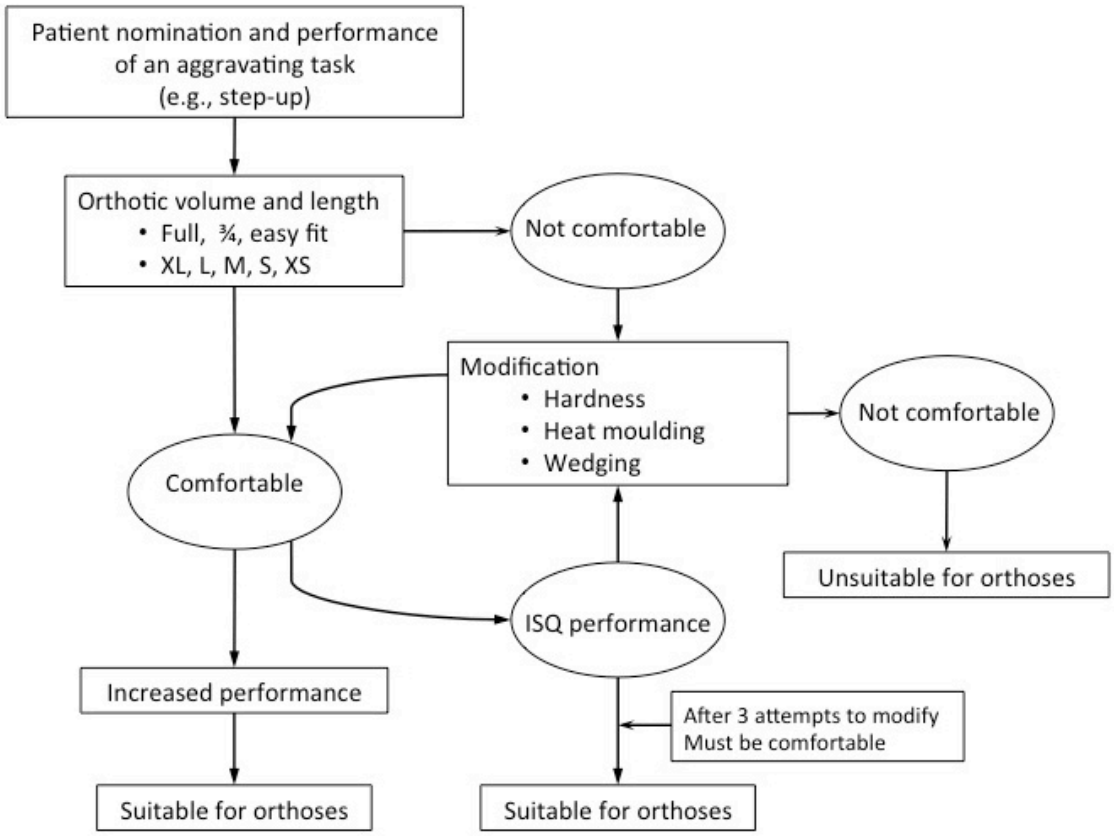

Figure 5.2 Flowchart of orthoses fitting procedure

The prescribing physiotherapist will have 3 attempts to modify the foot orthoses to primarily be comfortable and then improve performance of the participant selected task. In the unlikely event that the foot orthosis cannot be modified sufficiently to the participant's satisfaction by the third session, then the participant will be deemed unsuitable for foot orthoses.. That is, no participant will be asked to wear orthoses that they perceive is uncomfortable. Previous trials of the same population using the same fitting procedure reported that no participants were unsuitable for this intervention. [92, 142]

To encourage wearing of the orthoses, participants will be prescribed up to four pairs to fit a wide range of footwear as well as contoured (in the form of the orthoses) sandals for everyday use. Participants will be encouraged to wear the orthosis or contoured sandal whenever weight bearing. The sandal and orthoses have been shown to similarly increase arch height in healthy participants. [179]

Participants receiving orthoses will also be asked to perform a home foot and ankle exercise program twice per day (Figure 5.3). The program will include (i) stretches for the triceps surae/tendo-Achilles complex (3 x 30 sec weight-bearing), and (ii) anti-pronation postural foot exercises. The anti-pronation foot exercises aim to improve the participant's awareness from a relaxed pronated posture to a more supinated posture. Therapists will initiate training of the foot exercises with participants seated with the knees flexed and bare feet on the ground. Training consists of verbal and manual facilitation of participants to supinate the rear foot (manual facilitation: therapist upward pressure under the navicular as well as palpating the talocrural joint space for medio-lateral symmetry), while maintaining the first metatarsal head firmly on the floor and the toes relaxed. This foot posture will be held for 5 x 10 s. The exercises will be performed on each foot separately. Participants will attend a total of six sessions over six weeks.

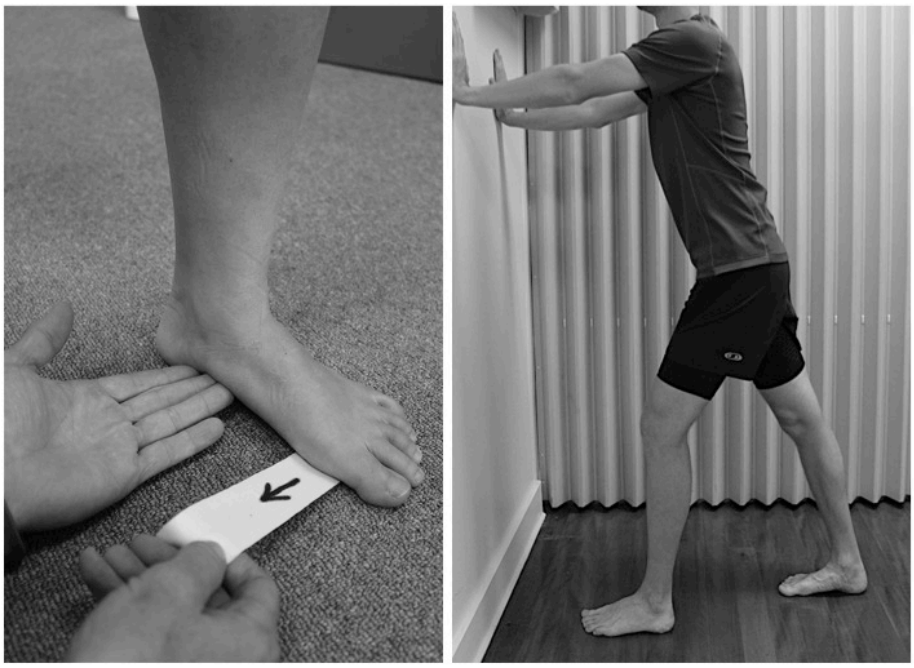

Figure 5.3. Foot and ankle exercises
(*Left)*: Anti-pronation exercise: The rearfoot is supinated (with tactile feedback) whilst maintaining first metatarsal head in ground contact. The white non-elastic tape is placed under the distal first metatarsal and the participant asked to prevent it from being removed (i.e., through plantarflexion

of the first ray) by the clinician who exerts traction on the tape. *(Right)* Calf stretch exercise, which is performed with the foot in netural position and the midline of the foot and the mid-point of the patella kept perpendicular to the wall

5.2.6.2 Hip exercises

The progressive resisted hip exercise protocol is modified from a protocol successfully used to improve outcomes at 12 months in women with PFP. [180] Exercise therapy focused on hip muscle groups, in particular hip abductor, external rotator, and extensor muscle groups, as well as a knee strengthening and stretching program targeting quadriceps, hamstrings and triceps surae muscle groups [180]. Results from intervention studies [94, 98, 102, 105, 168, 180] support that exercises targeting the postero-lateral hip musculature can improve long-term function and reduce PFP when compared to no exercises or knee exercises alone. [181]

Participants in the progressive resisted hip exercise group will attend three sessions per week for four weeks (12 sessions) [180] to perform exercises focused on the hip abductor, extensor and external rotator muscles groups. The exercises will be performed alternately on both sides and are described in appendix 9. [182] Elastic bands will provide resistance for the exercises and will be standardized to allow the participant to achieve a maximum of 10 repetitions. Resistance (denoted by band colour) and length (50, 60, 70 cm loops) of the band (Theraband™) (Figure 5.4A-D) will be selected by the physiotherapist to suit individual participant capacity, re-evaluated at each treatment session and progressed accordingly. Using an 11-point scale of perceived exertion, participants will be encouraged to exercise at a rate of 5-7 (‘Hard’ to ‘very hard’) (Figure 5.5). The contraction phase for each repetition will be 2 s concentric, 1 s isometric, 2 s eccentric and 1 s rest; with approximately a 90 s rest between each set of 10 repetitions, while training the contralateral side.

Figure 5.4A Hip abduction exercise in side lying

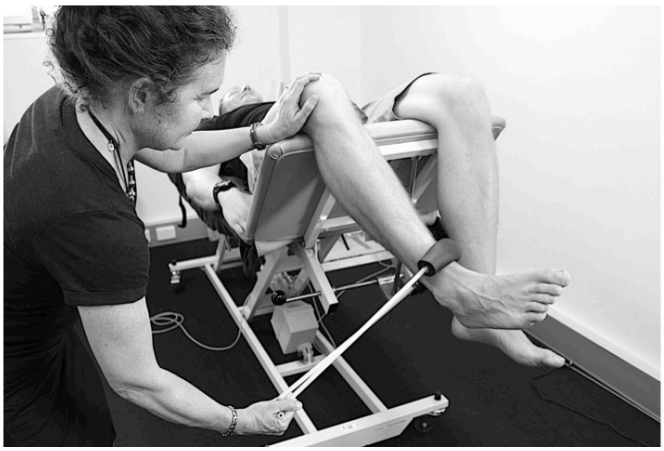

Figure 5.4B Hip external rotation exercise in supine and with the hip in 30° flexion

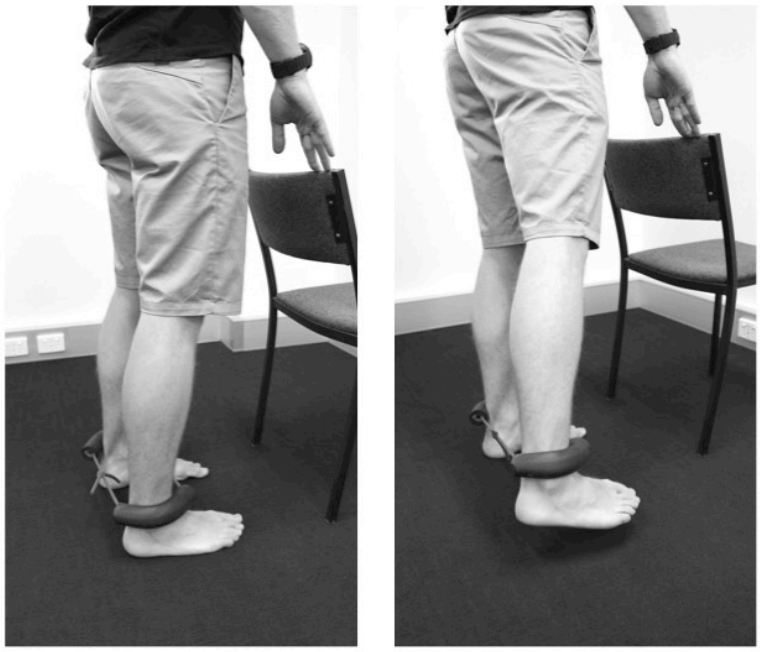

Figure 5.4C Hip abduction exercise in standing

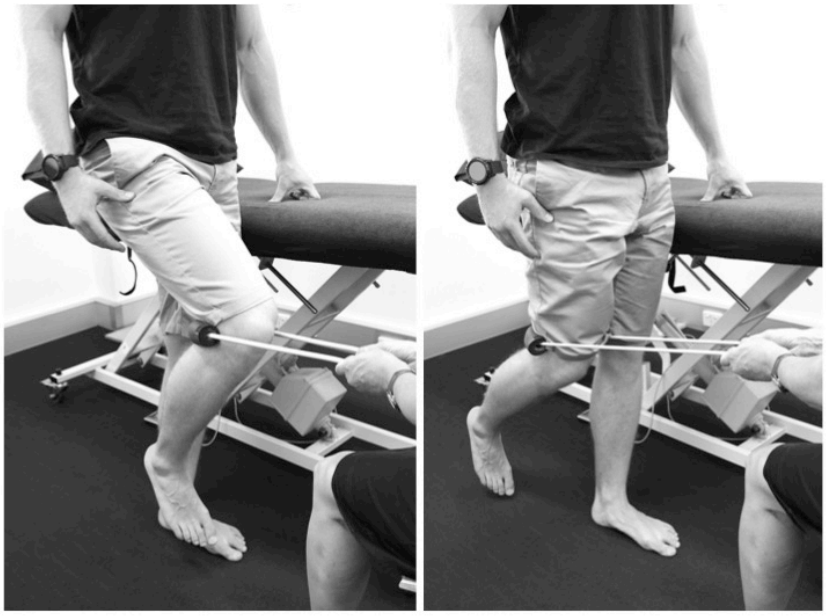

Figure 5.4D Hip extension exercise in standing

1-10 Borg Scale of Percieved Exertion	
0	Rest
1	Really Easy
2	Easy
3	Moderate
4	Sort of Hard
5	Hard
6	
7	Really Hard
8	
9	Really, Really Hard
10	Maximal

Figure 5.5 Borg scale of perceived exertion

For each of the twelve sessions, the treating physiotherapist will record attendance, strength (colour) and length of band used for each exercise, number of sets and repetitions completed as well as any adverse effects. At the completion of the program, participants will be instructed to continue with normal activities of daily living with no instructions to continue on with a home exercise program.

5.3 Outcome measures

The outcome measures will be a range of self-reported questionnaires, including psychological and quality of life measures as these are often involved in persistent musculoskeletal pain conditions, and functional tasks that load the patellofemoral joint. Participants will not be made aware of the specific study aim to evaluate midfoot width mobility as a treatment effect modifier so as to minimise the impact of participant expectation of treatment response on the basis of their foot type (or their allocated treatment group). Baseline and follow up (6 and 12 weeks after the commencement of

intervention) outcome measures will be administered by an assessor at each trial site who will be blind to the participant's midfoot width mobility measurement and intervention allocation.

5.3.1 Primary outcome measurement (6 & 12 weeks)

The global rate of change scale (GROC) is the primary outcome measure with the primary endpoint at 12 weeks. The GROC is a participant rating of the direction and magnitude of overall change in symptoms. [183] Participants will be asked: "How would you describe your knee pain now, compared to before you began the treatment." They will answer this question by selecting a descriptor on a 7-point Likert scale that best represents any change in their symptoms (much better, better, a little better, no change, a little worse, worse, much worse). Global rating of change scales have been frequently used in studies investigating treatment outcome in those with PFP and shown to be a flexible, simple and sensitive method for measuring meaningful individual improvement. [92, 93, 142, 184, 185] For analysis purposes, the GROC will be dichotomized so that 'much better' and 'better' represent success with treatment.

5.3.2 Secondary outcome measures

Single assessment numeric evaluation (SANE)

Single assessment numeric evaluation questions have been used previously in participants with neck pain [186], shoulder surgery [187] and anterior cruciate ligament reconstruction [188] and been shown to correlate well with other outcome measures. Participants will be asked:

1. "*How would you rate your knee **today** as a percentage of normal on a scale of 0% to 100%?"* with 100% being defined as having no problems at all with the knee. (at 0, 6 and 12 weeks)
2. *"On a scale of 0 (not at all) to 100% (totally recovered), how well do you feel you have recovered from your knee pain?"* (at 6 and 12 weeks)

Patient acceptable symptom state (6 & 12 weeks)

Patient acceptable symptom state is defined as the highest level of symptom beyond which patients consider themselves well. [189] Patient acceptable symptom state has been used in musculoskeletal and rheumatic conditions and shown to provide information about a patient's improvement exceeding the minimally clinically important improvement. [189-191] Participants will be asked to answer yes or no to a structured question: "*Is your **current** condition satisfactory, when you take your general functioning and your current pain into consideration?*"

Perception of success and willingness to recommend the treatment (6 & 12 weeks)

Participants will be asked to answer yes or no to two questions in regard to their perception of the success of their treatment

1. *"Overall, would you agree that the treatment you have received has been successful for your knee pain?"*
2. *"If a good friend has the same knee pain as you, would you recommend the same treatment you received?"*

Patient satisfaction (6 & 12 weeks)

Participants will be asked two questions in regard to the satisfaction of their treatment with a selection of five possible responses (very satisfied, somewhat satisfied, neither satisfied not dissatisfied, somewhat dissatisfied, very dissatisfied). The questions will be:

1. *"Over the course of treatment for your knee pain, how satisfied were you with your overall treatment?"*
2. *"If you had to live with the symptoms you have right now, how would you feel about it?"*

Numerical pain rating scale (0, 6 & 12 weeks)

The numerical pain rating scale (NPRS) can be a verbal or visual scale to grade the intensity of pain experienced by the participant and is recommended for research purposes. [192] Participants will be asked to indicate a score that best represents the intensity of their knee pain on an 11-

point scale where 0 represents no pain and 10 represents worst pain imaginable. Participants will provide two ratings; their average pain over the previous seven days and their worst pain over the previous seven days. An improvement of ≥ 2 on the NPRS indicates clinically meaningful change. [193, 194]

Patient specific functional scale (0, 6 & 12 weeks)
Participants will self-select up to five tasks or activities that are impaired due to their symptoms. Participants will then rate the level of impairment of each task/activity on an 11-point scale from 0 ("unable to perform activity") to 10 ("able to perform activity at same level as before the injury or problem"). The patient specific functional scale is a reliable and valid tool that is sensitive to changes in patient's symptoms. [195] [196] It has been reported that a change of three or more on an individual patient-nominated activity indicates a true change in functional capacity. [196]

Kujala Patellofemoral Scale (0, 6 & 12 weeks)
This questionnaire comprises 13 items designed specifically for PFP. Categories within the questionnaire cover a range of knee functions under varying loads. Participants select a response to each of the 13 items that best depicts their symptoms. Each item is weighted separately and then summed overall, with the highest possible score of 100 points representing pain free full function and 0 representing total incapacity. This questionnaire has been recommended for knee pain because it is reliable and sensitive to changes in symptoms. [197-199] A change of 10 points is considered as the minimum clinically important difference [198] in patients with PFP.

Knee injury and osteoarthritis outcome scale (KOOS) (0, 6 & 12 weeks)
This questionnaire is comprised of five separate subscales that assess the patient's opinion of their knee and symptoms. The subscales cover pain, symptoms, activities of daily living function, sporting and recreation function and quality of life. Each subscale consists of standardized answers (five Likert boxes), with each question scored 0-4 separately. The questionnaire will be scored according to the 2012 KOOS scoring manual. Participants select a

response to each question in each subscale that best depicts their symptoms. Each subscale will be normalised to a scale of 0-100 (0 = extreme problems, 100= no problems). A change of 8-10 points is suggested to represent a clinically significant change in symptoms. [200]

Hospital anxiety and depression scale (HADS) (0, 6 & 12 weeks)
This 14-item scale will be used to investigate emotional states of those with PFP. It has been found to be a reliable instrument for detection of anxiety and depression in an outpatient setting and a valid indicator of severity. [201, 202] Participants are required to select the best of four responses to questions pertaining to either anxiety or depression (seven questions each), which are scored from 0–3. The scores for the anxiety and depression questions are summed separately to give total scores for each component, where 0–7 represents no anxiety or depression, 8–10 is borderline, and 11–21 indicates the presence of an anxious or depressive state.

Euro-Qol™ (EQ-5D 3L version) (0, 6 & 12 weeks)
This validated questionnaire is used as a measure of health outcome and provides a simple descriptive profile and a single index value for health status. It compromises of five domains about mobility, usual activities, selfcare, pain and discomfort, and anxiety or depression. [203] Participants will be asked to rate their impairment on each domain (none, moderate or severe problems). Each health state is scored (1-3) and transformed into an index score. This score is used to derive quality-adjusted life years as an outcome measure and is one of the most commonly used economic evaluations used to inform decisions in health care. [204] The participant scores their overall health on a 0 to 100 scale, where 100 represents complete health and well-being. [203]

Tampa scale for kinesophobia (TSK) (0, 6 & 12 weeks)
The TSK is a 17-item questionnaire aimed at assessing fear of reinjury due to physical movement. [205] Each item is scored on a 4-point Likert scale that ranges from strongly disagree (1) to strongly agree (4). The inverse scores from items 4, 8, 12, and 16 are used to calculate the total score. Total TSK

scores range between 17 and 68, with higher scores suggestive of higher levels of fear of physical movement and vulnerability.

Pain Catastrophising Scale (PCS) (0, 6 & 12 weeks)
The PCS is a 13-item valid and reliable questionnaire that evaluates a participant's level of pain catastrophic thinking, and classifying this into levels of rumination, magnification and helplessness. [206] Participants are asked to reflect on past painful experiences, and to indicate the degree to which they experienced certain thoughts or feelings when experiencing pain, on 5-point scales from not at all (0) to all the time (4). The PCS yields a total score and three subscale scores for rumination, magnification and helplessness respectively. The total score ranges from 0 – 52, with higher scores indicating higher levels of pain catastrophization.

Functional tests: Step down, step up and squat (0, 6 & 12 weeks)
These functional tests are commonly reported as aggravating activities by patients with PFP because they load the patellofemoral joint and have been previously used in clinical trials. [92] Repeated step testing will be performed on a single 25 cm step in time with a metronome set at 96 beats per minute (e.g., stepping up/ down on each beat). Repeated squats will be performed in time with a metronome set to 96 beats per minutes feet shoulder width apart, squatting down in two beats, until the participant can touch both lateral malleoli with their fingers, and standing up over two beats. Activities will be stopped when either a) onset of symptoms occurs, or b) there is an increase in existing symptoms or c) when a maximum of 25 repetitions has been reached without the onset of pain.

5.3.3 Physical measurements

An examiner at each trial site, who is blinded to treatment allocation and midfoot width mobility stratification, will collect self-reported questionnaires (i.e., pain scores, Kujala Patellofemoral Scale, etc.), physical measurements and demographic data prior to commencement of the intervention and at follow-up. Physical measurements will include foot posture measurements,

ankle, hip and first metatarsophalangeal range of motion measurements and maximal isometric hip strength testing. These measures will be used in post-hoc analyses of prognostication and identification of other possible candidates for treatment effect modifiers.

Midfoot width and height mobility:
Measurement of the width and height at the midfoot (i.e. 50% of total foot length) has been previously described and demonstrated to be reliable. [76] In brief, these measurements are performed on a foot measurement platform that can standardize foot position by placing heels 15.24 cm apart with the first metatarsal heads against a guide with body weight equally distributed on both feet.

Midfoot width in weight bearing is measured using a digital caliper with extend arms, which are positioned perpendicular to the sole of foot and adjacent to lateral and medial aspect of the foot at the 50% length (Figure 5.6A). This is repeated in non-weight bearing with the patient seated on a height adjustable table and legs hanging freely (Figure 5.6B). Midfoot height (dorsal arch height) measurements at 50% of the total foot length in weight bearing (bipedal stance) and minimal weight bearing postures will also be taken (Figure 5.7). [76] To measure the arch height in a minimal weight bearing posture, the participant sits on a height adjustable plinth with their feet hanging freely. The assessment platform is positioned under both feet and the plinth is lowered until the point of the heel being assessed just contacts the platform. The vertical height of the arch is then measured.

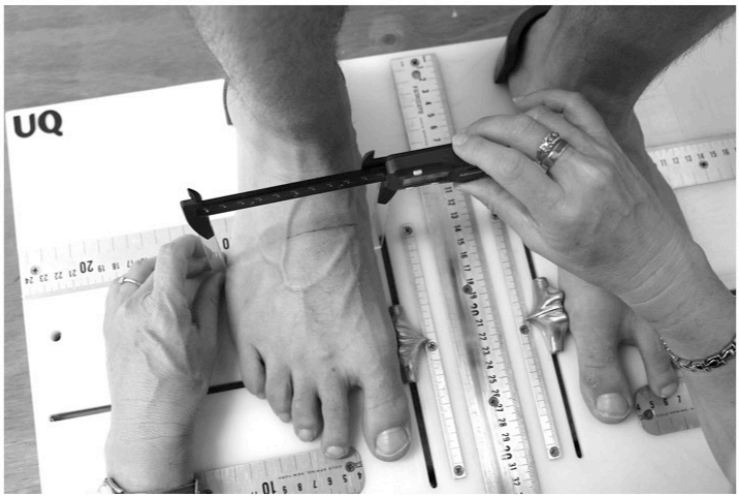

Figure 5.6A Midfoot width measured in weight bearing

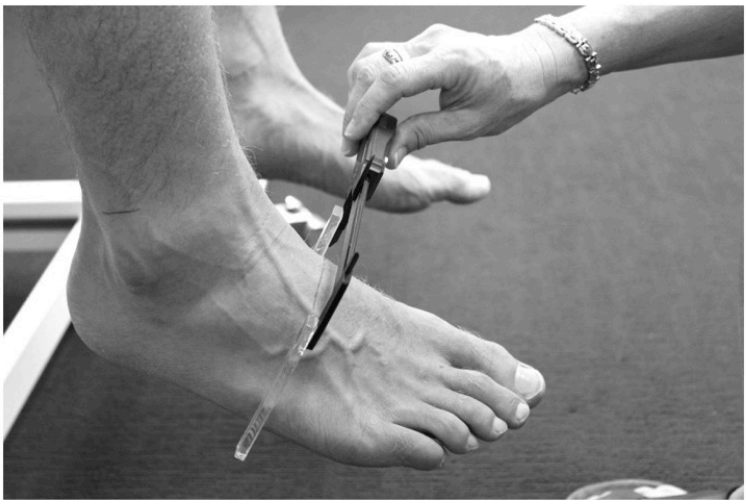

Figure 5.6B Midfoot width measured in non-weight bearing

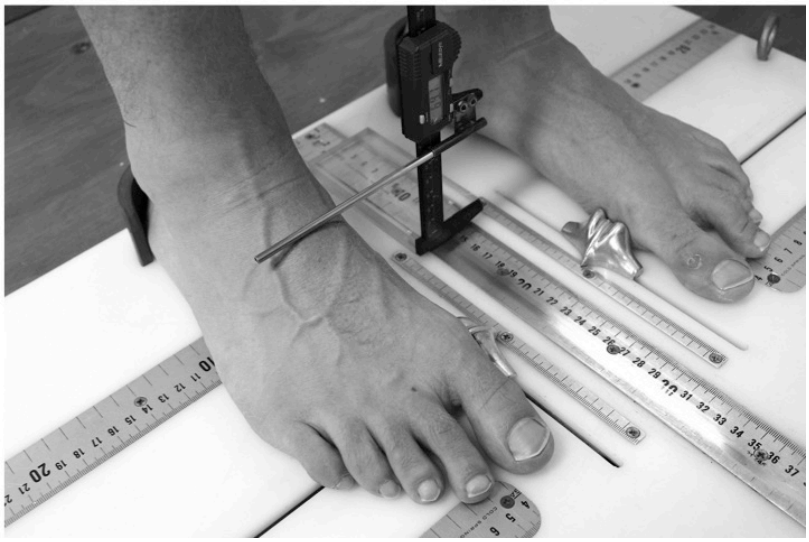

Figure 5.7 Midfoot arch height measurement

The height and width measurements of each foot in weight bearing and non (or minimal) weight bearing will be recorded separately three times and then averaged to give a single value for the analysis. The change in midfoot height and width is calculated by subtracting the measures in the two weight bearing conditions.

Navicular drop:
The participant stands barefoot with equal weight on both feet. The navicular tuberosity will be identified using palpation and the most prominent point marked using a water-soluble ink pen. With the patient standing in subtalar joint neutral position (defined by palpation of the talus in the mortise and scored '0' on the foot posture index [207]), the height of the navicular tuberosity will be measured using a clear angle ruler. The participant is instructed to relax their feet and the navicular tuberosity height is re-measured. The difference in height measurements between a subtalar joint neutral and relaxed foot position will be calculated to determine the amount of navicular drop. [74, 152, 208, 209]

The Foot Posture Index (FPI-6)
Relaxed foot posture will be assessed using the FPI-6, which consists of six criteria: 1) talar head palpation, 2) curves above and below the lateral malleoli, 3) inversion/eversion of the calcaneus, 4) bulge in the region of the talonavicular joint, 5) congruence of the medial longitudinal arch and 6) abduction/adduction of the forefoot on the rearfoot [207]. Each criterion is examined and scored on a 5-point scale between –2 and +2, which are then totaled to categorize the foot as being highly pronated, pronated, normal, supinated, or highly supinated. [207] Intrarater reliability has been reported to be very good with interrater reliability being only moderate between three raters. [210] [211]

Weight bearing bent knee ankle dorsiflexion (Lunge Ankle Dorsiflexion Device - LAD)

Bent knee ankle dorsiflexion will be measured using a bespoke device, the Lunge Ankle Dorsiflexion measurement device (LAD). The LAD device has been previously described. [212] In brief, the LAD was designed with only one degree of freedom of motion in the sagittal plane. The patient's foot is aligned in a sagittal plane with a line that bisects the 2nd and 3rd phalanges and the midline of the posterior calcaneus. Whilst maintaining the toe in light contact with the front of the reference block, the participant slowly lunges forward, with the knee in contact with a mobile measurement indicator. The therapist focuses on ensuring that the three points remain in the sagittal plane by watching for heel drift (usually medially) and heel lift, which indicates that full dorsiflexion has been reached. The linear measurement of horizontal distance between anterior knee and the fixed reference block at the longest toe is read from a ruler (mm).

Hip Strength

Strength of the hip abductors, adductors and external rotators will be measured at baseline, 6 and 12 weeks as dysfunction in these muscle groups has been identified as a common impairment within the PFP population, [213-215] and will be used in post hoc exploratory prognostic analyses. Force produced during a maximal voluntary isometric contraction (MVIC) will be measured with a hand held dynamometer (Nicholas, Lafayette, IN47903, USA) Measurements will take place in supine to minimize the effect of gravity during testing and compensatory contractions. [216] Each participant will complete two practice contractions (50% MVIC followed by 100% MVIC) followed by three experimental MVICs where the participant will be asked to contract maximally for 5 s. Participants will have a 30 s rest between each contraction. The peak force (Newtons) will be recorded for each contraction and converted to torque (using the distance between the point or rotation and placement of dynamometer as the lever arm) standardized to body mass (Nm/kg). Hip abductor and hip adductor muscle strength will be tested using a dynamometer 5 cm proximal to the lateral and medial malleolus respectively, and stabilised by a rigid belt. The test leg will be extended in 0° abduction and 0° flexion, with the non-test hip and knee flexed (Figure 5.8). Hip external rotation will be measured in supine with the hips in 30° of flexion with the

dynamometer 5 cm proximal to the medial malleolus, stabilised in a solid bracket, fixated to the testing device (Figure 5.9). This testing position was chosen because it: corresponds to biomechanical data on muscular actions of the external rotators in various degrees of hip flexion (i.e., piriformis being an external rotator muscle at 0° flexion and functionally switch rotation action to internal rotation at >60° hip flexion); [217, 218] replicates the position of exercise in the hip intervention protocol [180]; and approximates the degrees of hip flexion relative to the pelvis during foot contact/ limb loading in the initial stance phase of gait. [219-221]

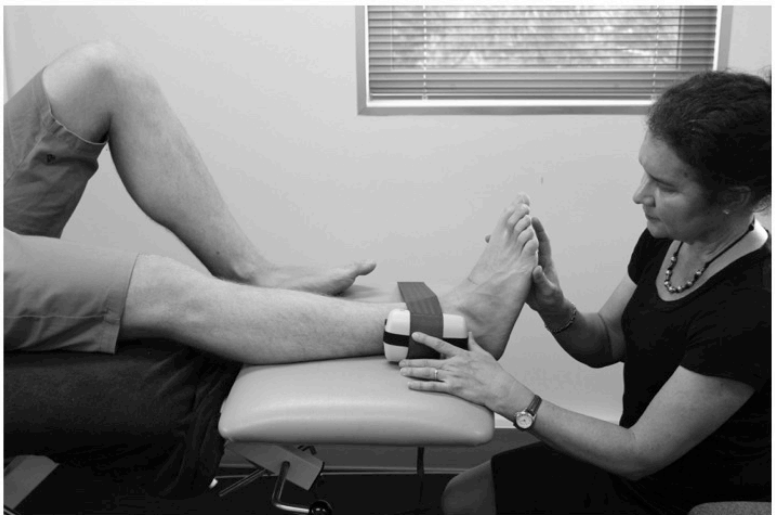

Figure 5.8 Hip abduction strength testing

Figure 5.9 Hip external rotation strength testing in 30° hip flexion

Limb length for the hip abductor and adductor measurements, will be measured from the participant's anterior superior iliac spine to a mark 5 cm

proximal from the lateral and medial malleolus, respectively. For hip external rotation, distance will be measured from the medial joint line to a mark 5 cm proximal to the medial malleoli. Participants will be instructed to hold the sides of the plinth for stabilization and receive a standard verbal encouragement with consistent level of volume and enthusiasm.

Hip Range of Motion

Passive hip internal and external rotation range of motion will be measured in upright sitting, arms crossed, knees flexed to 90° over the edge of the plinth and the non-test leg stabilised by a rigid belt. The hip will be passively rotated to the point of resistance with no compensatory pelvic motion. Range will be measured using a plurimeter placed 5 cm proximal to the tip of the tibial malleoli on the medial border of the tibia for external rotation, and 5 cm proximal to the tip of the lateral malleoli to measure internal rotation (Figure 5.10).

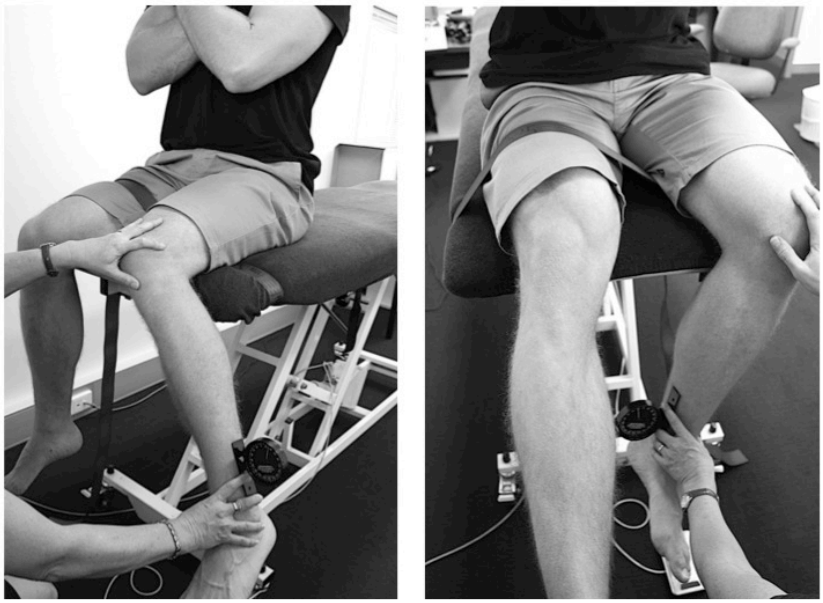

Figure 5.10 Hip internal and external range of motion measuring

5.4 Demographic and other information

Other baseline measurements to be collected will include age, sex, height, weight, body mass index (BMI), unilateral and bilateral symptoms, duration of

symptoms, use of medications, physical activity levels, joint mobility using the Beighton and Horan Joint Mobility Index [207, 210] and reported crepitus during daily living activities.

5.5 Participant timeline

Volunteers will be recruited into the study through a structured process involving a comprehensive advertising campaign followed by verbal and physical examination screening of eligibility by a registered physiotherapist. Participants who meet the eligibility criteria will be offered enrolment into the study, complete consent forms then undergo baseline measurements and randomly allocated to an intervention (Figure 5.11). Participants with bilateral symptoms will nominate their most symptomatic knee to be used in analysis. The timeline for events (e.g., outcome measure timepoints and close out) are shown in appendix 10.

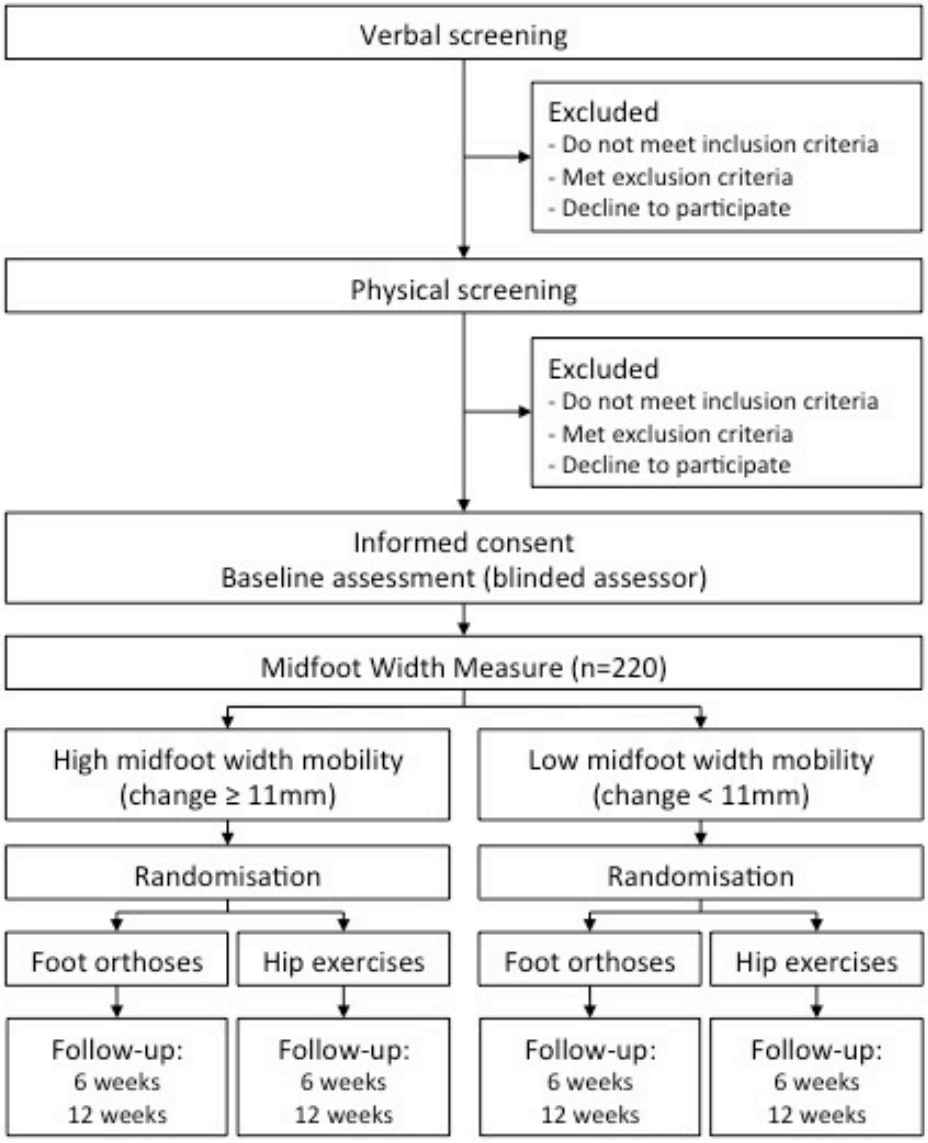

Figure 5.11 Proposed flowchart of participants through trial (CONSORT)

5.6 Sample size

Sample size was based on proportions of patients rating themselves as "better" or "much better" on the Global Rating of Change (GROC) score in the foot orthoses and hip exercise treatment groups. The primary aim of the study is to determine whether midfoot width mobility is a treatment effect modifier for foot orthoses when compared to progressive resisted hip exercises. This requires testing for an interaction between midfoot width mobility, dichotomised as high (≥11 mm) or low (<11 mm), and treatment group. Based on previous findings, which indicated a strong effect of foot orthoses in

patients with PFP who had a midfoot mobility ≥11mm, [142] we wanted to be able to detect an interaction effect of 50 percentage points. This means that the difference between the foot orthoses and hip exercise groups in the proportions of participants who are improved at 12 weeks will be 50 percentage points higher (favoring foot orthoses) in participants with high midfoot width mobility than in those with low midfoot width mobility. A sample of 30 participants (15 per group) who have high midfoot width mobility provides 80% power using a two-sided significance level of 0.05 to detect a difference between the proportions of participants with improvement of 30% in the hip exercises group compared to 80% in the foot orthoses group. Assuming that 20% of participants will be in the high midfoot width mobility group, we inflated the sample size to 188 participants (94 per group) to ensure adequate power to detect this interaction effect of 50 percentage points. [222] To allow loss to follow-up of up to 15%, the final sample size was 220 participants (110 per group).

5.7 Recruitment

A comprehensive recruitment strategy, successfully utilized in previous clinical trials [95, 142] will be used in regions of Brisbane, Australia and Aalborg, Denmark. The recruitment strategy involves paid advertisements in local and regional newspapers, supplemented by advertisements on university, gymnasium and community websites, online social media, electronic and paper noticeboards within the catchment area at regular intervals during the recruitment period. Further referrals may come from physiotherapists involved in the study and general practitioners, through the provision of information and advertising packages at their practices. Volunteers who express interest in participating will be screened through the previously described two-stage screening process to determine eligibility.

5.8 Allocation

Once informed consent and baseline measurements have been obtained, each participant will be randomly allocated to one of two intervention groups

via concealed allocation and assigned a participant code. An independent off-site body will generate a randomization schedule for all participants at both the Australian and Danish sites. The randomization schedule will be generated by computer and allocate on a 1:1 basis to each of the treatments with stratification on the midfoot width mobility measure.

5.9 Data collection and management

All data will be collected in paper format and subsequently entered into an electronic study database. A number of strategies have been employed to ensure fidelity of data entry, such as entries will be screened at random by a second investigator to ensure entry is correct. The study database has been developed in a regulatory approved electronic medical records platform (OpenClinica®) by the Clinical Trials and Biostatistics Unit. This database will be used to comprehensively collect all safety and efficacy related data, along with additional information for possible exploratory analyses. The database development, testing, validation and management strictly follow the regulatory guidelines for clinical trial data management. All participant data will be analysed on an intention-to-treat basis. Once a participant is enrolled, every reasonable effort will be made through paper and electronic media to maintain contact and follow the participant for the duration of the trial period. It is anticipated that the rate of loss-to-follow-up will be at most 10%. Participants will be informed they may withdraw from the study at any time, for any reason without any consequences. Participants may be withdrawn from the study in order to protect their safety (e.g., the foot orthoses intervention is unable to be made comfortable to wear) after consulting with the senior investigator (BV)

5.10 Statistical Methods

A biostatistician who is blind to treatment group allocation and midfoot width mobility will conduct analysis. All participants who have missing data and did not fully comply with the treatment protocol will be included in analyses. Demographic characteristics will be inspected to assess baseline comparability of treatment groups and compare those participants who remain

in the study and those who withdraw. If the proportion of missing data for endpoints exceeds 5%, multiple imputation methodology will be applied. To test the hypothesis of interaction between randomised group and foot mobility, terms for randomised group and foot mobility group, together with an interaction between the two, will be included in models. For the primary outcome (dichotomised GROC) and other binary secondary outcomes, binary regression models with a logarithmic link will be fit. For other outcomes, linear regression models will be fitted, and assumptions will be assessed using standard diagnostic plots. To test for an overall treatment effect, regression models for outcomes will include terms for randomised group and foot mobility (as foot mobility is a stratifying variable).

We will also undertake a secondary analysis to further explore the relationship between midfoot width mobility and the outcome, whereby midfoot width mobility will be included in the model as a continuous variable, together with an interaction term with randomised group. Relationships will be investigated using fractional polynomials. [223] We elected to perform this secondary analysis because previous studies that identified midfoot width mobility as a potential predictor of outcome after foot orthoses used data-dependent techniques in relatively small samples to establish a cut-off value for “high” midfoot width mobility. The concern with establishing cut-off values with data-dependent techniques is that, while the cut-off value may have been “optimal” for the original sample, this same cut-off value may not be optimal in the larger population. [134, 224]

5.11 Monitoring

A safety committee will be established when the need arises. It is not anticipated that a safety committee will need to convene much or at all, because the treatments have been previously studied with no reported serious adverse events, are common to everyday practice for this condition and there is low perceived risk to participants. Participants and the treating physiotherapists are instructed to report any adverse effects. Adverse effects reported by participants or documented by the physiotherapists during the

treatment phases of the trial will be managed and reported (to ethics and relevant institutional unit) as per appropriate policies and procedures at the relevant site.

5.12 Adverse events

Participants will be instructed to report any adverse events to the treating physiotherapists, and/or the trial investigators. Adverse effects reported by participants or treating physiotherapists during the treatment phases of the trial will be recorded, managed and reported (to ethics and relevant institutional unit) as per appropriate policies and procedures at the relevant site immediately. Appropriate follow up health and medical care will be recommended should it be required for any adverse event. All cases of adverse events will be followed up to ensure resolution.

5.13 Discussion

The primary aim of this trial is to determine whether midfoot width mobility is a treatment effect modifier for foot orthoses compared to hip exercises. The ability to confidently predict a preferential response to any physical treatment for PFP, such as foot orthoses, has proven elusive to date and has at times been somewhat contentious. [164, 172, 225] Follow up analyses of previous work in our research unit [95, 142] on two different samples of participants with PFP has revealed that a reliable and easily administered measure of midfoot width mobility might predict those who will report a successful outcome after receiving foot orthoses. For example, a randomized clinical trial reported a success rate of 78% (7 of 9 cases) with foot orthoses in patients with PFP who had high midfoot width mobility compared to only a 20% success rate (2 of 10 cases) in those who had low midfoot width mobility. [142] Methods for defining a successful outcome and categorizing midfoot width mobility were similar to those being used in this current protocol. A successful outcome was unlikely to be related to natural history because only 5% (1/20) of the participants in the wait-and-see group had a successful outcome. A significant limitation of these data is that single group analyses

were used. [172] Absence of a comparison group in the analysis means it is not possible to differentiate predictors of the general course of the condition regardless of treatment (i.e. prognostic factors) from predictors of outcome to a specific treatment (i.e. treatment effect modifiers). [125]

The design of the FOHX trial allows for robust testing of midfoot width mobility as a treatment effect modifier for foot orthoses compared to progressive resisted hip exercises in individuals who have PFP. It will first test if midfoot width mobility of ≥11 mm, which was defined on the basis of our previous work [142] will predict a preferential response to foot orthoses versus hip exercises. Given that this previous work was based on small sample sizes, we will also conduct a secondary analysis, in which midfoot width mobility will be treated as a continuous level measure to ensure that we have fully evaluated the hypothesis that midfoot width mobility is a treatment effect modifier. If the hypothesis is confirmed, then midfoot width mobility could help clinicians tailor treatment for patients who have PFP.

Apart from our previous research suggesting that midfoot width mobility may be predictive of a success following treatment with foot orthoses, there is *prima facie* evidence to support that foot orthoses will be more successful when the patient has a mobile foot. Distal to the knee, abnormal foot pronation has been hypothesised to induce adverse lower limb kinematic motions, which are associated with excessive load at the patellofemoral joint [226, 227]. Foot orthoses have a mechanical effect on foot pronation [96], so it is plausible that foot orthoses might have a mechanical effect on the patellofemoral joint [228-230] Interestingly, a modeling study of foot orthoses on patellofemoral joint load indicated that while there was a significant effect, there was considerable inter-individual variation in the response [228] which further underpins the need to determine whether midfoot width mobility is a treatment effect modifier for foot orthoses. There is also a growing body of evidence that supports the efficacy of foot orthoses for people with PFP [92, 142, 231] but these clinical trials did not specifically examine if the foot orthoses were most useful in patients with mobile feet.

The head-to-head comparison between treatments that target regions distal and proximal to the patellofemoral joint has not been done, making the clinical trial outlined in this protocol novel. Proximal to the knee, neuromuscular dysfunctions at the hip and pelvis have been hypothesised to impact upon the patellofemoral joint kinematics. [227, 232, 233] Evidence suggests weakness of the postero-lateral hip musculature in primarily the hip abductor and external rotator muscle groups as a common impairment in those with PFP. [213, 214, 234, 235] Clinical trials that have compared isolated postero-lateral hip musculature exercises to no exercises or as part of a rehabilitative program have reported beneficial outcomes for patients who have PFP. [94, 98, 102, 105, 168, 180] This evidence supports exercises targeting the posterolateral hip musculature as a viable treatment option for those with PFP, and an appropriate comparator treatment option in this trial.

This trial protocol aims to minimise potential biases, optimise methodological quality and report pragmatic clinical findings by addressing key methodological limitations of previous studies that have aimed to investigate treatment effect modifiers for PFP. Key strengths of the trial include: (i) randomization of participants according to a schedule that will be generated by an independent body, (ii) enrollment based on pre-determined criteria by registered physiotherapists and independent of treatment allocation, (iii) participant stratification into pre-determined subgroups based on preliminary data, (iv) blinding of participants, assessors and therapists to critical information (e.g., trial hypothesis, stratification status, treatment allocation, baseline and follow-up outcome measures), (v) head-to-head comparison of two efficacious treatments for PFP, (vi) sufficiently powered sample size to detect a significant and substantial effect of midfoot width mobility as a treatment effect modifier for foot orthoses, (vii) blinded analysis using a pre-determined statistical analysis plan, and (viii) conducting a pre-specified secondary analysis to further evaluate midfoot width mobility as a treatment effect modifier for foot orthoses when it is a continuous variable. The findings from this trial will be reported in accordance to the CONSORT statement [174] and widely disseminated.

5.14 Conclusion

In conclusion, this trial sets out to address two contentious issues that confront clinicians who treat patients with PFP. One looks to assist the clinician in determining who is likely to have a preferential response to foot orthoses treatment, compared to hip exercises, by testing if a simple, clinically applicable measurement of midfoot width mobility can be used to predict a better outcome. The second is to assist in optimising the management of PFP by comparing hip exercises to the use of foot orthoses.

5.15 Declarations

5.15.1 Ethical approval

Ethical approval is granted by the University of Queensland Medical Research Ethics Committee (2013000981) (appendix 11) and by the local ethics committee in the North Denmark Region (N-20140022). All participants will provided with information (appendix 12) and give informed consent (appendix 13) prior to being enrolled in the study,

5.15.2 Competing interests

Vicenzino reports grants from Commonwealth of Australia National Health and Medical Research Council and from Vasyli International for this research. Vicenzino and McPoil are voluntary (non-compensated) members by invitation on the Vasyli Think Tank.

5.15.3 Funding

The trial is funded by a National Health Medical Research Council program grant (Ref no: 631717). Vionic Group LLC contributed funds to enable the conduct of the research in an international site (Denmark) as well as donated the foot orthoses and contoured sandals for the trial but where not involved in the study design, recruitment, data collection, analysis or write-up of the

manuscript. Matthews is supported by an Australian Postgraduate Award Scholarship.

5.15.4 Authors Contributions

Vicenzino attained the project funding. All authors contributed to the conception and design of the trial protocol. All authors contributed to the manuscript and have read and approved the final manuscript.

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M. Matthews (Candidate)	Conception and design (30%), Analysis and interpretation (30%), Drafting and production (30%)
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Chapter 6. Management of patellofemoral pain: A randomised clinical trial comparing foot orthoses versus hip exercises to determine if greater foot mobility is associated with a better outcome to foot orthoses

The results from the systematic review (chapter 4) provided preliminary evidence for the research aims and design of the randomised clinical trial (chapter 5). This chapter covers the implementation and results of the trial to address the previously mentioned aims. Those aims were to: (i) evaluate midfoot width mobility as a treatment effect modifier for foot orthoses treatment, when compared to hip exercises, and (ii) compare the treatment superiority between foot orthoses and hip exercises at 12 weeks, irrespective of midfoot mobility.

6.1 Introduction

Persistent pain affects approximately 126 million people in the United States, costs over $560 billion annually and severely affects the quality of life of the individual [236, 237]. One such recalcitrant pain condition is patellofemoral pain (PFP). The prevalence of PFP is between 23 and 29% in the population [238]. It is associated with a high risk of long-term pain, as one in two will continue to suffer after 5-8 years [239]. Evidence suggests PFP could be one of the earliest manifestations of patellofemoral joint osteoarthritis [240]. The aetiology of PFP remains unknown, but is considered multifactorial with a combination of underlying biomechanical, neuromuscular and/or psychological contributors [44, 241, 242]. Patellofemoral pain is a clinical diagnosis based on a typical presentation of pain around or behind the patella during daily activities such as negotiating stairs, squatting or sitting [4].

Systematic reviews [243, 244] and international consensus [181] recommend foot orthoses [92, 245] and hip exercises [94, 180] in the management of

PFP, yet the quandary is how to best match these treatments to individual patients to ensure optimal outcomes [86]. Evidence suggests that greater mobility of the midfoot (defined as a change of 11mm or more in midfoot width when moving from non-weight bearing to weight bearing [76]), is associated with better outcomes following foot orthoses [95, 142]. Crucially, lack of a comparator treatment and potential over-fitting of models for outcomes may have created spurious findings, compromising their clinical applicability [125, 243]. Further investigation is needed to examine if a simple clinical measurement of the foot [76] can be used to determine which treatment, (e.g. foot orthoses or hip exercises) the patient will benefit from the most.

The aims of this trial were to: (i) evaluate if greater midfoot width mobility is associated with a better outcome following treatment with foot orthoses when compared to hip exercises, and (ii) compare the treatment effectiveness between foot orthoses and hip exercises at 12 weeks, irrespective of midfoot mobility, in the management those with PFP. The hypotheses were that (i) those with greater midfoot width mobility will have greater benefit with foot orthoses, compared to hip exercises, and (ii) those that receive hip exercises will report greater successful outcomes, than those who receive foot orthoses.

6.2 Methods

6.2.1 Study Design

A two-arm parallel, multi-centre randomised superiority clinical trial was conducted in a community setting in Brisbane, Australia, and hospital outpatient department in Aalborg, Denmark. The trial was prospectively registered (ACTRN12614000260628) and the protocol published elsewhere [246]. The trial adhered to the principles of the Declaration of Helsinki [247] with ethical approval granted by the University of Queensland Medical Research Ethics Committee (2013000981) (appendix 11) and the ethics committee in the North Denmark Region (N-20140022). The trial was conducted in agreement with the registration and more specifically the published protocol [246], with the exception that the patient specific functional

scale and international physical activity questionnaire were not analyzed. The reporting of this clinical trial follows the CONSORT statement and TIDieR for describing interventions [174-176].

6.2.2 Participants

Volunteers from Brisbane, Australia and Aalborg, Denmark responded to advertisements or were referred by health care practitioners. Inclusion criteria were: age 18-40 years; insidious onset of anterior, retro or peri-patellar pain aggravated by at least two activities (e.g. stair ambulation, squatting, jogging/running); reported worst pain of at least 3 out of 10 on a numerical pain rating scale (10 representing worse pain imaginable) over the last 7 days; greater than six weeks' duration and tenderness on palpation of the patellar borders with reproduction of pain completing a step down or double leg squat. Participants were excluded if they reported traumatic onset of symptoms; concomitant injuries or pain from the hip, lumbar spine, or other knee structures that manifested with similar symptoms; patellar dislocation or instability; previous knee surgery; evidence of knee joint effusion; any foot condition that precluded use of foot orthoses; the use of anti-inflammatory drugs or corticosteroid medication; or previous treatment for PFP that included foot orthoses or hip exercises. Eligible participants were required to have comprehension of written and spoken English (Brisbane, Australia) or Danish (Aalborg, Denmark).

6.2.3 Stratification

Midfoot width mobility at baseline was defined as the difference between non-weight bearing and weight bearing measurements of the width of the participant's midfoot (defined as 50% of total foot length) [76]. This measurement is highly reliable (inter-rater ICC>0.83, intra-rater ICC >0.97) [76]. Stratification occurred using a pre-determined cutoff for midfoot width mobility of 11mm [95, 142]; those who presented with equal to, or greater than 11mm midfoot width mobility were defined as *'high mobility'* and those with less than 11mm as *'low mobility'* [246].

6.2.4 Randomisation and blinding

An independent off-site body generated a randomisation schedule by computer for all participants at both the Australian and Danish sites before trial initiation. They were sent to the two study sites and kept in a locked cabinet. Allocation to each treatment via sealed and opaque envelopes was done in a 1:1 ratio using random permuted blocks of sizes 8 to 16; with stratification by midfoot width mobility and site (Brisbane or Aalborg). A researcher determined eligibility and collected all baseline measurements, except midfoot width mobility status. A separate researcher, blind to all baseline information, measured each participant's midfoot width prior to allocation to one of the treatments. Randomisation occurred once participants were stratified on midfoot width mobility. A separate researcher communicated with the randomisation centre, trial participants, and physiotherapists and sites. The outcome assessor was blind to treatment allocation and midfoot width mobility status. Physiotherapists were kept blind to the participant's stratification and study hypothesis. Participants were informed the study involved two evidence-based treatments (foot orthoses or hip exercises) but were kept blind to midfoot width mobility status and study hypothesis.

6.2.5 Interventions

Registered physiotherapists completed pre-trial familiarisation sessions prior to applying both interventions [246]. Prescription of foot orthoses followed the protocol utilised in a previous randomised clinical trial [92].The hip exercises replicated those from a previous randomised clinical trial [180], and their efficacy has been supported in subsequent trials [94, 180].

6.2.5.1 Foot orthoses

Physiotherapists fitted commercially available prefabricated foot orthoses (Vionics International, Australia) and a pair of orthosis-like contoured sandals [179]. Physiotherapists followed a standardised fitting process that prioritised

comfort [178], with scope to review size, length and hardness [246]. Participants performed a home exercise program twice per day, consisting of calf stretches and anti-pronation foot exercises, aimed to improve foot awareness. No instructions were given with regards to continuing or discontinuing foot orthoses after the six sessions.

6.2.5.2 Hip exercises

The hip exercise protocol followed recommended guidelines [182]. Full details of the exercise protocol are previously published [246]. Progressive, resisted hip exercises were performed bilaterally and focused on the hip abductor, external rotator, and hip extensor muscle groups in side lying, supine and standing. Participants attended a physiotherapist-supervised one-on-one exercise session, three times per week for four weeks (12 sessions total). Physiotherapists selected predetermined lengths and grade of elasticated band at each session, which provided sufficient resistance for participants to achieve a maximum of 10 repetitions and perceived exertion of 5 to 7/10 (*Hard* to *Very hard*) per exercise. No instructions were given with regards to continuing or discontinuing hip exercises after the 12 sessions.

6.2.6 Primary outcome

The primary outcome measure was a 7-point Likert global rating of change (GROC) scale with categories of *much better*, *better*, *a little better, no change, a little worse, worse* or *much worse*. This measure has been previously utilised in similar trials on PFP [92, 93]. A successful outcome was a-priori defined as being *much better* or *better* at the primary time point of interest at 12 weeks.

6.2.7 Secondary outcomes

Secondary participant rated outcomes included the single assessment numeric evaluation (SANE) to rate the normality of their knee and their recovery out of 100% (100% being defined as having no problems at all and fully recovered respectively), patient acceptable symptom state (PASS) by answering if their current condition was satisfactory (yes/no), perception of

success by answering if they agreed their treatment was successful (yes/no) Kujala anterior knee pain scale, knee injury and osteoarthritis outcome scale (KOOS) , numerical rating of pain severity over the last seven days, hospital anxiety and depression scale , Euro-Qol™ (EQ-5D) , kinesiophobia , and pain catastrophising [246]. Physical performance tests included hip strength measures and a step up and step down task (25cm step), and squatting to a metronome set to 96 beats per minute [246].

6.2.8 Statistical analysis

Sample size calculations were based on proportions of patients in each group rating themselves as “much better” or “better” on the GROC score. The primary aim was to detect an interaction effect of 50 percentage points between midfoot mobility stratum and treatment group. This would mean that a treatment effect favoring foot orthoses (the difference between the foot orthoses and hip exercise groups in the proportions of participants who had successful outcomes at 12 weeks) was 50 percentage points higher in participants with *high mobility* than in those with *low mobility*. Assuming that: (i) in participants with *high mobility*, 80% would have successful outcomes with foot orthoses compared to 30% with hip exercises, (ii) 20% of participants would have *high mobility* (based on previous data [142]), and (iii) loss to follow-up would be up to 15%, 220 participants (110 per group) were required to have 80% power to detect the aforementioned interaction effect using a two-sided significance level of 0.05 [222, 246].

A statistical analysis plan was published prior to analysis and is available on request (https://espace.library.uq.edu.au/view/UQ:623536) (appendix 14). A biostatistician blinded to group allocation conducted all analyses. Characteristics of treatment groups were summarised as mean (standard deviation) for continuous variables and as count (percentage) for categorical variables. Data were analysed on an intention to treat basis using Stata v14.1 (StataCorp), including all randomised participants in their assigned group. Missing baseline variables were imputed using single mean imputation [248]. Estimates from 20 imputed datasets were combined using Rubin’s rules [249].

Datasets were imputed using chained equations, with predictive mean matching from the three nearest neighbours for continuous outcomes and logistic regression for binary outcomes. Imputation was done separately for each treatment arm, including a range of variables in the imputation models. For dichotomous outcomes, binary regression models with a logarithmic link were fitted using generalised estimating equations with an exchangeable working correlation matrix to account for the two follow-up measurements per participant (at 6 and 12 weeks). That is, baseline measures were not included as outcomes in the models. Models included a three-way interaction between treatment group, midfoot mobility stratum, and follow-up visit number (1 or 2), all two-way interactions, main effects, and a term for country (Australia or Denmark). The relative risk (RR) comparing treatment groups in each midfoot mobility by time stratum was calculated with 95% confidence intervals. To compare outcomes between treatment groups, similar models including only a main effect for midfoot mobility were fitted. Similar models for continuous outcomes were fitted, again using generalised estimating equations, additionally including a term for the baseline level of the outcome.

6.2.9 Patient involvement

Patient representatives were engaged in the development stages of the study. Prior to providing consent, all participants were informed of the study requirements, asked if they were willing to undergo their allocated intervention, and informed they will be emailed the final results.

6.3 Results

6.3.1 Participants

Between June 2014 to April 2017, 220 participants enrolled in the study. Two non-randomised cases were erroneously included and were removed when identified as such after close out, resulting in 218 participants (138 in Australia, 80 in Denmark). Forty-nine (22%) participants were classified as *high* mobility and 169 (78%) as *low* mobility (Figure 6.1). Treatment groups

and treatment-by-mobility groups were well matched at baseline (appendix 15). One participant in the *low* mobility foot orthoses group received hip exercises incorrectly. Participants who did not provide a GROC score were deemed to have been lost to follow-up. There were 197 (90%) participants followed up at 6 weeks and 192 (88%) at 12 weeks.

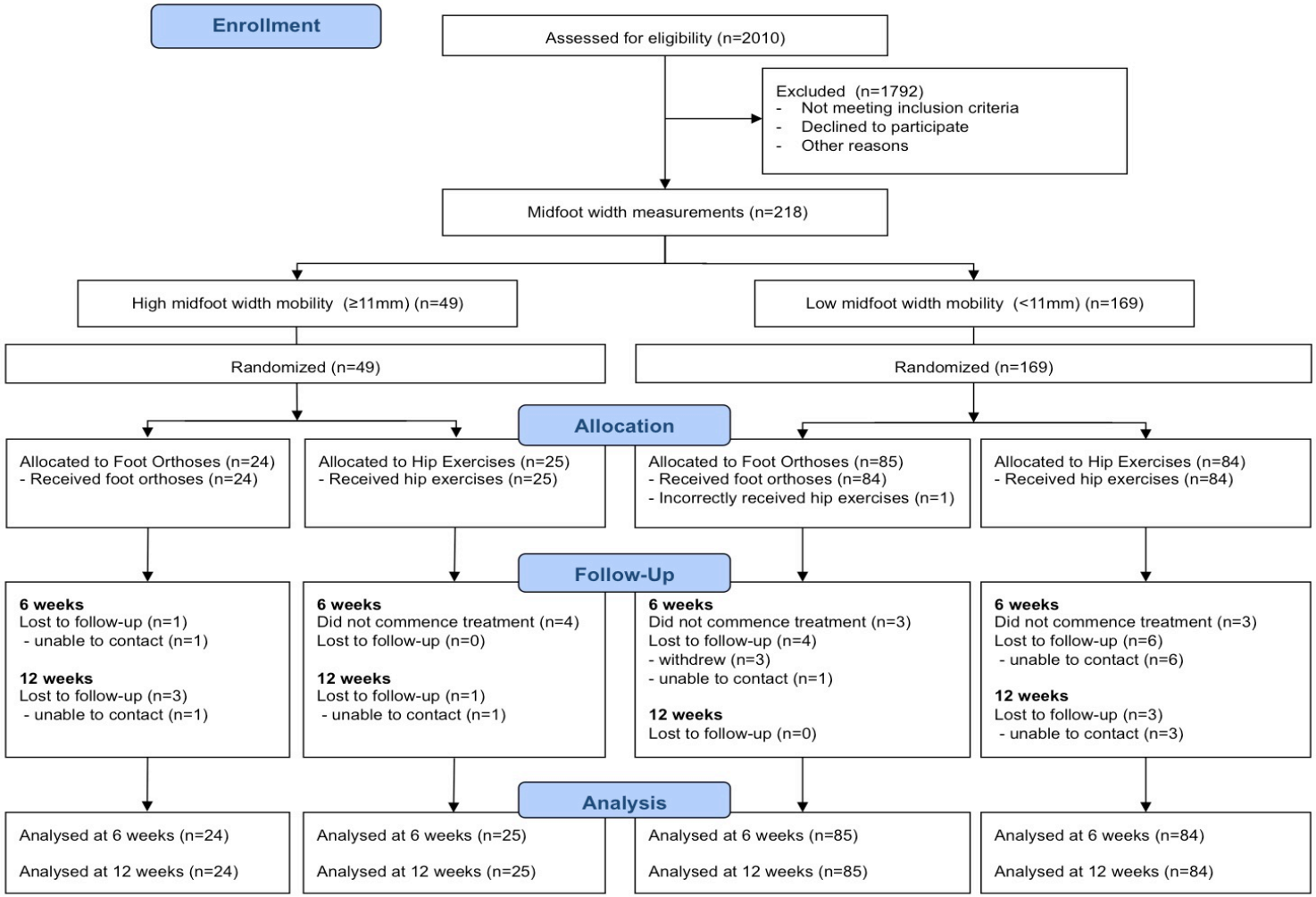


Figure 6.1 CONSORT Flow of participants through the study

6.3.2 Adherence:

Ten participants did not attend any of their allocated treatment sessions (n=3 foot orthoses, n=7 hip exercises). Participants allocated to foot orthoses attended on average 5.5/6 (92%, (1-6)) of the sessions and reported to have worn their foot orthoses for 74% of waking hours. Participants allocated to hip exercises attended on average 10.1/12 (84%, (1-12)) of their sessions.

6.3.3 Effect of midfoot width on success rates

There was no difference in success rates following foot orthoses or hip exercises in either the *high* (29% v 45% respectively) or *low* midfoot mobility (53% v 51% respectively) strata at 12 weeks (interaction *P*=0.19) (Figure 6.2, Table 6.1). A secondary analysis including midfoot width mobility as a continuous interval measure showed similar results (P-value 0.66, Appendix 16). There was no evidence of any significant interactions between treatments and midfoot mobility strata in any of the secondary outcome measures (Appendix 16).

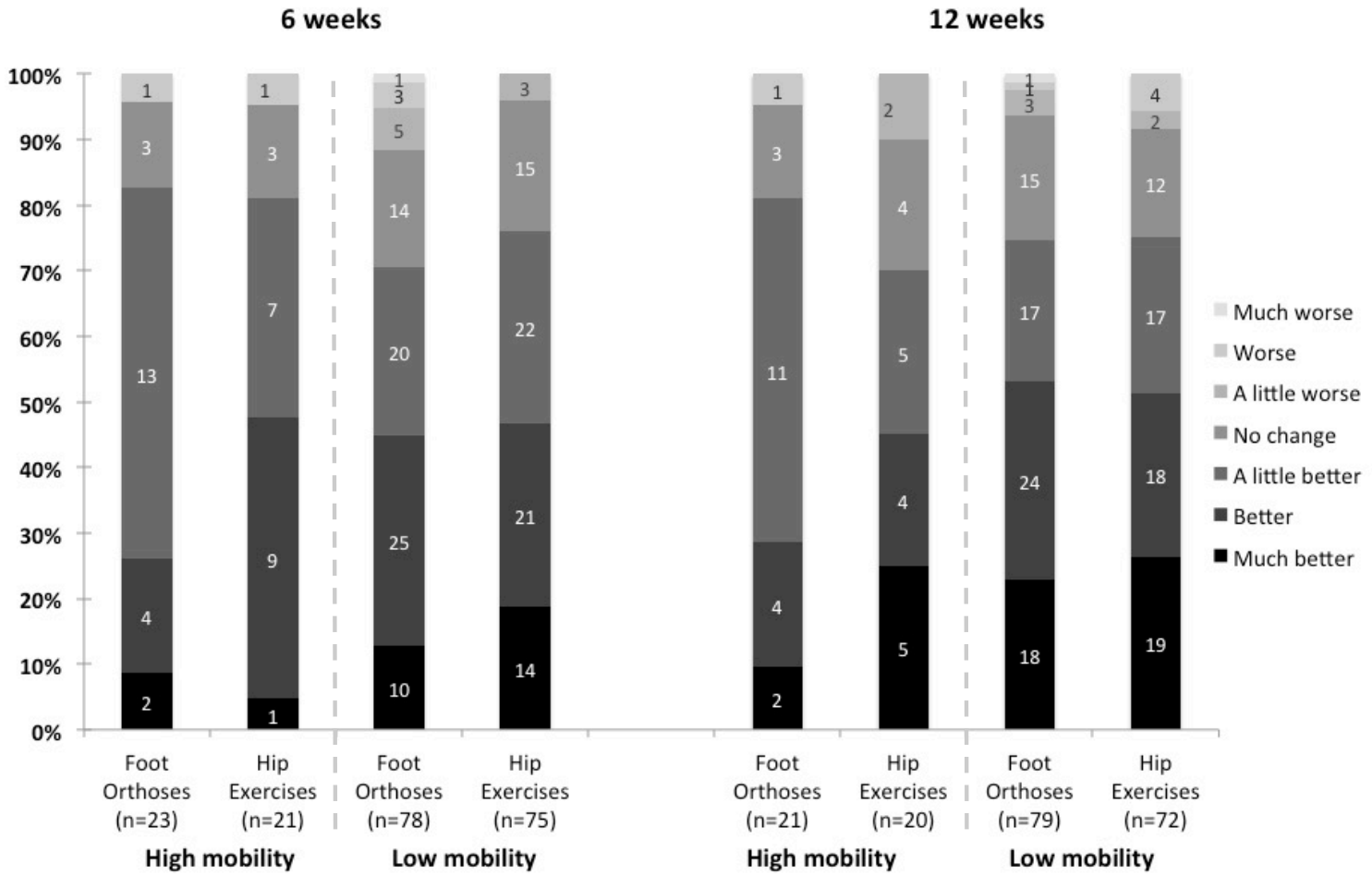


Figure 6.2 Percentage and number of participants rating perceived global change across categories from *much better* to *much worse*

Table 6.1 Treatment outcomes for hip exercises versus foot orthoses at 12 weeks, grouped according to midfoot width mobility stratification (treatment by foot mobility strata interaction p value = 0.19).

Midfoot Width Mobility	Hip Exercises (successful[+]/total (%))*	Foot orthoses (successful[+]/total (%))*	Foot orthoses vs Hip exercises^	
			Relative Risk (95% CI)	*P*-value
High (≥11 mm)	9/20 (45.00)	6/21 (28.57)	0.58 (0.26, 1.32)	0.20
Low (<11 mm)	37/72 (51.39)	42/79 (53.16)	1.02 (0.76, 1.36)	0.91
All	46/92 (50.00)	48/100 (48.00)	0.94 (0.72, 1.24)	0.67

[+] successful defined as *much better* or *better* on GROC, * frequency counts are complete-cases, ^ point estimates (Relative Risk) are based on multiply imputed data

6.3.4 Foot orthoses versus hip exercises

There was no difference in success rates between patients randomised to foot orthoses (48%) or hip exercises (50%) (RR 0.94, 95% CI (0.72 to 1.24)) Table 6.1). Although there appeared to be small p-values favoring hip exercises versus foot orthoses at 12 weeks on three KOOS subscales (symptoms (75.8 vs. 71.7, coefficient -2.92 (-5.52 to -0.32), p=0.028), pain (80.7 vs. 76.4, coefficient -4.09 (-7.63 to -0.55), p=0.023) and daily living (88.6 vs. 84.9, coefficient -3.37 (-6.54 to -0.20), p=0.037)), the clinical significance of these findings are questionable. There was no evidence of any differences between groups with respect to the other 22 secondary outcome measures (Appendix 17).

6.3.5 Co-interventions

Two participants reported undertaking additional treatments. One participant from the low mobility-foot orthoses group commenced yoga between the 6 and 12-week follow-up sessions, and another used knee wraps while exercising with heavy weights.

6.3.6 Adverse events

Fourteen participants allocated to foot orthoses (14/109, 13%) reported temporary toe and/or foot discomfort (n=7) or rubbing/ blistering (n=7) of the skin. Five participants allocated to hip exercises (5/109, 5%) reported increased discomfort in the hip region after exercises. No adverse events prevented participants from continuing treatment.

6.4 Discussion

There was no moderating effect of foot mobility on treatment effects

The results do not support the hypothesis that greater midfoot width mobility, as a cut-off (≥11mm) or as a continuous measurement, as a treatment effect modifier for prescribing foot orthoses over hip exercises. There was no evidence to indicate hip exercises or foot orthoses were more effective than the other in improving PFP outcomes.

Previous clinical trials have shown foot orthoses to be effective compared to a wait-and-see or flat inserts [92, 142]. Theoretical and preliminary evidence [95, 142, 241] suggested that individuals with greater foot pronation (measured as midfoot width mobility) would benefit most from foot orthoses intervention. Our study contradicts these preliminary findings and suggests midfoot mobility should not be used primarily as a deciding factor in their prescription.

There was no difference between foot orthoses and hip exercise: is this because there was no response to treatment in both groups?

Our finding that there was no interaction or treatment effects could stem from both treatments producing no response. When we compare the response to foot orthoses using a similar success criterion (i.e. global rating of change), our study observed similar responses to a previous one (48% vs 47% [142]). Likewise, when we use similar success criteria for exercise programs that included hip exercises (i.e. change in self-reported pain and/or anterior knee pain scales), we similar response profiles (71% vs 80% [94]). Overall the response to the foot orthoses or hip exercise treatments is similar across a number of studies and various self-reported outcome measures [16, 20, 30] which increases our confidence that the results are reproducible in clinic.

Is four weeks of exercise sufficient?

Whilst our study did not compare different durations of exercise interventions, the response to four weeks of exercise was sufficient to induced comparable strength changes and success rates to previous trials [94]. Exercise therapy is recommended for those with PFP [181] but exercise protocols vary between trials, [94, 180] and generally lack specific exercise descriptors [182]. A study with the highest success rates (80%) after six weeks of hip and core exercises [94], reported a notable increase in hip external rotator and abductor muscle strength (8% and 11% increases respectively) . Their six-week exercise protocol consisted of a supervised and home-based program (6 days/week) that targeted hip abductor, extensor, internal and external rotator muscle groups (three-sets of 10 repetitions), and a balance air-pad exercise (three-sets of 30-60seconds). We observed a similar success rate (71%) and change in muscle strength of the same muscle groups, 11% and 6% respectively, with our four-week physiotherapist-supervised program (3 days/ week). The exercises targeted the hip abductor, external rotator and extensor muscles, performed at a *hard* to *very hard* perceived level of exertion with each repetition having a five second time-under-tension cycle (three-sets of 10 repetitions). Adherence was high (84%). We noted that hip strength improvements were maintained between week 6 and 12, despite the cessation of exercises after four weeks (Appendix 17). Despite some differences in exercise parameters between studies, there were comparable

success rates and increases in muscle strength suggesting improvements can be gained by doing simple exercises.

6.4.1 Limitations

Several limitations need to be considered when inferring from our results. One is the imbalance in the number of sessions between the hip exercise group (12) and the foot orthoses groups (6). Whilst regular visits to the clinician would assure adherence and fidelity to the treatment, this would plausibly be more resource intensive. Resource and cost implications of the imbalance in treatment sessions between groups was not collected. Another consideration is the use of only one form of prefabricated foot orthoses, and while it was previously shown to be effective, this might well be a limitation. Other foot orthoses may be more or less effective and their outcome predictable from basic foot measures. This study focused on only hip exercises as an intervention, whilst international consensus recommends the use of both hip and quadricep exercises in the management of PFP. Future studies may look to incorporate quadricep exercises into their interventions. Sample size calculations were based on one follow-up visit per participant, however, in our analyses we analysed both outcomes for each participant simultaneously using generalised estimating equations. Our sample size calculations thus did not account for multiple measurements per participant: doing so would have reduced the required number of participants. Due to the presence of nonadherence to assigned treatments, the estimated effects in this study must be interpreted as estimating the effect of assignment to either foot orthoses or hip exercises, rather than the effect of actually engaging with the assigned treatments [250, 251]. However, in this study there were relatively high levels of adherence to foot orthoses and hip exercise programs, implying that estimates from an analysis of the effect of hypothetical full adherence are likely to be similar to those obtained here.

6.4.2 Clinical implications

In the management of individuals with PFP, hip exercises or foot orthoses are equally effective as treatment choices. In the absence of any differences between those with greater midfoot width mobility and between the treatments, other determinants ought to be considered in clinical decisions when managing PFP. For example, patient preference, resource requirements, and time required for each intervention should guide treatment selection.

6.5 Conclusion

Greater midfoot width mobility was not associated with greater patient-perceived improvement with foot orthoses versus hip exercises. Both hip exercises and foot orthoses offer similar outcomes in reducing pain, improving function and hip muscle strength.

6.6 Contributors

MM contributed to the study conception and design, recruitment of participants, management of study proceedings, data collection, and drafting and revision of the manuscript. AC, TM, RN, and KC contributed to the study conception and design, and drafting and revision of the manuscript. MR contributed to the study design, recruitment of participants, management of study proceedings, data collection, and reviewed the manuscript. JK contributed to the statistical analysis and reviewed the manuscript. BV contributed to the study conception and design, recruitment of participants, data management, and the drafting and revision of the manuscript. BV and MM act as guarantors to affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

6.7 Declaration of interest

BV reports grants from Commonwealth of Australia National Health and Medical Research Council (Ref: 631717) and from Vionics International for this research. MM was the recipient of an Australian Postgraduate Award scholarship (No 351663). BV and TM are voluntary (non-compensated) members by invitation on the Vasyli Think Tank. The funders of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

6.8 Acknowledgements

We thank those who enabled the study to be conducted, the participants who volunteered into the study and the physiotherapists that carried out treatments.

Chapter 7 is adapted from a publication, as a book chapter:

Matthews, M., Vicenzino, B., Rivett, D. (2019) Targeting treatment distally at the foot for bilateral persistent patellofemoral pain in a 23-year-old: a new answer to an old problem. *Clinical Reasoning in Musculoskeletal Practice 2ed.* Chapter 10, 164-178 Elsevier Health Sciences.

Contributor	**Statement of contribution**
M. Matthews (Candidate)	Conception and design (50%), Analysis and interpretation (50%), Drafting and production (50%)
B. Vicenzino	Conception and design (35%), Analysis and interpretation (35%), Drafting and production (30%)
D. Rivett	Conception and design (15%), Analysis and interpretation (15%), Drafting and production (20%)

Chapter 7. Targeting treatment distally at the foot for bilateral persistent patellofemoral pain in a 23-year-old: a new answer to an old problem?

This (book) chapter presents a clinical case, along with reasoning questions put forward by one the book authors (DR), our answers to the reasoning questions (MM, BV), and a closing clinical commentary for each section (DR).

7.1 Patient interview

Ellie is a 23year old female who recently commenced working in a hospitality job that involved prolonged hours of standing and walking. She presented to the University of Queensland clinical Sports Injury Rehabilitation and Prevention for Health (SIRPH) research unit with a 10year history of non-traumatic bilateral anterior knee pain symptoms, with the left knee symptoms more severe than the right (Figure 7.1). Ellie had previously been a gymnast from the age of six, training up to 25-35 hours per week, until the age of 12 years. She then commenced trampolining activities, training up to 6-12 hours per week, until the age of 16 years. Now Ellie worked as a bartender doing shift work for 15-20 hours per week. Outside of work she led a sedentary lifestyle, with her hobbies including photography and laptop computer work.

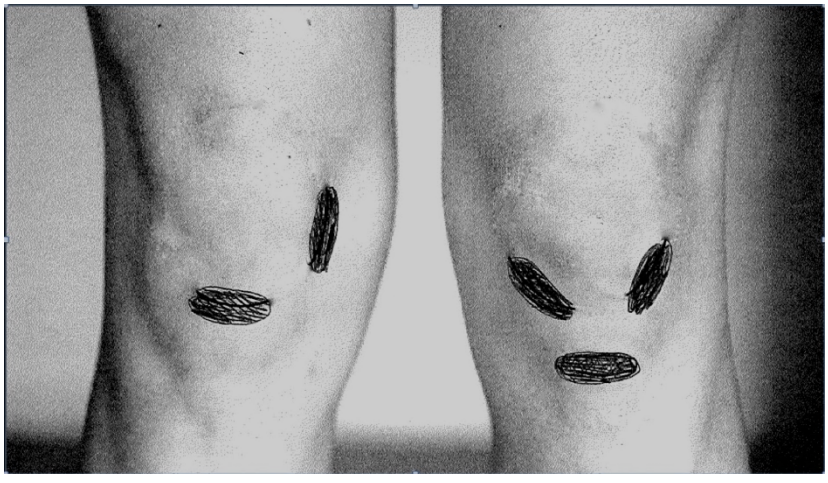


Figure 7.1 Body chart depicting Ellie's anterior knee pain

7.1.1 Symptom behaviour

Since commencing the new job three months earlier, her knee symptoms had deteriorated to the extent that she now reported a dull ache at the beginning of the shift which progressed to a tense, cramping, buzzing-like feeling by the end of the shift. Her worst symptoms occurred when ascending stairs, especially after work, with pain increasing after one to two steps, up to an intensity of 5/10 on a pain numerical rating scale (NRS, 0 = no pain; 10 = worst pain imaginable) after one flight. In the previous seven days, Ellie rated her worst pain as being 8/10 after working more than eight hours. Her symptoms were also aggravated when sitting for longer than 90 minutes (4/10) or driving a manual car for longer than 30 minutes, which resulted in an uncomfortable ache. Colder weather caused an increase in the knee symptoms, as did a rapid change in room temperature (for example, when walking in/out of a large refrigerator at work). Throughout the day, Ellie's symptoms were only aggravated by activity or being in positions of knee flexion for a prolonged period of time.

Symptoms were relieved with avoidance of aggravating activities, ice for 20 minutes after working and by modifying resting knee positions. Ellie wore an elastic knee support to assist in symptom management during work. She reported audible crepitus in the left knee and to a lesser extent in the right knee, with a relieving 'crack' felt in the left knee at times after moving out of flexion from prolonged sitting.

7.1.2 Self-report forms

During the assessment, Ellie completed the Kujala Anterior Knee Pain Scale [252] scoring 68/100, which indicated a severe restriction in functional abilities

due to knee pain. She also completed a Patient Specific Functional Scale (PSFS) to evaluate her ability to perform individually selected activities (scored from 0 = ‘able to do for as long as I wish’, to 10 = ‘unable to do’) [195], for which she nominated the activities of walking up/down stairs (3/10), working for greater than eight hours (5/10) and sitting for more than one hour (3/10).

Ellie reported she had seen her local general practitioner for her knee pain and had not undergone any investigations. This medical practitioner essentially advised that the pain would ‘go away’. She had not consulted any other health care professionals.

7.1.3 Reasoning Questions

1. Following the patient interview, and considering the chronicity of symptoms, what is your hypothesis regarding the most likely ‘Pain Type’ (nociceptive, peripheral neuropathic, maladaptive central nervous system sensitisation)? What is your reasoning process behind your decision?

Answer to Reasoning Question:

It was hypothesized that Ellie’s pain was most likely to be predominantly of nociceptive origin. Her pain only came on with loading activities of the knee, such as negotiating stairs and with sustained knee flexion in sitting and driving, suggesting a mechanical load-related cause for her pain. These physical activities are known to particularly increase stress at the patellofemoral joint. Ellie’s report of a long history of persistent symptoms, recent deterioration with increased workloads, and moderate level of symptom irritability could also suggest the presence of secondary peripheral sensitivity.

2. Can you please discuss which features of Ellie’s reported history led you to your primary and secondary diagnostic hypotheses?

Answer to Reasoning Question:

The impression following the patient interview was of a primary hypothesis of persistent patellofemoral pain, with a secondary hypothesis of fat pad irritation. The primary hypothesis of persistent patellofemoral pain was supported by the exclusion of findings in Ellie's history which may be indicative of other pathologies. That is, there was no history of trauma, no mention of symptoms suggestive of ligamentous instability and little likelihood of referral of symptoms from the lumbar spine or hip. Patellofemoral pain is typically aggravated by activities that load the patellofemoral joint (e.g., squatting/crouching, stair ambulation and running) or which involve sustained knee flexion (e.g., prolonged sitting), consistent with the activities that Ellie reported to be painful. Further supporting this hypothesis is Ellie's reported audible joint sounds, which is sometimes reported in those with patellofemoral pain. [159] It is thought this noise is the result of the aberrant patella motion though the trochlear groove of the femur during flexion and extension of the knee, and may reflect the integrity of articular cartilage. [253] It has been suggested that audible grinding noises and/or palpable vibrations may indicate the presence of early osteoarthritic features of the patellofemoral joint on MRI in women without tibiofemoral joint changes. [254]

The secondary hypothesis of fat pad irritation was supported by the location and description of symptoms (anterior knee, inferior to the patella), and by the provocation of pain during dynamic activities, such as knee extension during stair ascent.

3. It is interesting that cold environments aggravated Ellie's symptoms, yet she indicated that she used ice for pain relief, which could appear a little contradictory. Are you able to make any comment on this? Has this been a consideration in determining your hypothesis regarding the dominant 'Pain Type'?

Answer to Reasoning Question:

The pain aggravation induced by cold ambient temperatures is not consistent with our hypothesis of a nociceptive 'Pain Type', but the relief of pain with ice

could possibly be consistent with nociceptive pain. A study of patients with patellofemoral pain has reported that those with cold sensitivity indicate higher pain severity, tolerate less physical activity, and demonstrate less improvement to lower limb stretching, vastus medialis training and patellar taping treatment [255]. Ellie's presentation did not align well with those reported findings. Perhaps in cold environments, she might have adopted more flexed lower limb postures, which she had reported were provocative of her knee pain. However, this was not explored with her at the time and so this is purely conjecture. Regarding her use of ice to modulate patellofemoral pain, this could be subserved by a peripheral inhibitory mechanism through cooling effects on nociceptors and small afferent fibre function.

Pain is seldom the result of solely peripheral or solely central pathophysiology but is more likely a combination thereof. So it is conceivable that while Ellie's predominant pain presentation was nociceptive in nature, she could concurrently have had some central nervous system changes (sensitisation) due to the long term nature of her condition.

7.1.4 Clinical Reasoning Commentary

It is a common clinical reasoning error for the practitioner to only consider the 'positive' or supportive clinical findings in the patient examination, and to fail to give similar consideration to absent or non-supportive findings in determining likely hypotheses. This was not the case in the clinician's response to the question of which clinical features supported the primary diagnostic hypothesis of persistent patellofemoral pain where the absence of clinical features indicative of some alternative or competing hypotheses (such as knee ligamentous pathology) was given due weighting in their reasoning process. This suggests that the clinician is actively and simultaneously considering multiple diagnostic hypotheses (tissue/structural; and/or physical impairments) and ordering these based on the presence and absence of features typically to be expected in the associated clinical patterns. Pain Type cannot be measured clinically and needs to be a hypothesis based on pain science and current understanding of expected clinical patterns. While clinical

patterns are helpful, they are often not fully validated, features can overlap with other patterns and patients will not necessarily present with every feature. This is nicely illustrated in the reasoning here, where features of a nociceptive dominant pattern are recognised along with features of central nervous system sensitisation.

7.2 Physical examination

7.2.1 Observation

On observation of the lower limb in bipedal stance, the hips were internally rotated, and the feet were pronated, left greater than right. The knees were in hyperextension and appeared normal, with no apparent swelling. Based on the pronated foot posture and knee hyperextension, the Beighton Hypermobility Scale was applied [256], with Ellie scoring 6/9 with bilateral hyperextension of the 5th metacarpophanageal joints, elbows and knees. This score indicates the presence of generalized joint laxity [256, 257]. Single leg stance resulted in 3/10 retropatellar pain in the left knee only. Performing a small single knee bend on the left leg resulted in 4/10 peripatellar pain, described as an ‘ache’, at approximately 30 degrees of flexion.

7.2.2 Functional tests

Each functional test was performed either until the onset of pain or performance of 25 pain-free repetitions. These tests included squats (i.e., full deep squat/full knee flexion, onto the balls of the feet, touching the floor with hands either side of the ankles) where Ellie achieved 6/25 repetitions; step-ups onto a 25cm step at the speed of a metronome set to 96 beats/minute (7/25 repetitions on the left, 18/25 on the right); and step-downs from a 25cm step (2/25 repetitions on the left, 3/25 on the right).

On active range of motion testing with overpressure at end-range, there was full pain-free active range of motion of both knees.

7.2.3 Knee tests

The patella borders were tender to palpation both medially and laterally on the left, with no swelling or joint effusion present. The Hoffa test was conducted to test for fat pad irritation [258]. The test is designed to irritate the fat pad by applying firm pressure via the thumb inferior to the patella outside the margin of the patellar tendon with the knee in 30 degrees of knee flexion, and then in full knee extension (hyperextension). The test is regarded as positive for impingement if pain is produced during the last 10 degrees of extension indicating involvement of the fat pad in the presenting symptoms [259], although little is known about the Hoffa test's diagnostic properties [260]. The test was repeated on both the medial and lateral sides of both knees but did not reproduce Ellie's symptoms. Further testing designed to irritate the fat pad was undertaken, which involved isometric quadriceps contraction in full extension and passive extension overpressure, again with no symptoms reproduced [258]. There was also no pain elicited on firm palpation of the proximal, mid or distal portions of the patella tendon.

Valgus and varus ligamentous tests of the medial and lateral collateral ligaments respectively, anterior drawer test and Lachman's test, posterior drawer test and sag sign, and McMurray's and Apley's tests were all negative for both knees, indicating that the ligamentous structures and menisci were not likely to be the source of symptoms. The patellar apprehension sign for instability was also negative. Manual compression of the patella into the trochlear groove at both 0 degrees and 20 degrees of knee flexion was positive for symptom reproduction for the left knee only. Clarke's test was performed with Ellie lying in supine, with both knees supported in slight flexion [261]. The patella was pressed distally (with the therapist's hand on the superior border of the patella) and she was instructed to gradually perform an isometric contraction of the quadriceps muscle [262]. This test is thought to

actively compress and stress the articular surfaces of both the patella and the femoral trochlear groove. Reproduction of symptoms is regarded as a positive test and suggestive of a patellofemoral joint disorder, and whilst Ellie tested positive for both knees, this test's diagnostic utility is questionable [263]. Similarly, no assessment of patella translation mobility was conducted as the ability of patella mobility to assist in diagnosis is marginal [264]

7.2.4 Foot tests

Foot posture index [265], navicular drop [74], and midfoot mobility measurements [76] were recorded. For the foot posture index, the left foot scored +7 and the right +8, indicating a pronated foot posture bilaterally [207]. Navicular drop is measured by the change in height of the navicular tuberosity relative to the floor between a subtalar neutral posture and a relaxed stance foot posture. Ellie's navicular drop was 7mm on the left and 9mm on the right. Midfoot mobility is measured by recording the difference between the midfoot width in weight bearing (WB) and non-weight bearing (NWB) and is expressed as midfoot width (MFW) difference (DiffMFW=WB–NWB). Ellie's midfoot width measurements in weight bearing were 87.7mm on the left and 87.6mm on the right, and in non-weight bearing were 75.6mm on the left and 76.4mm on the right. Thus, the DiffMFW was 12.1mm and 11.2mm on the left and right respectively. Ellie's change in midfoot width was more than the 11mm previously reported to be associated with a greater benefit from foot orthoses intervention [95, 142].

7.2.5 Treatment Direction Test (TDT)

Given the findings on observation, foot posture and mobility testing, a Treatment Direction Test (TDT) was next applied. The TDT has been previously reported [164], however, in brief, it involves applying a physical manipulation (e.g., anti-pronation taping in this case) during the client-specific impairment measure (e.g., pain-free step-ups on a 25cm step with Ellie).

According to Vicenzino [164], if a significant improvement in the client-specific impairment measure is observed (i.e., ≥75% number of pain-free step-ups), then treatment of the foot with orthoses and exercises would have a high likelihood of success. Ellie achieved nine pain-free step-ups on the left (i.e., her most problematic knee) before the onset of her knee pain. After applying the anti-pronation tape (Figure 7.2), Ellie was able to achieve 14 pain-free step-ups on the left, suggesting a high probability of a successful outcome with foot orthoses for Ellie.

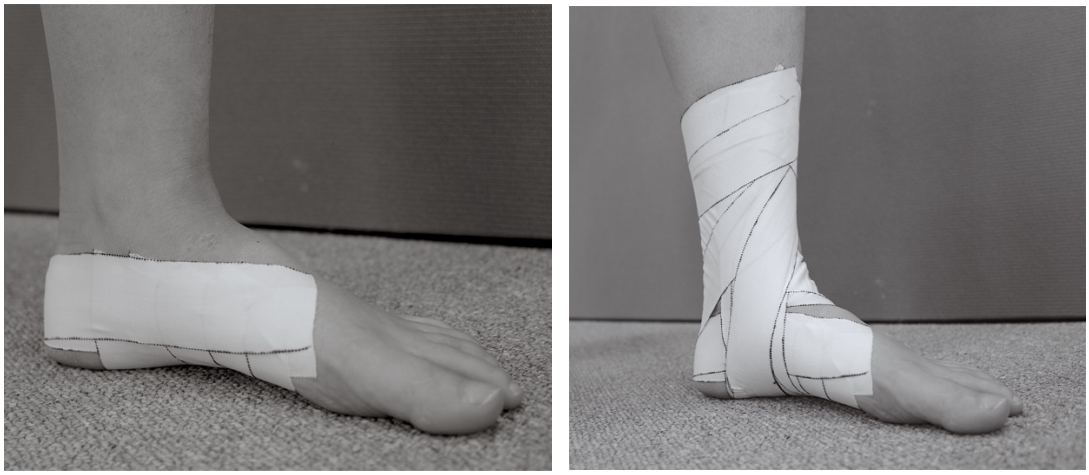


Figure 7.2 Anti–pronation taping
(Left) low Dye technique (just the foot taped); (Right) augmented low Dye technique (taping up the lower leg)

7.2.6 Ankle range of motion

Reduced ankle dorsiflexion range has been previously associated with lower limb pathologies, including an association with aberrant hip patho-mechanics in a single leg squat task in those with patellofemoral pain. [266-269] Ellie's bent-knee ankle dorsiflexion range was measured using a modified knee-to-wall test [212] , (146mm left and 128mm right) and straight-knee ankle dorsiflexion using an inclinometer placed mid tibia (48° left and 45° right)

7.2.7 Hip muscle strength tests

Deficits in hip muscle function have been associated with altered movement patterns of the lower limb [170, 235, 270]. Recent studies have identified reduced hip muscle strength, particularly of the hip abductors and external rotators, in people with patellofemoral pain as compared to an asymptomatic group [213, 214, 271]. On the basis of this evidence, maximal voluntary isometric hip strength measurements of hip abduction, adduction and external rotation were recorded (in supine lying) using a hand-held dynamometer that was fixated by a belt (Table 7.1).

Table 7. 1 Maximal voluntary isometric hip muscle strength scores at baseline

Hip muscle group	**0 weeks**	
	Left	**Right**
Abduction (N)	71.1	70.2
Adduction (N)	70.7	61.13
External Rotation (N)	67.2	64.7

7.2.8 Reasoning Questions

4. Can you explain how the physical examination findings supported/refuted your primary diagnostic hypothesis of persistent patellofemoral pain, and your secondary hypothesis of fat pad irritation? How did your treatment hypothesis of foot orthoses fit with these findings?

Answer to Reasoning Question

On physical examination, Ellie presented with hyperextended knees and internally rotated femurs in standing. On observation of the knees, there was no evident swelling or enlargement of the fat pad. Ellie tested negative for fat

pad irritation on palpation and on pain reproduction techniques (Hoffa test, isometric quadriceps contraction in full extension and extension overpressure) suggesting the fat pad was not the primary source of pain. Tests were also negative for other local knee pathologies (i.e., ligamentous, tendon etc). Most importantly, Ellie's symptoms were reproduced with techniques that loaded and stressed the patellofemoral joint (squats, step up/down, and single leg squats). Ellie also had marked tenderness on the medial and lateral borders of the patellae, and symptom reproduction on Clarke's test.

When physical examination findings were taken into consideration with her patient interview, and importantly the exclusion of other differential diagnoses, the overall findings were indicative of Ellie having bilateral persistent patellofemoral pain. Based on the findings of pronated foot posture on the foot posture index, DiffMFW ≥11mm, and a positive response to the TDT, it was decided that foot orthoses would be the initial treatment in managing Ellie's patellofemoral pain.

5. You performed a comprehensive assessment of foot biomechanics in this patient. Is this an assessment approach you take with all of the patients in your clinic with patellofemoral/knee pain or were there features in the history and physical examination that led you to pursue that direction, rather than perhaps another approach?

Answer to Reasoning Question

The focus on the foot assessment was based on Ellie's report that her most provocative activity was stair climbing, a weight bearing under load task, combined with the initial observation of her marked pronated foot posture. Physical examination of stair walking confirmed it provoked her pain and correcting her foot posture with anti-pronation taping allowed the patient to perform substantially more steps. These findings led to further examination of foot posture with the foot posture index and measures of midfoot height and weight, which confirmed her feet to be more pronated than normal. If it had not been possible to reproduce Ellie's pain on stair walking and if there had

been no observable pronation of her feet, then the assessment would likely have focussed more on the knee and the hip.

7.2.9 Clinical Reasoning Commentary

These responses demonstrate how the clinician has come to diagnostic and treatment decisions based on a combination of knowledge/evidence derived from prior experience with similar clinical presentations and also scientific evidence obtained from the published research. Hypotheses tentatively formulated during the patient interview have now been tested in the physical examination to determine whether expected clinical findings are indeed present, based on this previously acquired experiential and empirical data. Impairments were specifically tested to determine their relevance to key presenting symptoms (such as the correction of foot pronation on the knee pain experienced during stair walking) and were not simply assumed to be supportive of the primary structural hypothesis (persistent patellofemoral pain). Similarly, it was not assumed that competing hypotheses (e.g., fat pad irritation, ligament pathology) were not to be accepted in conjunction with, or instead of the primary hypothesis, but were each specifically physically tested to ensure their exclusion at this time was appropriate. In the 'Hypothesis Category' framework presented in Chapter 1, assessment and trial correction of foot posture represents reasoning about potential 'Contributing Factors', as might the assessment of femoral posture and hip strength where trial intervention may similarly have had a positive effect. Treatment decisions were therefore based on supportive derived clinical findings and applied scientific evidence built during both the patient interview and the physical examination, as well as the absence of any convincing supportive evidence for competing hypotheses.

7.3 Treatment

Ellie was provided with comprehensive information and education about patellofemoral pain. In particular, she was given an in-depth explanation of the

proposed mechanisms by which excessive foot pronation might impact upon patellofemoral mechanics [226]. In brief, Ellie was made aware of the effect of excessive foot pronation in inducing greater lower limb internal rotation and the flow-on effect on patellofemoral joint stress. She was further informed of the emerging evidence which suggests that a change of ≥11mm in midfoot width (from non-weight bearing to weight bearing) is associated with a successful outcome with the use of foot orthoses, and that her positive response to the anti-pronation taping technique indicated a higher probability of a successful outcome with this approach to treatment.

The foot orthoses were subsequently fitted as previously described [272]. In short, the fundamental aim of the fitting was to ensure the foot orthoses were comfortable in order to maximise compliance, with an overall aim of improving pain-free function. The foot orthoses fitted were commercially available, prefabricated orthotics (Vasyli International) made from ethylene-vinyl acetate with a manufacturer specified six-degree varus wedge and arch support. Ellie was fitted with a full-length foot orthosis of the lowest density (Shore A 52°) to her work footwear (sports running shoes), that were subsequently heat moulded to optimise comfort (Figure 7.3). She was instructed to wear her work shoes during the day and at work, with to remove the orthoses if they began to feel uncomfortable.

Figure 7.3 Full length foot orthoses

7.3.1 Appointment 2 (three days after initial appointment)

Ellie returned three days later for a review of her foot orthoses and to be taught a home exercise program. She reported that she had noticed a reduction in the severity of pain in both knees, and that symptoms took longer to commence while she was working. There were no adverse effects at her foot-to-orthoses interface beyond a mild general ache. Ellie's work and casual footwear were reviewed and were all found to have minimal heel counter stiffness, midfoot sole sagittal stiffness (bending the midfoot in the sagittal plane), and midfoot sole frontal stability (torsional movement or twisting of the midfoot section by counter-rotating the rearfoot and forefoot components). She was asked to seek more stable footwear that would meet the requirements for her work but also complement the application of the foot orthoses.

Ellie was supplied with a second set of full-length foot orthoses of medium density (Shore A 60°) that were heat moulded to optimise comfort. She was instructed to swap the foot orthoses into whatever footwear she would be

wearing. This change was done on the basis of tolerability to the initial lower density orthosis and a desire to provide an orthosis that would likely have a longer life.

Ellie was then taught a home exercise program consisting of anti-pronation foot exercises and calf stretches with the knee extended. The arch forming exercises commenced in partial weight bearing (seated) with the knees flexed and bare feet flat on the floor. To help facilitate the exercise, a piece of paper or non-adhesive tape was placed under the distal end of the first metatarsal and Ellie was instructed to maintain firm pressure on the paper/tape (in order to prevent the paper from being slid out from under the foot by the clinician) whilst keeping her toes relaxed. She was also instructed on the technique of supinating the rearfoot, which was initially assisted with manual facilitation (using finger pressure under the arch) (Figure 7.4). This was sustained for ten seconds and then repeated on the opposite foot. Ellie was asked to repeat the foot supination task five times for each foot, twice daily. As she became more proficient at performing this exercise, Ellie was to progress practicing this in bipedal stance.

Finally, Ellie was asked to perform straight-knee calf stretches for 30 seconds, three times, twice daily, either by a lunge stretch against a wall or over the edge of a step whilst keeping the rearfoot in neutral supination/pronation as per the arch forming exercise. The lunge stretch against the wall involved facing the wall in step-stance with both hands on the wall and both feet flat on the floor aligned perpendicular to the wall. The lunge calf stretch was performed to a comfortable but firm stretch felt in the back of the calf. Alternatively, Ellie could lower the heel down over the edge of a step whilst maintaining a straight knee.

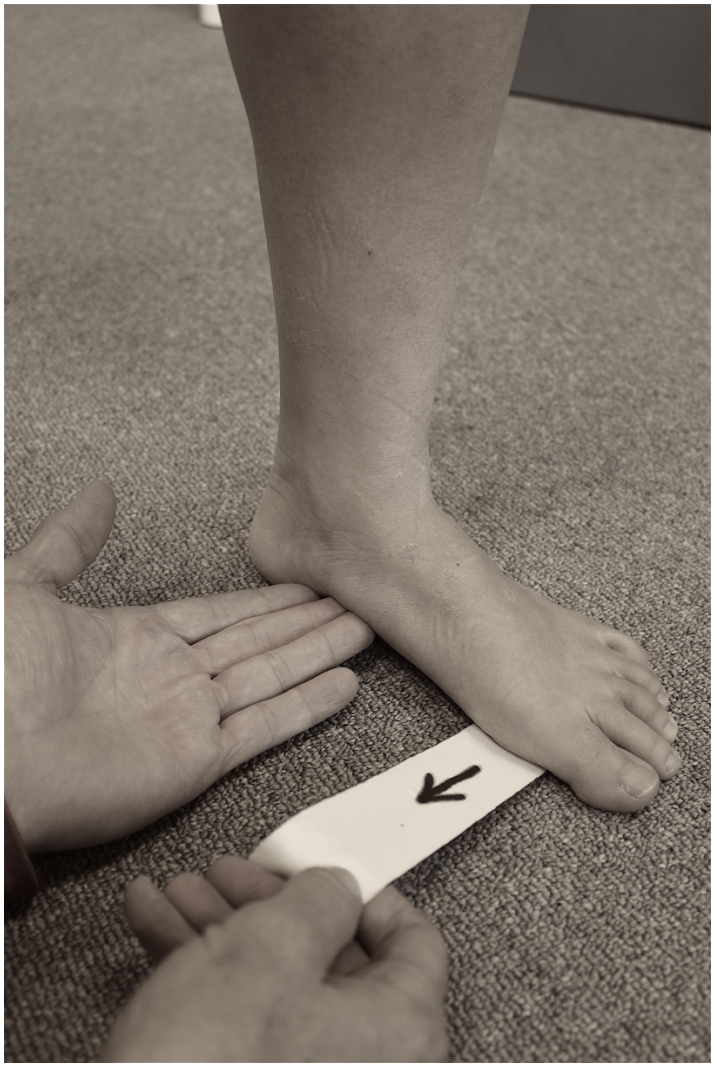


Figure 7.4 Anti-pronation foot exercise

7.3.2 Appointment 3 (11 dyas after initial appointment)

Ellie reported a notable bilateral improvement in her knee pain since the last visit. She found the foot orthoses did not fit all of her footwear, but when she was unable to fit the orthoses, she instead focused on the anti-pronation foot exercises and holding this position momentarily at various times during standing, especially at work. No physical re-examination was conducted at this time. The anti-pronation foot exercises were reviewed and progressed from sitting to bipedal stance to bilateral isometric heel raise holds (i.e., holding heels just off the floor) whilst maintaining the rearfoot in a neutral position. Ellie was still yet to seek more supportive footwear. She was to

continue to use the foot orthoses where able, particularly at work, but was to remove them if they were uncomfortable or not fitting the footwear properly, and to rather focus on the anti-pronation foot exercises with increasing periods of incorporating this posture during standing throughout the day.

7.3.3 Appointment 4 (27 days after initial appointment)

Ellie returned to report significantly less knee pain, especially at work and while ascending stairs after work, which was previously the most aggravating activity and time of day. She reported that she had decided to stop wearing the foot orthoses during the previous week, because she had difficulty fitting them to her footwear selection and preferred to do the anti-pronation foot exercises. She had been focusing on the exercises consistently throughout the day and particularly at work. The anti-pronation foot exercises were progressed from bipedal standing with increasing duration of isometric holds to bipedal dynamic heel raises whilst maintaining a more subtalar neutral position.

7.3.4 Appointment 5 (48 days after initial appointment)

Ellie returned to report she was only experiencing slight twinges in her left knee at work (0.5/10). She now reported feeling no symptoms walking upstairs and only an ‘awareness’ of symptoms in her left knee at other times. Importantly, her knee was not painful after work. The anti-pronation foot exercises were progressed from bipedal dynamic heel raises to single calf raises whilst maintaining a subtalar neutral position. Ellie was to perform these throughout the day as she remembered, especially at work. As Ellie was making substantial improvements, no physical re-examination or assessment was conducted. Ellie felt comfortable to now self-manage with anti-pronation exercises and return for a review and re-assessment in 7 weeks.

7.3.5 Appointment 6 (16 weeks after initial appointment

Ellie was reviewed at 16 weeks and reported she was 'much better' on a seven-point global rating of change scale (much better, better, a little better, no change, a little worse, worse, much worse). On a scale of 0% (not recovered) to 100% (totally recovered), Ellie rated her knees as 100% totally recovered from her presenting knee pain. On the day of assessment, Ellie rated her knees as being 100% normal on a scale of 0% to 100% (100% normal being defined as having 'no problems at all with your knee'). She no longer felt any pain in cold environments. On the Kujala Anterior Knee Pain Scale she scored 100/100 and the only activity rated on the PSFS (0= able to do for as long as I wish, 10 = unable to do) was climbing stairs (0.5/10), as Ellie had experienced a one-off slight twinge ascending stairs after work the week prior. She had now returned to doing moderate physical activity for 30 minutes, five times a week.

On retesting of the pain-free functional task of squatting, Ellie was able to complete 25/25; on step-ups onto a 25cm step, Ellie was able to complete 25/25 on the left and 22/25 on the right with slight pain (1/10), at the speed of a metronome set at 96 beats/minute; and on step-downs Ellie completed 25/25 on both the left and the right knee. Ellie's maximal voluntary isometric hip strength measurements of hip abduction, adduction and external rotation were re-measured (Table 7.2), showing a bilateral increase in external rotation maximum isometric force (11% and 22% on left and right respectively) and an increase in adduction force on the right (21%).

Table 7. 2 Maximal voluntary isometric hip muscle strength scores at 0, 16 weeks.

Hip muscle group	**0 weeks**		**16 weeks**	
	Left	**Right**	**Left**	**Right**
Abduction (N)	71.1	70.2	*	*
Adduction (N)	70.7	61.13	71.2	74.1

External Rotation (N)	67.2	64.7	74.8	78.7

* unable to test maximally as back pain was present during abduction. Back pain had commenced in preceding week as a result of a fall.

Interestingly, Ellie reported she felt that she subconsciously held the foot in a more neutral position that was now her new 'normal' foot posture, and a pronated foot posture now felt very awkward. On measurement of her navicular drop, it was 2mm on the left and 1mm on the right (compared with initial measurements of 7mm and 9mm respectively). Ellie had continued to perform the single heel calf raises when she remembered to do so at work and during the day, as well as maintaining a neutral foot posture during activities of daily living, noting that this did not require much mental focus to achieve. Ellie was encouraged to keep up with the exercises she was currently doing and keep incorporating them into her activities of daily living.

7.3.6 Appointment 7 (32 weeks after initial appointment)

When Ellie was reviewed approximately eight months after treatment had commenced, she reported that she was still much better on a seven-point global rating of change scale and 100% recovered from her knee pain. Her knee pain did not limit any activity of her choice on the PSFS and she still scored 100/100 on the Kujala Anterior Knee Pain Scale. On the pain-free functional task tests, Ellie scored 25/25 repetitions for squats, step-ups and step-downs.

On measurement of her navicular drop, it was 0mm on both the left and right. On measurement of change in midfoot width moving from non-weight bearing to weight bearing, Ellie's midfoot difference was now 6.6mm on the left (previously 12.1mm at initial presentation) and 7.3mm on the right (previously 11.2mm). These measures were considered consistent with a less pronated foot posture type. Interestingly, the hip muscle strength had also increased (ranging from 8 to 33%) from the first session (Table 7.3).

Table 7.3 Maximal voluntary isometric hip muscle strength scores at 0, 16 and 32 weeks

Hip muscle group	0 weeks		16 weeks		32 weeks	
	Left	Right	Left	Right	Left	Right
Abduction (N)	71.1	70.2	*	*	79.4	75.7
Adduction (N)	70.7	61.13	71.2	74.1	79.9	79.2
External Rotation (N)	67.2	64.7	74.8	78.7	89.2	78.6

* unable to test maximally as back pain was present during abduction. Back pain had commenced in preceding week as a result of a fall.

7.3.7 Reasoning Questions

6. Reassessment revealed hip muscle strength had increased despite specific exercises for those muscles not being part of the treatment programme. Can you please propose the mechanism behind this increase in strength and how it may have contributed to the decrease in knee pain?

Answer to Reasoning Question

Improved hip muscle strength was not expected because the treatment was entirely focused at the foot. The mechanism by which this happened is likely multifaceted. One such mechanism might have involved the foot exercises and orthoses inducing changes at the foot, which countered the excessive foot pronation and internal rotation of the lower limb during weight bearing activities. The foot exercises were designed to control the amount of pronation the foot underwent in weight bearing. This was confirmed with a marked reduction in midfoot width mobility after commencing the exercises (e.g., 12.1mm to 6.6mm on the left foot; 11.2mm to 7.3mm on the right foot). This reduction in foot pronation would plausibly reduce the amount of internal

rotation occurring in the lower limb, notably causing a reduction in the internal rotation and adduction of the hip during the stance phase of gait. It can be hypothesised that the hip abductor and external rotator muscles would be working at a disadvantage during the stance phase of gait with the foot pronated excessively, with concomitant increased internal hip rotation and hip adduction. The changes in foot posture observed in this case might have improved the mechanical efficiency of force production of the hip abductor and external rotator muscles by reducing the amount of lower limb internal rotation during loading in single limb stance (e.g., during gait or negotiating stairs). With improved lower limb function and reduced pain, Ellie could feasibly have moved more freely and often, leading to strength adaptations of the hip muscles. Studies have shown that isolated exercises targeting the hip abductors and external rotators have had a positive effect on patellofemoral pain [98, 105, 168, 180], which might have been a means by which the foot treatment led to the observed hip muscle strength improvements.

Another mechanism might have been through unintended exercise of the hip muscles when Ellie performed the anti-pronation exercises of the foot. These exercises focussed on the coupling between the leg and foot, and not just the sagittal plane of the foot in isolation. That is, the exercises involved a coupling of external rotation of the tibia with supination of the rearfoot and plantarflexion of the forefoot, rather than focussing primarily only on the foot in the sagittal plane (e.g., as with foot shortening exercises that primarily target sagittal plane posture locally at the foot). In performing these exercises, Ellie could have used her hip external rotators, which could have led to some conditioning of the hip muscles and the observed strength adaptations.

It is also feasible that the alteration in foot posture, and flow on effects to the lower limb, served to de-stress the patellofemoral joint, which was posited as the nociceptive source of the patellofemoral pain. The resultant reduction in patellofemoral pain would likely lead to more efficient use of the thigh and hip muscles, which in turn might facilitate restitution of hip muscle strength.

It must be stated that it is difficult to explain how the foot treatment changed both the hip muscle strength and the patellofemoral pain, or indeed the causal direction of such effects, and that a combination of these proposed mechanisms along with others not considered may have been responsible for the observed effects.

7. Can you please discuss the preference of Ellie to exercise rather than comply with the change in footwear, and how this may have influenced your management and the ultimate outcome?

Answer to Reasoning Question

Ellie had certain requirements for work footwear; she used a variety of casual footwear and spent time in bare feet at home. During Ellie's initial session she received a detailed explanation of active retraining of foot posture and the biomechanical effect on patellar tracking, thus addressing a potential contributor to her knee pain. After discussion of these factors, and the possible long-term benefit of active versus passive intervention, she felt that an active approach with exercises was the most likely to be beneficial. Ellie felt the immediate change in her knee-pain symptoms with the anti-pronation taping at the initial appointment and the effect of the foot orthoses over the following sessions, all of which assisted with her engagement with the treatment approach and her view of progressing to active exercises. It is highly likely that an understanding of the potential mechanisms contributing to her symptoms, plus an immediate positive response to treatment contributed greatly to Ellie's compliance and adherence to regularly performing the exercises.

8. A midfoot width change ≥11mm was described as being associated with a successful response to treatment aimed at the foot for those with patellofemoral pain. Are there any other factors (such as severity of symptoms, chronicity, 'Pain Type', age of patient, psychosocial considerations, etc) that may need consideration in selecting your treatment approach in similar cases?

Answer to Reasoning Question

Symptoms of patellofemoral pain are typically consistent between patients, however biomechanical, physiological and external factors contributing to the onset of a patient's symptoms vary between individuals, due to the multifactorial nature of the condition. Patients may present with one or more combinations of contributing/associated factors proximally at the hip, locally at the knee or distally at the foot and ankle.

Current evidence suggests a multimodal treatment approach has the best outcome for reducing patellofemoral pain, but it is not a 'one size fits all' approach. Of importance is a comprehensive and appropriate clinical examination, in order to tailor the multimodal program to the patient. Identifying key characteristics that are associated with the patient's symptoms improves the optimal selection of management approach. In Ellie's case, her foot mobility indicated targeting treatment to her foot. If Ellie did not present with such a mobile foot, then evidence suggests exercises targeted more proximally at the hip to improve neuromuscular activity [181] might be more successful. It is not unusual for these exercises to take some time to bring about an improvement, so in the meantime it could be advantageous to consider complementary treatments to reduce pain and improve the patient's ability to be more active and adhere to the exercises (e.g., patellar taping, acupuncture, stretching).

In cases where there are severe and persistent symptoms with associated psychosocial issues, such as such as negative fear-avoidance beliefs, anxiety, depression and pain catastrophising [273-275], which likely mitigate against a good response to mechanically-based treatments, it would be advisable to take a pain sciences approach to management. This approach would require consideration of referral to other clinicians (e.g., psychologist, pain specialist). Fundamentally however, the key is to tailor the treatment to the individual and their presenting case, and to educate them about their knee condition with the most up-to-date and relevant evidence available. It is

important to involve the patient in some informed decision-making in designing the treatment plan, which can then be tailored to their preferences and lifestyle. Crucial to a good outcome is patient confidence in the rationale behind the treatment plan, in order to facilitate adherence, which is vital to recovery.

The key consideration in the treatment approach applied in Ellie's case was the aim of reducing pain and educating her as early as possible to help to gain her confidence in the treatment approach and to facilitate greater adherence to treatment (e.g., active exercises).

9. Given this condition has been described as self-limiting by some authors, do you think Ellie may have recovered without any intervention? What led you to hypothesise a favourable prognosis?

Answer to Reasoning Question

Patellofemoral pain is a common and persistent knee condition that affects teenagers and young adults [6, 115-117, 119, 120]. Conservative treatments for patellofemoral pain such as strengthening, stretching and functional movement retraining of quadriceps and gluteal muscles, foot orthoses, patellar taping and manual therapy have been reported to produce modest effects of short to moderate term duration [92]. Despite these interventions, a substantial proportion of patients still report persistent long-term symptoms [116], with approximately 1 in 4 reporting symptoms up to 20 years later [121].

It is erroneous to consider this condition as being self-limiting, especially in adolescents when patellofemoral pain could be dismissed as 'growing pains'. A substantial body of evidence points to the contrary, with 50% of 12-15 year olds reporting persistent knee pain 12 months later [276], 55% of 15-19 year olds reporting persistent pain two years later, [1] and more notably 78% of females diagnosed with patellofemoral pain during adolescence still experiencing pain after 14 to 20 years [115, 116, 121]. Ellie appears to be in this long-term, non-self-limiting category, because she was diagnosed with

patellofemoral pain at 13 years of age and has had persistent symptoms that have continued to significantly impact her life into her early twenties.

Taking in consideration the evidence highlighting longer knee pain duration is predictive of a poor outcome [121, 138, 146], it is highly unlikely that Ellie would have recovered without any intervention. Whilst reducing the amount of knee loading activities may change a patient's symptoms, a reintroduction of knee loading activities will likely result in a recurrence of the symptoms. This is demonstrated in Ellie's case whereby she reported a cyclical history of improvement when activity was reduced (i.e., the knee was deloaded), but an exacerbation on attempting more activity, such as returning to hospitality work and spending more time on her feet. On commencing physiotherapy treatment, Ellie reported a significant improvement in her symptoms by appointment 3 (11 days). Given she had persistent symptoms for 10 years, it is highly unlikely this rapid improvement was a spontaneous recovery, especially as she remained improved 32 weeks later.

A favourable prognosis was indicated as Ellie responded favourably during the step-up test when an anti-pronation taping technique was applied, demonstrating an immediate effect of foot intervention on her patellofemoral pain. Over the following few weeks with foot orthoses and exercises, Elle reported a marked improvement in her pain, which continued to be the case afterwards. This is consistent with a series of studies by Barton et al [77, 143] in which patients who demonstrated immediate improvement in a physical pain provocative test with an anti-pronation device applied were more likely to be improved weeks later [143]. In another study, Barton et al [277] showed an immediate increase in the number of pain-free single-leg rises and single leg squats able to be performed when those patients with a pronated foot type wore a prefabricated foot orthoses [277]. These improvements were present at follow-up [278], indicating it is not a short lived response. In summary, the temporal response profile seen with Elle was commensurate with expectations and those reported in the literature. Had she not improved sufficiently however, then management directed at the femoral posture and weakness may have been added.

7.3.9 Clinical Reasoning Commentary

The importance of patient education and empowerment is well demonstrated in this case. Without a clear explanation regarding the likely cause of her knee pain and the reasons why it has persisted, Ellie may not have complied with the management program over several months and almost certainly would have been much less likely to have adhered to the tailored exercise program. Apart from the clarity and logic of the explanation provided by the clinician, the other key element in motivating Ellie to continue with the exercise program was the powerful demonstration of the effect on her knee symptoms during her most provocative activity (ascending stairs) of an anti-pronation intervention. This appears to have been the ‘cognitive clincher’ in Ellie understanding and believing that her persistent decade old problem could actually be changed for the better and that her chosen clinician could assist her to that end. Moreover, the relatively rapid improvement in her pain and function following the commencement of the exercise program provided Ellie with the knowledge that she had the ‘power’ to manage her symptoms herself, under the guidance of her clinician in whom she had confidence. Ellie embraced the responsibility of taking control of her own management, however importantly, the clinician facilitated this by allowing her to be a truly collaborative partner in the therapeutic alliance.

Chapter 8. Discussion and Conclusions

The aim of this research was to explore specific ways of optimising the management of those with patellofemoral pain. In particular, to determine if a presenting patient's characteristic could guide the clinician in matching the right treatment to the patient to achieve an improved success rate. This chapter will summarise the key findings from trial, how the findings fit within the body of current knowledge on PFP management and considerations on their clinical impact, as well as future research directions. A central consideration in relation to the outcomes of this research is that they may represent a combination of biological, articular, and neuromuscular function at the lower limb, as well as psychosocial aspects of a patient's perception of pain and their functional ability.

8.1 Brief review of the research

8.1.1 Management of PFP

In the management of PFP, evidence supports recommendation of either hip exercises or foot orthoses [181].These interventions target the proximal and distal parts of the lower limb, with different biomechanical approaches (i.e. hip exercises versus foot orthoses respectively) to address a pain distant from, and in between, the targeted areas. The recommendations and contrasting paradigms place considerable emphasis on the clinician's reasoning skills to determine which treatment is best for which patient. One clinical tool that can assist clinicians in the decision-making process is utilizing clinical prediction rules. Clinical prediction rules quantify the contribution of certain patient characteristics, known as treatment effect modifiers, to provide the clinician and patient with a probability of a response to a particular treatment [279-281].The greatest benefit of treatment effect modifiers can be with patients who present with a homogeneous, but multifactorial condition, such as PFP, and assist the clinician to classify the patient into a subgroup, based on a likely response to a specific treatment approach.

Two questions stem from the recommendation of both hip exercises and foot orthoses for managing PFP. Does greater midfoot width mobility modify the effect of foot orthoses treatment over hip exercises for PFP; and are foot orthoses or hip exercises a superior treatment PFP? To address these questions, this research project developed and implemented a a two-arm parallel, superiority randomised clinical trial.

8.1.2 Treatment effect modification

One aim of this research was to explore treatment effect modifiers for those with PFP. The systematic review undertaken in chapter 3 identified crucial methodological limitations within the reported evidence. Studies aiming to identify treatment effect modifiers failed to use a control or comparator treatment group and analyzed too many variables for the limiting sample size. These limitations increased the risk of type one error, spurious findings, and a greater higher likelihood the findings would not be reflected within a population of those with PFP. As such, current evidence did not support the ability to confidently predict the outcome after one specific treatment compared with another. In light of these limitations, preliminary evidence from the systematic review suggested patients with PFP with >11 mm midfoot width mobility moving from a non-weight to a weight bearing posture would benefit more from foot orthoses than those with lesser mobility [95, 142]. Previous identification of midfoot width mobility as a potential treatment effect modifier warranted further investigation.

8.1.3 Hypotheses and results

We hypothesized that (i) those with *high* midfoot width mobility would report greater benefit with foot orthoses, compared to hip exercises, and (ii) hip exercises would provide greater benefit compare to foot orthoses, in part due to direct effect upon the patellofemoral joint. Two hundred and twenty participants with PFP were recruited, stratified based on their midfoot width mobility (*high* ≥11mm, *low*, <11mm) and randomly allocated to foot orthoses or hip exercises (two were incorrectly included but later removed). Overall, we found midfoot width mobility was not associated with patient-perceived

improvement with foot orthoses, compared to hip exercises (interaction effect (*P*=0.19), and that foot orthoses and hip exercises have comparable outcomes (risk difference 0.94 (95% CI 0.72, 1.24). The results support the null hypotheses and are in contrast to commonly assumed clinical expectations.

8.2 Plausible explanation for results

The results from the clinical trial and case study shed some light onto plausible explanations for why midfoot width mobility was not associated with outcome and why contrasting treatments achieved similar outcome. Systematic review evidence suggested midfoot width mobility had the potential to be a treatment effect modifier for the prescription of foot orthoses. [243] This concept appeared plausible and clinically appealing, because a simple, quick and reliable measurement of foot motion could indicate the use of a device designed to regulate mobility that could provide greater benefit for those with greater mobility. Our study has conclusively shown that midfoot width mobility is not a patient characteristic that predicts those with PFP who would benefit from a foot orthosis and should not be used alone in the decision-making process. One explanation of our result could be due to the multifactorial nature of PFP. Factors in many domains of a biopsychosocial paradigm could influence a patient's response to a specific treatment, including intrinsic physiological and psychological factors and how these connect via behaviour in the social and physical context of their extrinsic environment. Three considerations are noteworthy for why midfoot width alone was not a treatment effect modifier for the rate of successful outcome with foot orthoses. These considerations take into account (i) the structure being measured, i.e. the foot, (ii) the potential effect with sensorimotor control and movement patterns, and (iii) more broadly the generation of nociceptive input, perception of pain and functional limitations. The multitude of potential contributing factors warrants consideration in future trials, i.e. to control or explore, as potential methods for tailoring evidence-based treatments.

8.3 Biological variables

Foot structure and excessive foot motion have been investigated as an associated factor in those with PFP [226, 241]. Previous studies have investigated measurements of the foot and associations with outcome with foot orthoses treatment. These have included joint and bone range of motion and foot posture [77, 95, 142, 143, 152, 153]. In light of the results of the trial (chapter 6) in this research, only greater rearfoot eversion relative to floor, has been reported with a successful outcome [77]. Due consideration is warranted as this finding is from a case series study, with no comparator treatment, of which 7/26 (27%) had successful outcome, with potential overfitting of the statistical models and as such a higher risk of type one error. The lack of association between clinical foot measurements and outcome in people with PFP could represent the inadequacy of clinical and imaging measures to capture the complex interplay and multi-plane motion of the foot. Whilst measurement of midfoot width tried to represent combined joint motions; more than just movement of a single bone, it is still predominately only in one plane of motion. Previous work looked at the combined effect midfoot width and arch height mobility to calculate the foot mobility magnitude [76]. Post-hoc analysis of a large clinical trial [92], and a separate randomised clinical trial comparing foot orthoses to wait-and-see approach [142], found only midfoot width measurement was associated with success [95]. It is conceivable a combination of characteristics could have a better likelihood of success. However, it is worth considering the complex interplay of structures within the foot and the knee, the small joint motions and the high forces transmitted might make it too challenging to capture the motion with simple clinical tools. Ultimately the ability to capture the intricacy of the structure and function of the foot in a simple index, for which to direct treatment selection, may overlook the likely complexity of other relevant factors.

Neuromuscular and biomechanical deficits have been widely reported in those with PFP [4]. These deficits are proposed to contribute to aberrant loading of the patellofemoral joint and a disruption in tissue homeostasis [2, 241]. It is theorized the treatments for PFP may address these underlying deficits, and

in turn, influence the loading and stress through the patellofemoral joint. Studies that have investigated these proposed theories have reported varying deficits [282-284] which may suggest individual motor control variations in response to pain [285]. Conversely, the mechanisms of effect for hip exercises and foot orthoses have not yet been clearly identified [286]. Results from current the trial found similar magnitude of improvements in hip abductor and external rotator muscle strength occurred for the hip exercise and the foot orthoses groups. It is understandable the direct effect exercises targeting hip musculature would improve muscle force output. It was unexpected to find foot orthoses having similar effects on muscle force output.

The current trial did not include a control group (i.e. a wait-and-see or alternative conservative approach), so the magnitude of strength improvement relative to a control group is not known, but the results open new research questions [287]. It could be hypothesised that both treatments may have had a shared mechanism of effect (e.g. a reduction in dynamic knee valgus during knee-loading tasks), which could explain the similarities in outcome. It is conceivable foot orthoses had a direct effect on reducing pain and improve function [277]. It could equally be plausible for the foot orthoses to influence lower limb biomechanics [169, 226, 241], modify loading of the patellofemoral joint and improve function. Whether mechanical or non-mechanical effects, foot orthoses appear to improve function which may allow better muscle force development. Whatever the mechanism of effect, the results of our clinical trial suggest an indirect treatment approach focused the opposite end of the kinetic chain can have a similar effect as one specifically directed at the tissue.

8.4 Psychosocial

The predominant paradigm of pain presentation in PFP assumes in isolation a direct mechanistic link that higher loads on the patellofemoral joint cause greater stress and greater pain [241]. Growing evidence suggests a rationale for a modified approach around the persistent nature of PFP, one that moves the clinician’s focus away from a solely biomedical/tissue pathology model

towards a consideration of the addition of non-physical contributors [44, 242, 288]. It is pertinent to consider for some with persistent PFP, previous injuries and repetitively performing knee-loading activities e.g. stairs, squatting and/or running, may amplify local nociceptive activity, and drive the development of mechanosensitivity, sensitisation of peripheral and/or central nervous systems, and persistent pain [289, 290]. Recent systematic review evidence indicates the presence and elevation of other non-physical contributors in PFP (i.e. a psychological profile that will have raised risk of symptom amplification and persistence), such as fear of movement, catastrophising and depression [44]. Such factors have the potential to adversely influence a patient's view of their physical function and behavior around activities. For some, they may be substantial contributors to pain perception and persistence [44, 242, 291]. Results from chapter 6 found that those who received foot orthoses had reduced anxiety at 6 weeks compared to those who performed hip exercises. It is plausible that foot orthoses may have had an immediate effect on reducing pain [164, 277], which facilitated reduced fear, better lower limb movement and utilisation of muscles. With due consideration, the primary outcome measure of this trial was a patient-rated perception of improvement scale. Neurophysiological and non-physical contributors to PFP may have modified as a result of the treatments during the trial, adding further considerations to explain the similarities in outcome between the two treatments. Future clinical trials could aim to track both biomedical and psychosocial outcomes over time, as interventions which are effective at modifying chronic pain conditions could have important mechanisms across both domains. The findings from our trial are in agreement with other studies that have compared effective treatments, such as foot orthoses versus physiotherapy versus foot orthoses plus physiotherapy [92], hip-and-core versus knee-focused programs [94], and education versus education-and-exercise versus education-and-gait retraining programs [292]. Trials with foot orthoses or strengthening at various regions had similar response rates, supporting validity of our findings. Trials with education that aimed improve understanding and modify behaviour had a similar response rate, reflecting that biological and psychosocial domains are inextricably linked in the management of musculoskeletal pain conditions.

8.5 Clinical predictors and treatment effect modifiers

Clinical prediction rules offer clinicians a range of clinical benefits such as assisting in diagnosis, prognosis, or identifying those who respond best to treatment. In regard to treatment selection, prediction rules are one method of deriving the probability of success with a certain intervention, based on a patient's presenting characteristics. However, identify responders to treatment the prediction rule still needs to meet all the criteria that a single effect modifier (e.g. in regard to this thesis; midfoot width mobility) would (e.g. tested in a randomised controlled trial using a proper test of interaction). Studies claim to have derived preliminary clinical prediction rules for managing PFP with hip and knee exercises, foot orthoses, and patient education [95, 293, 294]. With regards to foot orthoses, *post hoc* analysis identified greater midfoot width mobility, older age, reduced height and worst-pain rating to be associated with a successful outcome with foot [95]. More recently, studies have attempted the same process [293, 294]. In a study comparing hip-and-core to knee-focussed rehab, *post hoc* analyses to derive clinical predictions rules for each treatment found those individuals who had successful outcomes presented predominantly with neuromuscular factors (i.e. muscle endurance and weakness) around the hip and trunk. Methodological considerations aside, it is plausible the two interventions shared a common mechanism of activity modification via patient education whilst improving the overall neuromuscular capacity. One study investigated an education and load management program in runners with PFP, and the effect of combining it with exercise or gait retraining [292]. With no significant difference between the three groups, authors derived a clinical prediction rule for predicting a successful outcome with an education program. However, the issue with deriving clinical prediction rules, that these studies exemplify, is the over fitting of variables to the sample size in the analyses, the population investigated, and the potential for a multi-faceted interplay between patient characteristics and response to treatment. *Post hoc* analyses of single-groups cannot distinguish between treatment effect modifiers versus non-specific prognostic factors and have a much higher risk of spurious findings. As such, derivation

of clinical prediction rules and reported factors for PFP should ideally be validated in more appropriately design studies that replicate and extend on findings to date, in order to improve confidence that predictions will be reflected within true clinical populations and should be utilized in clinical practice.

Our research looked to explore and test an evidence-reasoned hypothesis for a potential treatment effect modifier. Research into treatment effect modifiers offers great potential in healthcare, and particularly in managing multifactorial conditions, to guide evidence-based clinical practice. We undertook an approach to test the evidence of greater midfoot width mobility as a potential treatment effect modifier for those with PFP [95, 142]. The rational for this study was to optimise the tailoring of treatment to those with PFP, using foot mobility to determine when foot orthoses many be the optimal intervention, and thereby assisting clinicians in the decision-making process. In contrast to preliminary evidence and a plausible biomechanical and clinical rationale, we found greater midfoot width mobility did not have a significant interaction effect between foot orthoses and midfoot width mobility, when compare to hip exercises. In light of our research findings and the absence of other potential treatment effect modifiers [243], future research, and clinicians, may do well to tailor evidence-based treatments on aspects such as patient contextual factors rather than tailoring treatment to physical characteristics of a patient's presentation. Clinicians often muse in the decision-making process, on multiple considerations, for the most appropriate treatment for those with PFP. International consensus recommends hip exercises and foot orthoses in the management of those with PFP. [181] Results from our trial found comparable success with hip exercises or foot orthoses across three key outcome measures of patient-perceived improvement, pain and self-reported functional ability. Until further evidence is provided to help guide treatment selection, clinicians may well be best suited to provide good training, technique and patient engagement to optimise compliance on the chosen treatment. In consideration of our results compared to other studies that utilised wait-and-see cohorts [93, 142], our results support that foot orthoses and hip exercises, as applied in chapter 6, can offer benefits to those with PFP, compared to wait

and see, and can readily be replicated in clinical practice. An obvious path for future research would be to combine both foot orthoses and hip exercises, with consideration given to the inclusions of quadricep strengthening exercises, to see if there is any summative effect for success rates.

8.6 Clinical implications

One critical consideration is what size of interaction between a patient characteristic (i.e. midfoot width mobility) and a treatment (i.e. foot orthoses or hip exercises) would be needed to be useful for guiding clinicians and patients in shared decision making [136]. In our study, results across a range of secondary outcome measures do not support midfoot width mobility, as a cut-off (≥11mm) or as a continuous measurement, as a treatment effect modifier for prescribing foot orthoses over hip exercises. Although there appeared to be small p-values favoring hip exercises versus foot orthoses at 12 weeks on three subscales of a single questionnaire, the clinical significance of these findings remains questionable as there was no evidence of any differences between groups with respect to the other 22 secondary outcome measures (Appendix 17).

A case study was undertaken, in parallel with the trial, as an exemplar of a clinical case. The case was a 23yr old female with 10yr history of PFP was presented in chapter 7. The treatment approach of addressing foot-posture factors was selected off symptoms reported from a combination of pain provocation on stairs identified in the patient interview, physical examination of >11 mm midfoot width mobility from non-weight bearing to weight bearing, and a beneficial response to a treatment direction test where anti-pronation tape was able to reduce the patient's pain and increase capacity to tolerate ascending stairs [164, 295].

The patient noted an immediate improvement with foot orthoses and foot exercises, and by the second week was progressed to only foot exercises, that were increased in difficulty over time. The patient reported a marked improvement in her symptoms, and eventually full resolution over the ensuing

3 months. This case study demonstrated a clinically reasoned treatment approach as an example of how to apply the research in clinical practice. The positive response to the treatment direction test and progression of exercises raises some pertinent considerations and questions. Our understanding and management of PFP has historically evolved from biomechanical and tissue stress paradigms, and the mechanical effects of the intervention. Yet the presentation of PFP, and outcomes often utilised encompass all perspectives of a biopsychosocial paradigm. Could a patient's response to a treatment direction test suitably capture a biological and psychosocial response to a treatment? Could treatment direction test be a suitable approach to inform clinicians in the selection of an appropriate treatment i.e. foot orthoses if a positive response as outline above for those with PFP? For example, a response to the treatment direction test could be the result of an effect on the biological and/ or neurosensory systems, be in alignment with a patient's beliefs or preferences, all of which could then drive the patient-therapist education and alliance. Overall, case study raises important considerations for further research.

Results of this trial are consistent with current evidence that hip exercises or foot orthoses are effective in reducing pain and improving functional outcomes in the short term. Each treatment has specific considerations that both the clinician and patient need to reflect upon during the shared-decision making process. Considerations such as patient preference and cost. For example, the hip exercises require diligence, patient engagement and a more active investment of time and effort. Foot orthoses are a more passive approach that require a financial cost in acquiring the orthoses, plus potential suitable footwear, and diligence in wearing them plus the accompanying exercises. Given comparable benefits between both treatments, an appropriate would be to adopt a shared decision-making process between the clinician and patient where treatment options of either foot orthoses or hip exercises are discussed and decided upon.

8.7 Implications for future research

Our study supports previous evidence that foot orthoses are an excellent treatment option for those with PFP but it remains unknown which patient would benefit most from foot orthoses [181]. Preliminary evidence from a small case series study reported foot orthoses benefit those with reduced ankle dorsiflexion and report an immediate reduction in pain doing a functional task (i.e. step-ups) when a foot orthoses is in place [277]. A plausible selection approach for foot orthoses could be the use of treatment-direction tests, using their immediate response to intervention(s) to infer prognosis for one intervention tested or prescription to select between interventions if two or more interventions are tested) [164]. This would help to capture informed patient engagement in the decision-making process and may help to optimise success rates. Future studies could investigate treatment that have an immediate reduction in pain doing a physical task as a tailoring approach to identify those who might benefit most from foot orthoses. It could be plausible to allocate treatment based on an initial response to a particular treatment and then randomised to an additional intervention, such as hip exercises and/ or education and activity modification.

It is worthwhile investigating if a combined approach of utilising both foot orthoses and hip exercise is more effective. The two treatments investigated in this research offer comparable benefits but address PFP from opposing ends. No studies have investigated a combined hip and foot focused program, to other interventions or a wait-and-see approach. Previously studies have reported comparable success rates, depending on the definition of success, with a hip-and-core focused program [94], foot orthoses[142], a McConnell approach focused on the knee, or a combination of both foot orthoses and knee focused program [92]. One approach could be a stepwise care approach to the management of PFP that includes an educational and activity modification aspect, progressing as required to more active exercises and psychology-informed rehabilitation based on the patient's contextual factors.

Results of the current trial found a lack of statistical differences between foot orthoses and hip exercises across a variety of domains of outcome measures. It is possible that the interventions with foot orthoses and hip exercises may have a shared mechanism of biomechanical / motor control effect, or share a combination of net effects across biomechanical, neurophysiological and psychosocial domains in the management of PFP. The body of literature around the aetiology and understanding of PFP has been focussed on biomechanical hypotheses for mechanisms of effect [241]. However, the mechanism(s) of effect of treatments for managing PFP remain relatively unknown. It was gratifying to observe the success rates of participants with PFP, irrespective of their foot mobility and proximal or distal intervention. This observation strengths the point that decisions about whether effects of treatment are meaningful or large enough to make the costs, inconvenience or harm worthwhile are best made by patients, not by clinicians or researchers [296]. Although applying the intervention protocols could achieve a lot to reduce the burden of this recalcitrant problem affecting up to 29% of society, it is also hoped that future research will offer new directions that further optimise outcomes. Future studies could look to utilise a ‘benefit-harm trade-off method’, for assessing clinically important effects of intervention [297]. This approach presents the involved patients with estimates of the benefits and harms associated with a certain intervention; to which they then to comment on whether they would choose the intervention (i.e. has meaningful benefit). Cost, time, the amount of benefit from combining effective treatments, individual patient profile and most importantly patient preferences may all be important considerations for future research to achieve these aims.

8.8 Limitations and considerations

While the trial was designed to be as clinically feasible and realistic as possible, replicating previously effective protocols, certain considerations need to be taken into account with regards to the clinical implications of this research. The hip exercise protocol required the participant to attend three sessions a week of face to face supervised exercise with a physiotherapist. This allowed monitoring of adherence and ensured compliance with the

exercises, however time and financial costs of this may present a barrier for patients. The hip protocol was only four weeks in duration and while this high stimulus will induce large neural adaptations in the short term [298] further progressions of exercises may be required to build greater capacity, assist a return to full functional demands and potentially greater success rates.

With a sample of 218 participants we found no significant difference between groups in the primary outcome, or of any real significance across multiple secondary outcome measures. Whilst the hip exercises primarily targeted the hip abductor, external rotator and extensor muscle groups, we only measured the hip abductor and external rotator muscle strength, as these are the one highlighted to have deficits in those with PFP. It is possible that a difference between treatment groups may have been found, but it is questionable if the difference would have any clinical relevance in light of no difference in other outcome measures. The secondary analysis of midfoot width as a continuous measure found no association between midfoot width mobility and treatment outcome. It could be proposed that the sample size in chapter 6 may have been insufficient to detect important differences in treatment effect. Further questions could be raised on the powering of the study for 50% difference in treatment success between foot orthoses and hip exercises. Given the fact that key comparisons did not approach statistical significance, it seems unlikely that a greater sample size would result in different findings.

The absence of a control group limits some comparison of results as natural resolution of symptoms or placebo effect cannot be excluded. Results from this trial found foot orthoses or hip exercises offer similar success rates (48% (48/100) vs 50% (48/96) respectively). It is unlikely that 48-50% would have improved with a wait-and-see or usual care approach. Previous research showed a success rate of 47% (9/10) with foot orthoses but a wait-and-see approach reported only 5% (1/19) success rates [142], while another study reported a 42%(26/62) success rate with exercise therapy, and only 35%(21/60) success rates with usual care (i.e. education and advice of cessation of provoking activites) [93].Given the average duration of PFP in the sample in chapter 6 was 53.8 (SD 61.2) months, there is a strong body of

evidence to extrapolate that both arms of the current trial achieved in the region of 13-45% over usual care or wait-and-see approaches.

A recent mixed methods study incorporating level one evidence with expert clinical reasoning reported tailoring treatment is one of four recommendations in effective management of PFP [86]. A key consideration is to tailor treatments to the individual and not the condition. This is a complex problem when dealing with multifactorial conditions. Patients with different intrinsic and extrinsic characteristics may respond differently to any particular treatment. This project demonstrated that midfoot width mobility does not predict response with foot orthoses or hip exercises, and that foot orthoses and hip exercises offer comparable benefits. If the problems presented in tailoring treatment can be solved, solutions might need to shift from focus on biomechanical factors to also actively engaging patients in the informed decision-making processes for treatment selection. Some patients may prefer a management approach that is less time and effort intensive, such as foot orthoses. Some may prefer to undertake an active management approach doing hip exercises, which requires dedicated time and effort to complete the exercises. Some may experience an immediate modification in symptoms and improved function with foot orthoses [164, 277] that could then encourage confidence and self-efficacy for addition of active exercises as well. Optimising treatment could be based as much on the patient's thoughts, presenting and explaining the evidence to the patient and enable a shared decision-making process, as the effects on proximal and distal function of the lower limb.

List of References

1. Gage, B.E., N.M. McIlvain, C.L. Collins, S.K. Fields, and R. Dawn Comstock, *Epidemiology of 6.6 Million Knee Injuries Presenting to United States Emergency Departments From 1999 Through 2008.* Academic Emergency Medicine, 2012. **19**(4): p. 378-385.
2. Dye, S.F., *The pathophysiology of patellofemoral pain: a tissue homeostasis perspective.*, in *Clin Orthop Relat Res*2005. p. 100-110.
3. Loudon, J.K., *Biomechanics and Pathomechanics of the Patellofemoral Joint.* Int J Sports Phys Ther, 2016. **11**(6): p. 820-830.
4. Crossley, K.M., J.J. Stefanik, J. Selfe, N.J. Collins, I.S. Davis, C.M. Powers, J. McConnell, B. Vicenzino, D.M. Bazett-Jones, J.-F. Esculier, D. Morrissey, and M.J. Callaghan, *2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: Terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures.* British Journal of Sports Medicine, 2016. **50**(14): p. 839-843.
5. Dye, S.F., *Patellofemoral Pain Current Concepts: An Overview.* Sports Medicine and Arthroscopy Review, 2001. **9**(4): p. 264.
6. Rathleff, M.S., E.M. Roos, J.L. Olesen, and S. Rasmussen, *High prevalence of daily and multi-site pain--a cross-sectional population-based study among 3000 Danish adolescents.* BMC Pediatrics, 2013. **13**(1): p. 191.
7. Myer, G.D., K.R. Ford, K.D. Barber Foss, A. Goodman, A. Ceasar, M.J. Rauh, J.G. Divine, and T.E. Hewett, *The incidence and potential pathomechanics of patellofemoral pain in female athletes.* Clinical Biomechanics, 2010. **25**(7): p. 700-707.
8. Boling, M., D. Padua, S. Marshall, K. Guskiewicz, S. Pyne, and A. Beutler, *Gender differences in the incidence and prevalence of patellofemoral pain syndrome.* Scandinavian journal of medicine & science in sports, 2010. **20**(5): p. 725-730.
9. Witvrouw, E., R. Lysens, J. Bellemans, D. Cambier, and G. Vanderstraeten, *Intrinsic Risk Factors For the Development of Anterior Knee Pain in an Athletic Population A Two-Year Prospective Study.* The American journal of sports medicine, 2000. **28**(4): p. 480-489.
10. Hetsroni, I., *A prospective biomechanical study of the association between foot pronation and the incidence of anterior knee pain among military recruits.*

The Journal of bone and joint surgery. British volume, 2006. **88-B**(7): p. 905-908.

11. Van Tiggelen, D., S. Cowan, P. Coorevits, N. Duvigneaud, and E. Witvrouw, *Delayed vastus medialis obliquus to vastus lateralis onset timing contributes to the development of patellofemoral pain in previously healthy men: a prospective study.* The American journal of sports medicine, 2009. **37**(6): p. 1099-1105.
12. Milgrom, C., A. Finestone, A. Eldad, and N. Shlamkovitch, *Patellofemoral pain caused by overactivity. A prospective study of risk factors in infantry recruits.* The Journal of bone and joint surgery. American volume, 1991. **73**(7): p. 1041-1043.
13. Thomas, M.J., L. Wood, J. Selfe, and G. Peat, *Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review.* BMC musculoskeletal disorders, 2010. **11**(1): p. 201.
14. Crossley, K.M., T.W. Dorn, H. Ozturk, J. van den Noort, A.G. Schache, and M.G. Pandy, *Altered hip muscle forces during gait in people with patellofemoral osteoarthritis.* Osteoarthritis and Cartilage, 2012. **20**(11): p. 1243-1249.
15. Collins, N., S. Bierma-Zeinstra, K. Crossley, R. van Linschoten, B. Vicenzino, and M. van Middelkoop, *Prognostic factors for patellofemoral pain: a multicentre observational analysis.* British Journal of Sports Medicine, 2013. **47**(4): p. 227-233.
16. Kannus, P. and S. Niittymäki, *Which factors predict outcome in the nonoperative treatment of patellofemoral pain syndrome? A prospective follow-up study.* Med Sci Sports Exerc, 1994. **26**(3): p. 289-96.
17. Powers, C., L. Bolgla, M. Callaghan, N. Collins, and F. Sheehan, *Patellofemoral pain: proximal, distal, and local factors, 2nd International Research Retreat.* J Orthop Sports Phys Ther, 2012. **42**(6): p. A1-54.
18. Tenforde, A.S., L.C. Sayres, M.L. McCurdy, H. Collado, K.L. Sainani, and M. Fredericson, *Overuse injuries in high school runners: lifetime prevalence and prevention strategies.* PM & R : the journal of injury, function, and rehabilitation, 2011. **3**(2): p. 125-31- quiz 131.
19. Collado, H. and M. Fredericson, *Patellofemoral pain syndrome.* Clinics in sports medicine, 2010. **29**(3): p. 379-398.
20. Witvrouw, E., S. Werner, C. Mikkelsen, D. Van Tiggelen, L. Vanden Berghe, and G. Cerulli, *Clinical classification of patellofemoral pain syndrome:*

guidelines for non-operative treatment. Knee Surg Sports Traumatol Arthrosc, 2005. **13**(2): p. 122-30.

21. Brukner, P. and K. Khan, *Clinical sports medicine*. 4th ed. ed. 2012: McGraw-Hill Australia Pty Ltd.
22. Thomee, R., J. Augustsson, and J. Karlsson, *Patellofemoral Pain Syndrome.* Sports Medicine, 1999. **28**(4): p. 245-262.
23. Rathleff, C.R., W.N. Baird, J.L. Olesen, E.M. Roos, S. Rasmussen, and M.S. Rathleff, *Hip and knee strength is not affected in 12-16 year old adolescents with patellofemoral pain - a cross-sectional population-based study.* PloS one, 2013. **8**(11): p. e79153.
24. Rathleff, M.S., E.M. Roos, J.L. Olesen, S. Rasmussen, and L. Arendt-Nielsen, *Lower Mechanical Pressure Pain Thresholds in Female Adolescents With Patellofemoral Pain Syndrome.* The Journal of orthopaedic and sports physical therapy, 2013. **43**(6): p. 414-421.
25. Piva, S.R., G.K. Fitzgerald, S. Wisniewski, and A. Delitto, *Predictors of pain and function outcome after rehabilitation in patients with patellofemoral pain syndrome.* Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 2009. **41**(8): p. 604-612.
26. Powers, C.M., L.A. Bolgla, M.J. Callaghan, N.J. Collins, and F.T. Sheehan, *Patellofemoral pain: proximal, distal, and local factors, 2nd International Research Retreat.* The Journal of orthopaedic and sports physical therapy, 2012. **42**(6): p. A1-54.
27. Willson, J.D. and I.S. Davis, *Lower extremity mechanics of females with and without patellofemoral pain across activities with progressively greater task demands.* JCLB, 2008. **23**(2): p. 203-211.
28. Powers, C.M., S.R. Ward, M. Fredericson, M. Guillet, and F.G. Shellock, *Patellofemoral kinematics during weight-bearing and non-weight-bearing knee extension in persons with lateral subluxation of the patella: a preliminary study.* The Journal of orthopaedic and sports physical therapy, 2003. **33**(11): p. 677-685.
29. Sheehan, F.T., A. Derasari, K.M. Fine, T.J. Brindle, and K.E. Alter, *Q-angle and J-sign: indicative of maltracking subgroups in patellofemoral pain.* Clinical orthopaedics and related research, 2010. **468**(1): p. 266-275.
30. Dye, S.F., *The Pathophysiology of Patellofemoral Pain.* Clinical orthopaedics and related research, 2005. **&NA;**(436): p. 100-110.

31. Sanchis-Alfonso, V., E. Roselló-Sastre, F. Revert, and A. García, *Histologic retinacular changes associated with ischemia in painful patellofemoral malalignment.* Orthopedics, 2005. **28**(6): p. 593-599.
32. Brechter, J.H. and C.M. Powers, *Patellofemoral stress during walking in persons with and without patellofemoral pain.* Medicine and science in sports and …, 2002.
33. Farrokhi, S., J.H. Keyak, and C.M. Powers, *Individuals with patellofemoral pain exhibit greater patellofemoral joint stress: a finite element analysis study.* Osteoarthritis Cartilage, 2011. **19**(3): p. 287-94.
34. Hinman, R.S., J. Lentzos, B. Vicenzino, and K.M. Crossley, *Is patellofemoral osteoarthritis common in middle-aged people with chronic patellofemoral pain?*, in *Arthritis Care Res (Hoboken)*2014. p. 1252-1257.
35. van der Heijden, R.A., E.H. Oei, E.E. Bron, J. van Tiel, P.L. van Veldhoven, S. Klein, J.A. Verhaar, G.P. Krestin, S.M. Bierma-Zeinstra, and M. van Middelkoop, *No Difference on Quantitative Magnetic Resonance Imaging in Patellofemoral Cartilage Composition Between Patients With Patellofemoral Pain and Healthy Controls.* Am J Sports Med, 2016. **44**(5): p. 1172-8.
36. van der Heijden, R.A., J.L. de Kanter, S.M. Bierma-Zeinstra, J.A. Verhaar, P.L. van Veldhoven, G.P. Krestin, E.H. Oei, and M. van Middelkoop, *Structural Abnormalities on Magnetic Resonance Imaging in Patients With Patellofemoral Pain: A Cross-sectional Case-Control Study.* Am J Sports Med, 2016. **44**(9): p. 2339-46.
37. Engel, G.L., *The clinical application of the biopsychosocial model.* Am J Psychiatry, 1980. **137**(5): p. 535-44.
38. O'Sullivan, P., J.P. Caneiro, M. O'Keeffe, and K. O'Sullivan, *Unraveling the Complexity of Low Back Pain.* J Orthop Sports Phys Ther, 2016. **46**(11): p. 932-937.
39. Melzack, R., *Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004.* Pain Pract, 2005. **5**(2): p. 85-94.
40. Rathleff, M.S., E.M. Roos, J.L. Olesen, S. Rasmussen, and L. Arendt-Nielsen, *Lower Mechanical Pressure Pain Thresholds in Female Adolescents With Patellofemoral Pain Syndrome*, in *J Orthop Sports Phys Ther*2013. p. 414-421.
41. Arendt-Nielsen, L. and T. Graven-Nielsen, *Translational musculoskeletal pain research.* Best Pract Res Clin Rheumatol, 2011. **25**(2): p. 209-26.

42. Kasch, H., E. Qerama, F.W. Bach, and T.S. Jensen, *Reduced cold pressor pain tolerance in non-recovered whiplash patients: a 1-year prospective study.* Eur J Pain, 2005. **9**(5): p. 561-9.
43. Sterling, M., G. Jull, B. Vicenzino, and J. Kenardy, *Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery.* Pain, 2003. **104**(3): p. 509-17.
44. Maclachlan, L.R., N.J. Collins, M.L.G. Matthews, P.W. Hodges, and B. Vicenzino, *The psychological features of patellofemoral pain: a systematic review.* Br J Sports Med, 2017. **51**(9): p. 732-742.
45. Wallwork, S.B., V. Bellan, M.J. Catley, and G.L. Moseley, *Neural representations and the cortical body matrix: implications for sports medicine and future directions.* Br J Sports Med, 2016. **50**(16): p. 990-6.
46. Pappas, E. and W.M. Wong-Tom, *Prospective Predictors of Patellofemoral Pain Syndrome: A Systematic Review With Meta-analysis.* Sports Health: A Multidisciplinary Approach, 2012. **4**(2): p. 115-120.
47. Lankhorst, N.E., S.M. Bierma-Zeinstra, and M. van Middelkoop, *Risk factors for patellofemoral pain syndrome: a systematic review.* The Journal of orthopaedic and sports physical therapy, 2012. **42**(2): p. 81-94.
48. Lankhorst, N.E., S.M. Bierma-Zeinstra, and M. van Middelkoop, *Factors associated with patellofemoral pain syndrome: a systematic review.* British Journal of Sports Medicine, 2013. **47**(4): p. 193-206.
49. Haim, A., M. Yaniv, S. Dekel, and H. Amir, *Patellofemoral pain syndrome: validity of clinical and radiological features.* Clinical orthopaedics and related research, 2006. **451**: p. 223-228.
50. Powers, C.M., *Patellar Kinematics, Part II: The Influence of the Depth of the Trochlear Groove in Subjects With and Without Patellofemoral Pain.* Physical therapy, 2000.
51. Souza, R.B., C.E. Draper, M. Fredericson, and C.M. Powers, *Femur rotation and patellofemoral joint kinematics: a weight-bearing magnetic resonance imaging analysis.* The Journal of orthopaedic and sports physical therapy, 2010. **40**(5): p. 277-285.
52. Eckhoff, D.G., W.K. Montgomery, R.F. Kilcoyne, and E.R. Stamm, *Femoral morphometry and anterior knee pain.* Clinical orthopaedics and related research, 1994(302): p. 64-68.
53. Laprade, J. and E. Culham, *Radiographic measures in subjects who are asymptomatic and subjects with patellofemoral pain syndrome.* Clinical orthopaedics and related research, 2003(414): p. 172-182.

54. McConnell, J., *Management of patellofemoral problems.* Manual Therapy, 1996. **1**(2): p. 60-66.
55. Cowan, S.M., K.L. Bennell, P.W. Hodges, K.M. Crossley, and J. McConnell, *Delayed onset of electromyographic activity of vastus medialis obliquus relative to vastus lateralis in subjects with patellofemoral pain syndrome.* Archives of physical medicine and rehabilitation, 2001. **82**(2): p. 183-189.
56. Witvrouw, E., C. Sneyers, R. Lysens, J. Victor, and J. Bellemans, *Reflex response times of vastus medialis oblique and vastus lateralis in normal subjects and in subjects with patellofemoral pain syndrome.* The Journal of orthopaedic and sports physical therapy, 1996. **24**(3): p. 160-165.
57. Chester, R., T.O. Smith, D. Sweeting, J. Dixon, S. Wood, and F. Song, *The relative timing of VMO and VL in the aetiology of anterior knee pain: a systematic review and meta-analysis.* BMC musculoskeletal disorders, 2008. **9**: p. 64.
58. Cowan, S.M., P.W. Hodges, K.L. Bennell, and K.M. Crossley, *Altered vastii recruitment when people with patellofemoral pain syndrome complete a postural task.* Archives of physical medicine and rehabilitation, 2002. **83**(7): p. 989-995.
59. Powers, C.M., *The influence of abnormal hip mechanics on knee injury: a biomechanical perspective.* The Journal of orthopaedic and sports physical therapy, 2010. **40**(2): p. 42-51.
60. Souza, R.B. and C.M. Powers, *Differences in hip kinematics, muscle strength, and muscle activation between subjects with and without patellofemoral pain.* The Journal of orthopaedic and sports physical therapy, 2009. **39**(1): p. 12-19.
61. Noehren, B., J. Hamill, and I. Davis, *Prospective evidence for a hip etiology in patellofemoral pain*, 2013.
62. Noehren, B., M.B. Pohl, Z. Sanchez, T. Cunningham, and C. Lattermann, *Proximal and distal kinematics in female runners with patellofemoral pain.* JCLB, 2012. **27**(4): p. 366-371.
63. Boling, M.C., D.A. Padua, S.W. Marshall, K. Guskiewicz, S. Pyne, and A. Beutler, *A Prospective Investigation of Biomechanical Risk Factors for Patellofemoral Pain Syndrome: The Joint Undertaking to Monitor and Prevent ACL Injury (JUMP-ACL) Cohort.* The American journal of sports medicine, 2009. **37**(11): p. 2108-2116.

64. Ireland, M.L., J.D. Willson, B.T. Ballantyne, and I.S. Davis, *Hip strength in females with and without patellofemoral pain.* The Journal of orthopaedic and sports physical therapy, 2003. **33**(11): p. 671-676.
65. Magalhães, E., T.Y. Fukuda, S.N. Sacramento, A. Forgas, M. Cohen, and R.J. Abdalla, *A comparison of hip strength between sedentary females with and without patellofemoral pain syndrome.* The Journal of orthopaedic and sports physical therapy, 2010. **40**(10): p. 641-647.
66. Thijs, Y., E. Pattyn, D. Van Tiggelen, L. Rombaut, and E. Witvrouw, *Is hip muscle weakness a predisposing factor for patellofemoral pain in female novice runners? A prospective study.* The American journal of sports medicine, 2011. **39**(9): p. 1877-1882.
67. Piva, S.R., E.A. Goodnite, and J.D. Childs, *Strength around the hip and flexibility of soft tissues in individuals with and without patellofemoral pain syndrome.* The Journal of orthopaedic and sports physical therapy, 2005. **35**(12): p. 793-801.
68. Bolgla, L.A., T.R. Malone, B.R. Umberger, and T.L. Uhl, *Hip strength and hip and knee kinematics during stair descent in females with and without patellofemoral pain syndrome.* The Journal of orthopaedic and sports physical therapy, 2008. **38**(1): p. 12-18.
69. Brindle, T.J., C. Mattacola, and J. McCrory, *Electromyographic changes in the gluteus medius during stair ascent and descent in subjects with anterior knee pain.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA, 2003. **11**(4): p. 244-251.
70. Cowan, S.M., K.M. Crossley, and K.L. Bennell, *Altered hip and trunk muscle function in individuals with patellofemoral pain.* British Journal of Sports Medicine, 2009. **43**(8): p. 584-588.
71. Bazett-Jones, D.M., S.C. Cobb, W.E. Huddleston, K.M. O'Connor, B.S.R. Armstrong, and J.E. Earl-Boehm, *Effect of patellofemoral pain on strength and mechanics after an exhaustive run.* Medicine and science in sports and exercise, 2013. **45**(7): p. 1331-1339.
72. Dierks, T.A., K.T. Manal, J. Hamill, and I.S. Davis, *Lower extremity kinematics in runners with patellofemoral pain during a prolonged run.* Medicine and science in sports and exercise, 2011. **43**(4): p. 693-700.
73. Tiberio, D., *The effect of excessive subtalar joint pronation on patellofemoral mechanics: a theoretical model.* The Journal of orthopaedic and sports physical therapy, 1987. **9**(4): p. 160-165.

74. Brody, D.M., *Evaluation of the injured runner.* Techniques in Orthopaedics, 1990. **5**(3): p. 15.
75. Redmond, A.C., J. Crosbie, and R.A. Ouvrier, *Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index.* JCLB, 2006. **21**(1): p. 89-98.
76. McPoil, T.G., B. Vicenzino, M.W. Cornwall, N.J. Collins, and M. Warren, *Reliability and normative values for the foot mobility magnitude: a composite measure of vertical and medial-lateral mobility of the midfoot.* Journal of Foot and Ankle Research, 2009. **2**: p. 6.
77. Barton, C.J., H.B. Menz, P. Levinger, K.E. Webster, and K.M. Crossley, *Greater peak rearfoot eversion predicts foot orthoses efficacy in individuals with patellofemoral pain syndrome.* British Journal of Sports Medicine, 2011. **45**(9): p. 697-701.
78. Barton, C.J., D. Bonanno, P. Levinger, and H.B. Menz, *Foot and ankle characteristics in patellofemoral pain syndrome: a case control and reliability study.* The Journal of orthopaedic and sports physical therapy, 2010. **40**(5): p. 286-296.
79. Levinger, P. and W. Gilleard, *Tibia and rearfoot motion and ground reaction forces in subjects with patellofemoral pain syndrome during walking.* Gait & Posture, 2007. **25**(1): p. 2-8.
80. Thijs, Y., D. Van Tiggelen, P. Roosen, D. De Clercq, and E. Witvrouw, *A prospective study on gait-related intrinsic risk factors for patellofemoral pain.* Clinical Journal of Sport Medicine, 2007. **17**(6): p. 437-445.
81. Thijs, Y., D. De Clercq, P. Roosen, and E. Witvrouw, *Gait-related intrinsic risk factors for patellofemoral pain in novice recreational runners.* British Journal of Sports Medicine, 2008. **42**(6): p. 466-471.
82. Noehren, B., M.B. Pohl, Z. Sanchez, T. Cunningham, and C. Lattermann, *Proximal and distal kinematics in female runners with patellofemoral pain.* Clinical Biomechanics, 2012. **27**(4): p. 366-371.
83. Duffey, M.J., D.F. Martin, D.W. Cannon, T. Craven, and S.P. Messier, *Etiologic factors associated with anterior knee pain in distance runners.* Med Sci Sports Exerc, 2000. **32**(11): p. 1825-32.
84. Barton, C.J., P. Levinger, K.E. Webster, and H.B. Menz, *Walking kinematics in individuals with patellofemoral pain syndrome: a case-control study.* Gait Posture, 2011. **33**(2): p. 286-91.

85. Duffey, M.J., D.F. Martin, D.W. Cannon, T. Craven, and S.P. Messier, *Etiologic factors associated with anterior knee pain in distance runners.* Medicine and science in sports and exercise, 2000. **32**(11): p. 1825-1832.
86. Barton, C.J., S. Lack, S. Hemmings, S. Tufail, and D. Morrissey, *The Best Practice Guide to Conservative Management of Patellofemoral Pain: incorporating level 1 evidence with expert clinical reasoning.* British Journal of Sports Medicine 2015. **49**: p. 923-934.
87. Rothermich, M.A., N.R. Glaviano, J. Li, and J.M. Hart, *Patellofemoral Pain: Epidemiology, Pathophysiology, and Treatment Options.* Clinics in Sports Medicine, 2015. **34**(2): p. 313-327.
88. Fulkerson, J.P., *Diagnosis and treatment of patients with patellofemoral pain.* Am J Sports Med, 2002. **30**(3): p. 447-56.
89. Post, W.R., *Anterior knee pain: diagnosis and treatment.* J Am Acad Orthop Surg, 2005. **13**(8): p. 534-43.
90. Kettunen, J.A., A. Harilainen, J. Sandelin, D. Schlenzka, K. Hietaniemi, S. Seitsalo, A. Malmivaara, and U.M. Kujala, *Knee arthroscopy and exercise versus exercise only for chronic patellofemoral pain syndrome: a randomized controlled trial.*, in *BMC Med*2007. p. 38.
91. Kettunen, J.A., A. Harilainen, J. Sandelin, D. Schlenzka, K. Hietaniemi, S. Seitsalo, A. Malmivaara, and U.M. Kujala, *Knee arthroscopy and exercise versus exercise only for chronic patellofemoral pain syndrome: 5-year follow-up.* Br J Sports Med, 2012. **46**(4): p. 243-6.
92. Collins, N.J., K.M. Crossley, E. Beller, R. Darnell, T. McPoil, and B. Vicenzino, *Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: randomised clinical trial.* British Medical Journal, 2008. **337**(3): p. 163-168.
93. van Linschoten, R., M. van Middelkoop, M.Y. Berger, E.M. Heintjes, J.A. Verhaar, S.P. Willemsen, B.W. Koes, and S.M. Bierma-Zeinstra, *Supervised exercise therapy versus usual care for patellofemoral pain syndrome: an open label randomised controlled trial.* British Medical Journal, 2009. **339**.
94. Ferber, R., L. Bolgla, J.E. Earl-Boehm, C. Emery, and K. Hamstra-Wright, *Strengthening of the Hip and Core Versus Knee Muscles for the Treatment of Patellofemoral Pain: A Multicenter, Randomized Controlled Trial.* Journal of athletic training, 2015. **50**(4): p. 366-377.
95. Mills, K., P. Blanch, A.R. Chapman, T.G. McPoil, and B. Vicenzino, *Foot orthoses and gait: a systematic review and meta-analysis of literature*

pertaining to potential mechanisms. British Journal of Sports Medicine, 2010. **44**(14): p. 1035-1046.

96. Willson, J.D. and I.S. Davis, *Lower extremity strength and mechanics during jumping in women with patellofemoral pain.* J Sport Rehabil, 2009.
97. Nakagawa, T.H., T.B. Muniz, R.d.M. Baldon, C. Dias Maciel, R.B. de Menezes Reiff, and F.V. Serrão, *The effect of additional strengthening of hip abductor and lateral rotator muscles in patellofemoral pain syndrome: a randomized controlled pilot study.* Clinical rehabilitation, 2008. **22**(12): p. 1051-1060.
98. Dolak, K.L., C. Silkman, J. Medina McKeon, R.G. Hosey, C. Lattermann, and T.L. Uhl, *Hip strengthening prior to functional exercises reduces pain sooner than quadriceps strengthening in females with patellofemoral pain syndrome: a randomized clinical trial.* The Journal of orthopaedic and sports physical therapy, 2011. **41**(8): p. 560-570.
99. Khayambashi, K., Z. Mohammadkhani, Ghaznavi, M. Lyle, and C. Powers, *The effects of isolated hip abductor and external rotator muscle strengthening on pain, health status, and hip strength in females with patellofemoral pain: a randomized controlled trial.* The Journal of orthopaedic and sports physical therapy, 2012. **42**(1): p. 22-29.
100. Fukuda, T.Y., W.P. Melo, B.M. Zaffalon, F.M. Rossetto, E. Magalhães, F.F. Bryk, and R.L. Martin, *Hip posterolateral musculature strengthening in sedentary women with patellofemoral pain syndrome: a randomized controlled clinical trial with 1-year follow-up.* The Journal of orthopaedic and sports physical therapy, 2012. **42**(10): p. 823-830.
101. Dolak, K.L., C. Silkman, J. Medina McKeon, R.G. Hosey, C. Lattermann, and T.L. Uhl, *Hip strengthening prior to functional exercises reduces pain sooner than quadriceps strengthening in females with patellofemoral pain syndrome: a randomized clinical trial.* Journal of Orthopaedic & Sports Physical Therapy, 2011. **41**(8): p. 560-570.
102. Fukuda, T.Y., F.M. Rossetto, E. Magalhães, F.F. Bryk, P.R.G. Lucareli, and N. de Almeida Aparecida Carvalho, *Short-term effects of hip abductors and lateral rotators strengthening in females with patellofemoral pain syndrome: a randomized controlled clinical trial.* The Journal of orthopaedic and sports physical therapy, 2010. **40**(11): p. 736-742.
103. Ferber, R., K.D. Kendall, and L. Farr, *Changes in knee biomechanics after a hip-abductor strengthening protocol for runners with patellofemoral pain syndrome.* Journal of athletic training, 2011. **46**(2): p. 142.

104. Khayambashi, K., A. Fallah, and A. Movahedi, *Posterolateral Hip Muscle Strengthening verses Quadriceps Strengthening for Patellofemoral Pain: A Comparative Control Trial.* Archives of Physical …, 2014.
105. Snyder, K.R., J.E. Earl, K.M. O'Connor, and K.T. Ebersole, *Resistance training is accompanied by increases in hip strength and changes in lower extremity biomechanics during running.* Clinical biomechanics, 2009. **24**(1): p. 26-34.
106. Vicenzino, B., *Foot orthotics in the treatment of lower limb conditions: a musculoskeletal physiotherapy perspective.* Manual Therapy, 2004.
107. Root, M.L., W.P. Orien, and J.H. Weed, *Normal and abnormal function of the foot.* 1977.
108. McPoil, T.G. and G.C. Hunt, *Evaluation and management of foot and ankle disorders: present problems and future directions.* The Journal of orthopaedic and sports physical therapy, 1995. **21**(6): p. 381-388.
109. Hertel, J., B.R. Sloss, and J.E. Earl, *Effect of foot orthotics on quadriceps and gluteus medius electromyographic activity during selected exercises.* Archives of physical medicine and rehabilitation, 2005. **86**(1): p. 26-30.
110. Nigg, B.M., M.A. Nurse, and D.J. Stefanyshyn, *Shoe inserts and orthotics for sport and physical activities.* … and science in sports and …, 1999.
111. Mills, K., P. Blanch, P. Dev, M. Martin, and B. Vicenzino, *A randomised control trial of short term efficacy of in-shoe foot orthoses compared with a wait and see policy for anterior knee pain and the role of foot mobility.* BMJ: British Medical Journal, 2012. **46**(4): p. 247-252.
112. Barton, C.J., H. Menz, and K.M. Crossley, *Effects of prefabricated foot orthoses on pain and function in individuals with patellofemoral pain syndrome: a cohort study.* Physical Therapy in Sport, 2011. **12**(2): p. 70-75.
113. Crossley, K.M., K.L. Bennell, S. Green, S. Cowan, and J. McConnell, *Physical therapy for patellofemoral pain: a randomized, double-blinded, placebo-controlled trial.* The American journal of sports medicine, 2002. **30**(6): p. 857-865.
114. Rathleff, M.S., C.R. Rathleff, J.L. Olesen, S. Rasmussen, and E.M. Roos, *Is Knee Pain During Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee Pain.* The American Journal of Sports Medicine, 2016. **44**(5): p. 1165-71.
115. Collins, N.J., S.M. Bierma-Zeinstra, K.M. Crossley, R.L. van Linschoten, B. Vicenzino, and M. van Middelkoop, *Prognostic factors for patellofemoral pain:*

a multicentre observational analysis. British Journal of Sports Medicine, 2013. **47**(4): p. 227-233.

116. Mølgaard, C., M.S. Rathleff, and O. Simonsen, *Patellofemoral pain syndrome and its association with hip, ankle, and foot function in 16- to 18-year-old high school students: a single-blind case-control study.* Journal of the American Podiatric Medical Association, 2011. **101**(3): p. 215-222.
117. Witvrouw, E., R. Lysens, J. Bellemans, D. Cambier, and G. Vanderstraeten, *Intrinsic risk factors for the development of anterior knee pain in an athletic population: A two-year prospective study.* The American journal of sports medicine, 2000. **28**(4): p. 480-489.
118. Boling, M., D. Padua, S. Marshall, K. Guskiewicz, S. Pyne, and A. Beutler, *Gender differences in the incidence and prevalence of patellofemoral pain syndrome.* Scandinavian Journal of Medicine & Science in Sports., 2010. **20**(5): p. 725-730.
119. Roush, J.R. and R. Curtis Bay, *Prevalence of anterior knee pain in 18-35 year-old females.* The International Journal of Sports Physical Therapy, 2012. **7**(4): p. 396-401.
120. Nimon, G., D. Murray, M. Sandow, and J. Goodfellow, *Natural history of anterior knee pain: A 14- to 20-year follow-up of nonoperative management.* Journal of Pediatric Orthopaedics, 1998. **18**(1): p. 118-122.
121. Lack, S., C. Barton, B. Vicenzino, and D. Morrissey, *Outcome Predictors for Conservative Patellofemoral Pain Management: A Systematic Review and Meta-Analysis.* Sports Medicine, 2014. **44**(12): p. 1703-1716.
122. Moons, K.G.M., P. Royston, Y. Vergouwe, D.E. Grobbee, and D.G. Altman, *Prognosis and prognostic research: what, why, and how?* Biritch Medical Journal, 2009. **338**: p. b375.
123. Collins, G.S., J.B. Reitsma, D.G. Altman, and K.G. Moons, *Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement.* BMC Medicine, 2015. **13**(1): p. b375.
124. Hancock, M., R.D. Herbert, and C.G. Maher, *A guide to interpretation of studies investigating subgroups of responders to physical therapy interventions.* Physical Therapy 2009. **89**(7): p. 698-704.
125. Moher, D., A. Liberati, and J. Tetzlaff, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* Annals of Internal Medicine, 2009. **151**(4): p. 264-269.

126. Heintjes, E.M., M. Berger, S.M. Bierma-Zeinstra, R.M. Bernsen, J.A. Verhaar, and B.W. Koes, *Exercise therapy for patellofemoral pain syndrome.* Cochrane Database Syst Rev, 2003(4).
127. van der Heijden, R.A., N.E. Lankhorst, R. van Linschoten, S.M. Bierma-Zeinstra, and M. van Middelkoop, *Exercise for treating patellofemoral pain syndrome.* Cochrane Database Syst Rev, 2015. **1**: p. CD010387.
128. Genaidy, A.M. and G.K. LeMasters, *The epidemiological appraisal instrument (EAI): a brief overview.* Theoretical Issues in Ergonomics Science, 2006. **7**(3): p. 187-189.
129. Nix, S.E., B.T. Vicenzino, N.J. Collins, and M.D. Smith, *Characteristics of foot structure and footwear associated with hallux valgus: a systematic review.* Osteoarthritis and Cartilage., 2012. **20**(10): p. 1059-1074.
130. Rathleff, M.S., C.R. Rathleff, K.M. Crossley, and C.J. Barton, *Is hip strength a risk factor for patellofemoral pain? A systematic review and meta-analysis.* British Journal of Sports Medicine, 2014. **0**: p. 1-12.
131. Genaidy, A.M., G.K. Lemasters, J. Lockey, P. Succop, J. Deddens, T. Sobeih, and K. Dunning, *An epidemiological appraisal instrument - a tool for evaluation of epidemiological studies.* Ergonomics, 2007. **50**(6): p. 920-960.
132. Cook, C., J.-M. Brismée, R. Pietrobon, J. Sizer, Philip, E. Hegedus, and D.L. Riddle, *Development of a Quality Checklist Using Delphi Methods for Prescriptive Clinical Prediction Rules: The QUADCPR.* Journal of Manipulative and Physiological Therapeutics, 2010. **33**(1): p. 29-41.
133. Moons, K.G., D.G. Altman, J.B. Reitsma, J.P. Ioannidis, P. Macaskill, E.W. Steyerberg, A.J. Vickers, D.F. Ransohoff, and G.S. Collins, *Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration.* Annals of internal medicine, 2015. **162**(1): p. W1-73.
134. Cook, C., E. Hegedus, R. Hawkins, F. Scovell, and D. Wyland, *Diagnostic accuracy and association to disability of clinical test findings associated with patellofemoral pain syndrome.* Physiotherapy Canada, 2010. **62**(1): p. 17-24.
135. Hancock, M.J., P. Kjaer, L. Korsholm, and P. Kent, *Interpretation of subgroup effects in published trials.* Physical Therapy, 2013. **93**(6): p. 852-859.
136. Jaeschke, R., G.H. Guyatt, D.L. Sackett, and G. Guyatt, *Guides to the Medical Literature: III. How to Use an Article About a Diagnostic Test B. What Are the Results and Will They Help Me in Caring for My Patients?* Journal of the American Medical Association, 1994. **271**(9): p. 703-707.

137. Collins, N.J., K.M. Crossley, R. Darnell, and B. Vicenzino, *Predictors of short and long term outcome in patellofemoral pain syndrome: a prospective longitudinal study.* BMC Musculoskelet Disorders, 2010. **11**: p. 11.
138. Peng, H.-T. and C.-Y. Song, *Predictors of treatment response to strengthening and stretching exercises for patellofemoral pain: An examination of patellar alignment.* The Knee, 2015. **22**(6): p. 494-498.
139. Vittinghoff, E. and C.E. McCulloch, *Relaxing the rule of ten events per variable in logistic and Cox regression.* American journal of epidemiology 2007. **165**(6): p. 710-718.
140. Vicenzino, B., N.J. Collins, J. Cleland, and T. McPoil, *A clinical prediction rule for identifying patients with patellofemoral pain who are likely to benefit from foot orthoses: a preliminary determination.* British Journal of Sports Medicine, 2010. **44**(12): p. 862-866.
141. Lan, T., W. Lin, C. Jiang, and H. Chiang, *Immediate effect and predictors of effectiveness of taping for patellofemoral pain syndrome: a prospective cohort study.* The American Journal of Sports Medicine, 2010. **38**(8): p. 1626-1630.
142. Mills, K., P. Blanch, P. Dev, M. Martin, and B. Vicenzino, *A randomised control trial of short term efficacy of in-shoe foot orthoses compared with a wait and see policy for anterior knee pain and the role of foot mobility.* British Medical Journal, 2012. **46**(4): p. 247-252.
143. Barton, C.J., H.B. Menz, and K.M. Crossley, *Clinical predictors of foot orthoses efficacy in individuals with patellofemoral pain.* Medicine & Science in Sports & Exercise 2011. **43**(9): p. 1603-1610.
144. Crowell, M.S. and N.H. Wofford, *Lumbopelvic manipulation in patients with patellofemoral pain syndrome.* Journal of Manual & Manipulative Therapy, 2012. **20**(3): p. 113-120.
145. Witvrouw, E., R. Lysens, J. Bellemans, D. Cambier, A. Cools, L. Danneels, and J. Bourgois, *Which factors predict outcome in the treatment program of anterior knee pain?* Scandinavian journal of medicine & science in sports, 2002. **12**(1): p. 40-46.
146. Blønd, L. and L. Hansen, *Patellofemoral pain syndrome in athletes: a 5.7-year retrospective follow-up study of 250 athletes.* Acta Orthopaedica Belgica, 1998. **64**(4): p. 393-400.
147. Kastelein, M., P.A.J. Luijsterburg, E.M. Heintjes, M. van Middelkoop, J.A.N. Verhaar, B.W. Koes, and S.M.A. Bierma-Zeinstra, *The 6-year trajectory of non-traumatic knee symptoms (including patellofemoral pain) in adolescents*

and young adults in general practice: a study of clinical predictors. British Journal of Sports Medicine, 2015. **49**(6): p. 400-405.

148. Pattyn, E., N. Mahieu, J. Selfe, P. Verdonk, A. Steyaert, and E. Witvrouw, *What predicts functional outcome after treatment for patellofemoral pain?* Medicine and science in sports and exercise, 2012. **44**(10): p. 1827-1833.
149. Kannus, P. and S. Niittymaki, *Which factors predict outcome in the nonoperative treatment of patellofemoral pain syndrome? A prospective follow-up study. .* Medicine & Science in Sports & Exercise, 1994. **26**(3): p. 289-296.
150. Natri, A., P. Kannus, and M. Jarvinen, *Which factors predict the long-term outcome in chronic patellofemoral pain syndrome? A 7-yr prospective follow-up study.* Medicine & Science in Sports & Exercise 1998. **30**(11): p. 1572-1577.
151. Wittstein, J.R., S.D. Brien, E.N. Vinson, and W.E. Garrett, *MRI evaluation of anterior knee pain: predicting response to nonoperative treatment.* Skeletal Radiology, 2009. **38**(9): p. 895-901.
152. Sutlive, T.G., S.D. Mitchell, S.N. Maxfield, C.L. McLean, J.C. Neumann, C.R. Swiecki, R.C. Hall, A.C. Bare, and T.W. Flynn, *Identification of individuals with patellofemoral pain whose symptoms improved after a combined program of foot orthosis use and modified activity: a preliminary investigation.* Physical Therapy, 2004. **84**(1): p. 49-61.
153. Rathleff, M.S., C. Richter, C. Brushøj, J. Bencke, T. Bandholm, P. Hölmich, and K. Thorborg, *Custom-Made Foot Orthoses Decrease Medial Foot Loading During Drop Jump in Individuals With Patellofemoral Pain.* Clinical Journal of Sport Medicine:, 2015. **26**(4): p. 335-337.
154. Iverson, C.A., T.G. Sutlive, M.S. Crowell, R.L. Morrell, M.W. Perkins, M.B. Garber, J.H. Moore, and R.S. Wainner, *Lumbopelvic Manipulation for the Treatment of Patients With Patellofemoral Pain Syndrome: Development of a Clinical Prediction Rule.* Journal of Orthopaedic & Sports Physical Therapy, 2008. **38**(6): p. 297-312.
155. Huang, B.-Y., Y.-F. Shih, W.-Y. Chen, and H.-L. Ma, *Predictors for identifying patients with patellofemoral pain syndrome responding to femoral nerve mobilization.* Archives of Physical Medicine and Rehabilitation, 2015. **96**(5): p. 920-927.
156. Lankhorst, N.E., M. van Middelkoop, Y.D.M. van Trier, R. van Linschoten, B.W. Koes, J.A.N. Verhaar, and S.M. Bierma-Zeinstra, *Can We Predict Which Patients With Patellofemoral Pain Are More Likely to Benefit From Exercise*

Therapy? A Secondary Exploratory Analysis of a Randomized Controlled Trial. Journal of Orthopaedic & Sports Physical Therapy, 2015. **45**(3): p. 183-189.

157. Barton, C.J., D. Bonanno, and H.B. Menz, *Development and evaluation of a tool for the assessment of footwear characteristics.* Journal of Foot and Ankle Research, 2009. **2**: p. 10.
158. McConnell, J., *The management of chondromalacia patellae: a long term solution.* Australian Journal of Physiotherapy, 1986. **32**(4): p. 215-223.
159. Crossley, K.M., M.J. Callaghan, and R. van Linschoten, *Patellofemoral pain.* BMJ, 2015. **351**: p. h3939.
160. Vlaeyen, J.W. and S.J. Linton, *Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art.* Pain, 2000. **85**(3): p. 317-332.
161. Finnoff, J.T., M.M. Hall, K. Kyle, D.A. Krause, J. Lai, and J. Smith, *Hip Strength and Knee Pain in High School Runners: A Prospective Study.* Physcial Medicine and Rehabilitation, 2011. **3**(9): p. 792-801.
162. Mallen, C.D., G. Peat, E. Thomas, K.M. Dunn, and P.R. Croft, *Prognostic factors for musculoskeletal pain in primary care: a systematic review.* British Journal of General Practice, 2007. **57**(541): p. 655-661.
163. Kent, P., M. Hancock, D.H.D. Petersen, and H.L. Mjøsund, *Clinimetrics corner: choosing appropriate study designs for particular questions about treatment subgroups.* Journal of Manual & Manipulative Therapy, 2010. **18**(3): p. 147-152.
164. Vicenzino, B., *Foot orthotics in the treatment of lower limb conditions: a musculoskeletal physiotherapy perspective.* Manual Therapy, 2004. **9**(4): p. 185-196.
165. Barber Foss, K.D. and M.E. Hornsby, Nicholas M. Myer, Gregory D. Hewett, Timothy E. , *Is Body Composition Associated with an Increased Risk of Developing Anterior Knee Pain in Adolescent Female Athletes?* The Physician and Sports medicine 2012. **40**(1).
166. Rathleff, M., E. Roos, J. Olesen, and S. Rasmussen, *Exercise during school hours when added to patient education improves outcome for 2 years in adolescent patellofemoral pain: a cluster randomised trial.* British Journal of Sports Medicine, 2015. **49**(6): p. 406-12.
167. Collins, N.J., L.M. Bisset, K.M. Crossley, and B. Vicenzino, *Efficacy of nonsurgical interventions for anterior knee pain: systematic review and meta-analysis of randomized trials.* Sports Medicine, 2012. **42**(1): p. 31-49.

168. Khayambashi, K., Z. Mohammadkhani, K. Ghaznavi, M.A. Lyle, and C.M. Powers, *The effects of isolated hip abductor and external rotator muscle strengthening on pain, health status, and hip strength in females with patellofemoral pain: a randomized controlled trial.* Journal of Orthopaedic & Sports Physical Therapy, 2012. **42**(1): p. 22-29.
169. Powers, C.M., *The influence of altered lower-extremity kinematics on patellofemoral joint dysfunction: a theoretical perspective.* Journal of Orthopaedic & Sports Physical Therapy, 2003. **33**(11): p. 639-646.
170. Powers, C.M., *The influence of abnormal hip mechanics on knee injury: a biomechanical perspective.* Journal of Orthopaedic & Sports Physical Therapy, 2010. **40**(2): p. 42-51.
171. Witvrouw, E., K. Crossley, I.S. Davis, J. McConnell, and C.M. Powers, *The 3rd International Patellofemoral Research Retreat: An international expert consensus meeting to improve the scientific understanding and clinical management of patellofemoral pain.* British Medical Journal, 2014. **48**(6): p. 408-408.
172. Stanton, T.R., M.J. Hancock, C.G. Maher, and B.W. Koes, *Critical appraisal of clinical prediction rules that aim to optimize treatment selection for musculoskeletal conditions.* Physical Therapy, 2010. **90**(6): p. 843-854.
173. Chan, A.-W., J.M. Tetzlaff, P.C. Gøtzsche, D.G. Altman, H. Mann, J.A. Berlin, K. Dickersin, A. Hróbjartsson, K.F. Schulz, W.R. Parulekar, K. Krleza-Jeric, A. Laupacis, and D. Moher, *SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials.* British Medical Journal, 2013. **346**: p. e7586.
174. Schulz, K.F., D.G. Altman, D. Moher, and C. Group, *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.* BMC Medicine, 2010. **8**(1): p. 18.
175. Boutron, I., D. Moher, D.G. Altman, K.F. Schulz, P. Ravaud, and C. Group, *Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments.* Annals of Internal Medicine, 2008. **148**(4): p. W60-6.
176. Hoffmann, T.C., P.P. Glasziou, I. Boutron, R. Milne, R. Perera, D. Moher, D.G. Altman, V. Barbour, H. Macdonald, M. Johnston, S.E. Lamb, M. Dixon-Woods, P. McCulloch, J.C. Wyatt, A.W. Chan, and S. Michie, *Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide.* British Medical Journal, 2014. **348**: p. g1687.

177. Chan, A.-W., J.M. Tetzlaff, D.G. Altman, K. Dickersin, and D. Moher, *SPIRIT 2013: new guidance for content of clinical trial protocols.* Lancet, 2013. **381**(9861): p. 91-92.
178. McPoil, T.G., B. Vicenzino, and M.W. Cornwall, *Effect of foot orthoses contour on pain perception in individuals with patellofemoral pain.* Journal of the American Podiatric Medical Association, 2011. **101**(1): p. 7-16.
179. Escalona-Marfil, C., T.G. McPoil, R. Mellor, and B. Vicenzino, *A radiographic and anthropometric study of the effect of a contoured sandal and foot orthosis on supporting the medial longitudinal arch.* Journal of Foot and Ankle Research, 2014. **7**(1): p. 38.
180. Fukuda, T.Y., W.P. Melo, B.M. Zaffalon, F.M. Rossetto, E. Magalhães, F.F. Bryk, and R.L. Martin, *Hip posterolateral musculature strengthening in sedentary women with patellofemoral pain syndrome: a randomized controlled clinical trial with 1-year follow-up.* Journal of Orthopaedic & Sports Physical Therapy, 2012. **42**(10): p. 823-830.
181. Crossley, K.M., M. van Middelkoop, M.J. Callaghan, N.J. Collins, M.S. Rathleff, and C.J. Barton, *2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 2: recommended physical interventions (exercise, taping, bracing, foot orthoses and combined interventions).* British Journal of Sports Medicine, 2016. **50**(14): p. 844-852.
182. Toigo, M. and U. Boutellier, *New fundamental resistance exercise determinants of molecular and cellular muscle adaptations.* European Journal of Applied Physiology, 2006. **97**(6): p. 643-663.
183. Steven J Kamper, C.G.M.G.M., *Global Rating of Change Scales: A Review of Strengths and Weaknesses and Considerations for Design.* Journal of Manual & Manipulative Therapy, 2009. **17**(3): p. 163.
184. Klooster, P.M., K.W. Drossaers-Bakker, E. Taal, and M.A. van de Laar, *Patient-perceived satisfactory improvement (PPSI): interpreting meaningful change in pain from the patient's perspective.* Pain, 2006. **121**(1-2): p. 151-7.
185. Kamper, S.J., C.G. Maher, and G. Mackay, *Global Rating of Change Scales: A Review of Strengths and Weaknesses and Considerations for Design.* Journal of Manual & Manipulative Therapy, 2013. **17**(3): p. 163-170.
186. Cook, C., K. Learman, S. Houghton, C. Showalter, and B. O'Halloran, *The addition of cervical unilateral posterior-anterior mobilisation in the treatment of patients with shoulder impingement syndrome: A randomised clinical trial.* Manual Therapy, 2013.

187. Williams, G.N., T.J. Gangel, R.A. Arciero, J.M. Uhorchak, and D.C. Taylor, *Comparison of the Single Assessment Numeric Evaluation method and two shoulder rating scales. Outcomes measures after shoulder surgery.* American Journal of Sports Medicine, 1999. **27**(2): p. 214-21.
188. Williams, G.N., D.C. Taylor, T.J. Gangel, J.M. Uhorchak, and R.A. Arciero, *Comparison of the single assessment numeric evaluation method and the Lysholm score.* Clinical orthopaedics and related research, 2000(373): p. 184-92.
189. Kvien, T.K., T. Heiberg, and K.B. Hagen, *Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean?* Annals of the Rheumatic Diseases, 2007. **66**((suppl 3)): p. iii40-iii41.
190. Tubach, F., P. Ravaud, G. Baron, B. Falissard, I. Logeart, N. Bellamy, C. Bombardier, D. Felson, M. Hochberg, D. van der Heijde, and M. Dougados, *Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state.* Annals of the Rheumatic Diseases, 2005. **64**(1): p. 34-7.
191. Tubach, F., T. Pham, J.F. Skomsvoll, K. Mikkelsen, O. BjØrneboe, P. Ravaud, M. Dougados, and T.K. Kvien, *Stability of the patient acceptable symptomatic state over time in outcome criteria in ankylosing spondylitis.* Arthritis Care & Research, 2006. **55**(6): p. 960-963.
192. Williamson, A. and B. Hoggart, *Pain: a review of three commonly used pain rating scales.* Journal of Clinical Nursing, 2005. **14**(7): p. 798-804.
193. Farrar, J.T., J.P. Young, Jr., L. LaMoreaux, J.L. Werth, and R.M. Poole, *Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale.* Pain, 2001. **94**(2): p. 149-58.
194. Abbott, J.H. and J. Schmitt, *Minimum important differences for the patient-specific functional scale, 4 region-specific outcome measures, and the numeric pain rating scale.* Journal of Orthopaedic & Sports Physical Therapy, 2014. **44**(8): p. 560-4.
195. Stratford, P., *Assessing Disability and Change on Individual Patients: A Report of a Patient Specific Measure.* Physiotherapy Canada, 1995. **47**(4): p. 258-263.
196. Chatman, A.B., S.P. Hyams, J.M. Neel, J.M. Binkley, P.W. Stratford, A. Schomberg, and M. Stabler, *The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction.* Physical Therapy, 1997. **77**(8): p. 820-9.

197. Watson J, C., M. Propps, J. Ratner, D.L. Zeigler, P. Horton, and S.S. Smith, *Reliability and Responsiveness of the Lower Extremity Functional Scale and the Anterior Knee Pain Scale in Patients With Anterior Knee Pain.* Journal of Orthopaedic & Sports Physical Therapy, 2005. **35**(3): p. 136-136.
198. Crossley, K.M., K.L. Bennell, S.M. Cowan, and S. Green, *Analysis of outcome measures for persons with patellofemoral pain: which are reliable and valid?* Archives of Physical Medicine and Rehabilitation, 2004. **85**(5): p. 815-822.
199. Wang, D., M.H. Jones, M.M. Khair, and A. Miniaci, *Patient-reported outcome measures for the knee.* Journal of knee surgery, 2010. **23**(3): p. 137-151.
200. Roos, E.M. and L.S. Lohmander, *The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis.* Health Qual Life Outcomes, 2003. **1**(1): p. 64.
201. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-370.
202. Bjelland, I., A.A. Dahl, T.T. Haug, and D. Neckelmann, *The validity of the Hospital Anxiety and Depression Scale.* Journal of Psychosomatic Research, 2002. **52**(2): p. 69-77.
203. Brooks, R., *EuroQol: the current state of play.* Health Policy, 1996. **37**(1): p. 53-72.
204. Dolan, P., *Modeling valuations for EuroQol health states.* Medical Care, 1997. **35**(11): p. 1095-108.
205. Miller, R.P., S.H. Kori, and D.D. Todd, *The Tampa Scale: a Measure of Kinisophobia.* The Clinical Journal of Pain, 1991. **7**(1): p. 51.
206. Sullivan, M.J.L., S.R. Bishop, and J. Pivik, *The Pain Catastrophizing Scale: Development and validation.* Psychological Assessment, 1995. **7**(4): p. 524-532.
207. Redmond, A.C., J. Crosbie, and R.A. Ouvrier, *Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index.* Clinical Biomechanics, 2006. **21**(1): p. 89-98.
208. Cornwall, M.W. and T.G. McPoil, *Relationship between static foot posture and foot mobility.* Journal of Foot and Ankle Research, 2011. **4**: p. 4.
209. McPoil, T.G., M.W. Cornwall, M.G. Abeler, K.J. Devereaux, L.J. Flood, S.E. Merriman, S. Sullivan, M.J. van Der Laan, and T.A.V.a.K. Wilson, *The Optimal Method to Assess the Vertical Mobility of the Midfoot: Navicular Drop versus Dorsal Arch Height Difference? .* Clinical Research on Foot & Ankle, 2013: p. 1-8.

210. Cornwall, M.W., T.G. McPoil, M. Lebec, B. Vicenzino, and J. Wilson, *Reliability of the modified Foot Posture Index.* Journal of the American Podiatric Medical Association, 2008. **98**(1): p. 7-13.
211. McLaughlin, P., B. Vaughan, J. Shanahan, J. Martin, and G. Linger, *Inexperienced examiners and the Foot Posture Index: A reliability study.* Manual Therapy, 2016. **26**: p. 238-240.
212. Larsen, P., H.B. Nielsen, C. Lund, D.S. Sørensen, B.T. Larsen, M. Matthews, B. Vicenzino, and R. Elsoe, *A novel tool for measuring ankle dorsiflexion: A study of its reliability in patients following ankle fractures.* Foot and Ankle Surgery, 2016.
213. Ireland, M.L., J.D. Willson, B.T. Ballantyne, and I.S. Davis, *Hip strength in females with and without patellofemoral pain.* Journal of Orthopaedic & Sports Physical Therapy, 2003. **33**(11): p. 671-676.
214. Robinson, R.L. and R.J. Nee, *Analysis of hip strength in females seeking physical therapy treatment for unilateral patellofemoral pain syndrome.* Journal of Orthopaedic & Sports Physical Therapy, 2007. **37**(5): p. 232-238.
215. Bolgla, L.A., T.R. Malone, B.R. Umberger, and T.L. Uhl, *Reliability of electromyographic methods used for assessing hip and knee neuromuscular activity in females diagnosed with patellofemoral pain syndrome.* Journal of Electromyography and Kinesiology, 2010. **20**(1): p. 142-147.
216. Thorborg, K., J. Petersen, S.P. Magnusson, and P. Holmich, *Clinical assessment of hip strength using a hand-held dynamometer is reliable.* Scandinavian journal of medicine & science in sports, 2010. **20**(3): p. 493-501.
217. Neumann, D.A., *Kinesiology of the hip: a focus on muscular actions.* Journal of Orthopaedic & Sports Physical Therapy, 2010. **40**(2): p. 82-94.
218. Delp, S.L., W.E. Hess, D.S. Hungerford, and L.C. Jones, *Variation of rotation moment arms with hip flexion.* Journal of Biomechanics, 1999. **32**(5): p. 493-501.
219. Hemmerich, A., H. Brown, S. Smith, S.S. Marthandam, and U.P. Wyss, *Hip, knee, and ankle kinematics of high range of motion activities of daily living.* Journal of Orthopaedic Research, 2006. **24**(4): p. 770-81.
220. Lamontagne, M., M.J. Kennedy, and P.E. Beaule, *The effect of cam FAI on hip and pelvic motion during maximum squat.* Clinical Orthopaedics and Related Research, 2009. **467**(3): p. 645-50.
221. Hara, D., Y. Nakashima, S. Hamai, H. Higaki, S. Ikebe, T. Shimoto, M. Hirata, M. Kanazawa, Y. Kohno, and Y. Iwamoto, *Kinematic analysis of healthy hips*

during weight-bearing activities by 3D-to-2D model-to-image registration technique. BioMed research international, 2014. **2014**.

222. Hsieh, F.Y., P.W. Lavori, H.J. Cohen, and J.R. Feussner, *An overview of variance inflation factors for sample-size calculation.* Evaluation & the Health Professions, 2003. **26**(3): p. 239-57.
223. Royston, P. and W. Sauerbrei, *Interaction of treatment with a continuous variable: simulation study of power for several methods of analysis.* Statistics in medicine, 2014. **33**(27): p. 4695-708.
224. Keegan, P.E., J.N.S. Matthews, J. Lunec, and D.E. Neal, *Statistical problems with 'optimal' thresholds in studies of new prognostic factors in urology.* Bju International, 2000. **85**(4): p. 392-397.
225. McPoil, T.G. and G.C. Hunt, *Evaluation and management of foot and ankle disorders: present problems and future directions.* Journal of Orthopaedic & Sports Physical Therapy, 1995. **21**(6): p. 381-388.
226. Tiberio, D., *The effect of excessive subtalar joint pronation on patellofemoral mechanics: a theoretical model.* Journal of Orthopaedic & Sports Physical Therapy, 1987. **9**(4): p. 160-165.
227. Barton, C.J., P. Levinger, K.M. Crossley, K.E. Webster, and H.B. Menz, *The relationship between rearfoot, tibial and hip kinematics in individuals with patellofemoral pain syndrome.* Clinical biomechanics 2012. **27**(7): p. 702-705.
228. Neptune, R.R., I.C. Wright, and A.J. van den Bogert, *The influence of orthotic devices and vastus medialis strength and timing on patellofemoral loads during running.* Clinical Biomechanics, 2000. **15**(8): p. 611-8.
229. Eng, J.J. and M.R. Pierrynowski, *The effect of soft foot orthotics on three-dimensional lower-limb kinematics during walking and running.* Physical Therapy, 1994. **74**(9): p. 836-844.
230. Barton, C.J., P. Levinger, K.E. Webster, and H.B. Menz, *Walking kinematics in individuals with patellofemoral pain syndrome: a case-control study.* Gait & Posture, 2011. **33**(2): p. 286-291.
231. Eng, J.J. and M.R. Pierrynowski, *Evaluation of soft foot orthotics in the treatment of patellofemoral pain syndrome.* Physical Therapy, 1993. **73**(2): p. 62-8- discussion 68-70.
232. Li, G., L.E. DeFrate, S. Zayontz, S.E. Park, and T.J. Gill, *The effect of tibiofemoral joint kinematics on patellofemoral contact pressures under simulated muscle loads.* Journal of Orthopaedic Research, 2004. **22**(4): p. 801-806.

233. Noehren, B., M. Pohl B, Z. Sanchez, T. Cunningham, and C. Lattermann, *Proximal and distal kinematics in female runners with patellofemoral pain.* Clinical biomechanics, 2012. **27**(4): p. 366-371.
234. Bolgla, L.A., T.R. Malone, B.R. Umberger, and T.L. Uhl, *Hip strength and hip and knee kinematics during stair descent in females with and without patellofemoral pain syndrome.* Journal of Orthopaedic & Sports Physical Therapy, 2008. **38**(1): p. 12-18.
235. Souza, R.B. and C.M. Powers, *Differences in hip kinematics, muscle strength, and muscle activation between subjects with and without patellofemoral pain.* Journal of Orthopaedic & Sports Physical Therapy, 2009. **39**(1): p. 12-19.
236. Gaskin, D.R., P. , *The Economic Costs of Pain in the United States.* The Journal of Pain, 2012. **13**(8): p. 715-724.
237. Nahin, R.L., *Estimates of Pain Prevalence and Severity in Adults: United States, 2012.* THe Journal of Pain, 2015. **16**(8): p. 769-780.
238. Smith, B.E., J. Selfe, D. Thacker, P. Hendrick, M. Bateman, F. Moffatt, M.S. Rathleff, T.O. Smith, and P. Logan, *Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis.* Plos One, 2018. **13**(1): p. e0190892.
239. Lankhorst, N.E., M. van Middelkoop, K.M. Crossley, S.M. Bierma-Zeinstra, E.H. Oei, B. Vicenzino, and N.J. Collins, *Factors that predict a poor outcome 5-8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis.* Br J Sports Med, 2016. **50**(14): p. 881-6.
240. Collins, N.J., E.H.G. Oei, J.L. de Kanter, B. Vicenzino, and K.M. Crossley, *Prevalence of radiographic and MRI features of patellofemoral osteoarthritis in young and middle-aged adults with persistent patellofemoral pain.* Arthritis Care Res (Hoboken), 2018.
241. Powers, C.M., E. Witvrouw, I.S. Davis, and K.M. Crossley, *Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: part 3.* Br J Sports Med, 2017. **51**(24): p. 1713-1723.
242. Vicenzino, B., L. Maclachlan, and M.S. Rathleff, *Taking the pain out of the patellofemoral joint: articulating a bone of contention.* Br J Sports Med, 2019. **53**(5): p. 268-269.
243. Matthews, M., M.S. Rathleff, A. Claus, T. McPoil, R. Nee, K. Crossley, and B. Vicenzino, *Can we predict the outcome for people with patellofemoral pain? A*

systematic review on prognostic factors and treatment effect modifiers. Br J Sports Med, 2016.

244. Lack, S., C. Barton, O. Sohan, K. Crossley, and D. Morrissey, *Proximal muscle rehabilitation is effective for patellofemoral pain: a systematic review with meta-analysis.* Br J Sports Med, 2015. **49**(21): p. 1365-76.
245. Molgaard, C.M., M.S. Rathleff, J. Andreasen, M. Christensen, S. Lundbye-Christensen, O. Simonsen, and S. Kaalund, *Foot exercises and foot orthoses are more effective than knee focused exercises in individuals with patellofemoral pain.* J Sci Med Sport, 2018. **21**(1): p. 10-15.
246. Matthews, M., M.S. Rathleff, A. Claus, T. McPoil, R. Nee, K. Crossley, J. Kasza, S. Paul, R. Mellor, and B. Vicenzino, *The Foot Orthoses versus Hip eXercises (FOHX) trial for patellofemoral pain: a protocol for a randomized clinical trial to determine if foot mobility is associated with better outcomes from foot orthoses.* J Foot Ankle Res, 2017. **10**: p. 5.
247. World Medical, A., *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.* JAMA, 2013. **310**(20): p. 2191-4.
248. White, I.R. and S.G. Thompson, *Adjusting for partially missing baseline measurements in randomized trials.* Statistics in medicine, 2005. **24**(7): p. 993-1007.
249. Carpenter, J. and M. Kenward, *Multiple imputation and its application*. 2012: John Wiley & Sons.
250. Kujala, U.M., L.H. Jaakkola, S.K. Koskinen, S. Taimela, M. Hurme, and O. Nelimarkka, *Scoring of patellofemoral disorders*, in *Arthroscopy: The Journal of Arthroscopic & Related Surgery*1993. p. 159-163.
251. Jiang, C.C., Y.J. Liu, K.M. Yip, and E. Wu, *Physiological patellofemoral crepitus in knee joint disorders.* Bull Hosp Jt Dis, 1993. **53**(4): p. 22-6.
252. Schiphof, D., M. van Middelkoop, B.M. de Klerk, E.H. Oei, A. Hofman, B.W. Koes, H. Weinans, and S.M. Bierma-Zeinstra, *Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis).* Osteoarthritis Cartilage, 2014. **22**(5): p. 631-8.
253. Selfe, J., C. Sutton, N. Hardaker, S. Greenhalgh, A. Karki, and P. Dey, *Cold females, a distinct group of patellofemoral pain syndrome patients?... Patellofemoral pain syndrome: proximal, distal, and local factors, an international research retreat, April 30-May 2, 2009, Fells Point, Baltimore, MD.*, in *J Orthop Sports Phys Ther*2010. p. A42-A42.

254. Boyle, K.L., P. Witt, and C. Riegger-Krugh, *Intrarater and interrater reliability of the Beighton and Horan Joint Mobility Index*, in *J Athl Train*2003, National Athletic Trainers Association. p. 281.
255. van der Giessen, L.J., D. Liekens, K.J. Rutgers, A. Hartman, P.G. Mulder, and A.P. Oranje, *Validation of beighton score and prevalence of connective tissue signs in 773 Dutch children.* J Rheumatol, 2001. **28**(12): p. 2726-30.
256. Dragoo L, J., C. Johnson, and J. McConnell, *Evaluation and Treatment of Disorders of the Infrapatellar Fat Pad.*, in *Sports Medicine*2012. p. 51-67.
257. Kumar, D., A. Alvand, and J.P. Beacon, *Impingement of infrapatellar fat pad (Hoffa's disease): results of high-portal arthroscopic resection.* Arthroscopy, 2007. **23**(11): p. 1180-1186 e1.
258. J, M., B. W, and A. S, *Infrapatellar fat pad syndrome: a review of anatomy, function, treatment and dynamics.* Acta Orthop Belg, 2016. **82**(1): p. 94-101.
259. Nijs, J., C. Van Geel, C. Van der auwera, and B. Van de Velde, *Diagnostic value of five clinical tests in patellofemoral pain syndrome*, in *Manual Therapy*2006. p. 69-77.
260. Malanga, G.A., S. Andrus, S.F. Nadler, and J. McLean, *Physical examination of the knee: a review of the original test description and scientific validity of common orthopedic tests.* Arch Phys Med Rehabil, 2003. **84**(4): p. 592-603.
261. Doberstein, S.T., R.L. Romeyn, and D.M. Reineke, *The diagnostic value of the Clarke sign in assessing chondromalacia patella.*, in *J Athl Train*. p. 190-196.
262. Sweitzer, B.A., C. Cook, J.R. Steadman, R.J. Hawkins, and D.J. Wyland, *The inter-rater reliability and diagnostic accuracy of patellar mobility tests in patients with anterior knee pain.* Phys Sportsmed, 2010. **38**(3): p. 90-6.
263. Redmond, A.C., Y.Z. Crane, and H.B. Menz, *Normative values for the Foot Posture Index*, in *Journal of Foot and Ankle Research*2008, BioMed Central Ltd. p. 6.
264. Backman J, L. and P. Danielson, *Low Range of Ankle Dorsiflexion Predisposes for Patellar Tendinopathy in Junior Elite Basketball Players: A 1-Year Prospective Study.*, in *Am J Sports Med*2011. p. 2626-2633.
265. Collins, N., H. Hart, L. Garrick, and A. Schache, *Single leg squat hip pathomechanics are associated with ankle dorsiflexion restriction in people with patellofemoral pain*, 2014, Journal of Science and ….
266. Rabin, A., Z. Kozol, and A.S. Finestone, *Limited ankle dorsiflexion increases the risk for mid-portion Achilles tendinopathy in infantry recruits: a prospective cohort study*, in *Journal of foot and ankle …*2014.

267. Ota, S., M. Ueda, K. Aimoto, Y. Suzuki, and S.M. Sigward, *Acute influence of restricted ankle dorsiflexion angle on knee joint mechanics during gait.*, in *Knee*2014. p. 669-675.
268. Souza, R.B. and C.M. Powers, *Predictors of Hip Internal Rotation During Running: An Evaluation of Hip Strength and Femoral Structure in Women With and Without Patellofemoral Pain.*, in *American Journal of Sports Medicine*2009. p. 579-587.
269. Nakagawa, T.H., E.T.U. Moriya, C.D. Maciel, and F.V. Serrão, *Trunk, pelvis, hip, and knee kinematics, hip strength, and gluteal muscle activation during a single-leg squat in males and females with and without patellofemoral pain syndrome.*, in *J Orthop Sports Phys Ther*2012. p. 491-501.
270. Vicenzino, B., N.J. Collins, K.M. Crossley, E. Beller, R. Darnell, and T. McPoil, *Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: a randomised clinical trial.*, in *BMC Musculoskelet Disord*2008. p. 27.
271. Grotle, M., N.E. Foster, K.M. Dunn, and P. Croft, *Are prognostic indicators for poor outcome different for acute and chronic low back pain consulters in primary care?* Pain, 2010. **151**(3): p. 790-7.
272. Crombez G, Vlaeyen J, Heuts P, and Lysensd R, *Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability.* Pain, 1999. **80**: p. 329-339.
273. Carroll, L.J., D.J. Cassidy, and P. Côté, *Depression as a risk factor for onset of an episode of troublesome neck and low back pain.* Pain, 2004. **107**(1): p. 134-139.
274. Rathleff, C.R., W.N. Baird, J.L. Olesen, E.M. Roos, S. Rasmussen, and M.S. Rathleff, *Hip and knee strength is not affected in 12-16 year old adolescents with patellofemoral pain - a cross-sectional population-based study.*, in *PLoS One*2013. p. e79153.
275. Barton, C.J., H.B. Menz, and K.M. Crossley, *The immediate effects of foot orthoses on functional performance in individuals with patellofemoral pain syndrome.*, in *BMJ : British Medical Journal*2011. p. 193-197.
276. Barton, C.J., H.B. Menz, and K.M. Crossley, *Effects of prefabricated foot orthoses on pain and function in individuals with patellofemoral pain syndrome: a cohort study.*, in *Physical Therapy in Sport*2011, Elsevier Ltd. p. 70-75.
277. Adams, S.T. and S.H. Leveson, *Clinical prediction rules*, in *BMJ*2012. p. d8312-d8312.

278. Beattie, P. and R. Nelson, *Clinical prediction rules: what are they and what do they tell us?*, in *Aust J Physiother*2006. p. 157-163.
279. Childs, J.D., J.M. Fritz, T.W. Flynn, J.J. Irrgang, K.K. Johnson, G.R. Majkowski, and A. Delitto, *A clinical prediction rule to identify patients with low back pain most likely to benefit from spinal manipulation: a validation study.*, in *Ann. Intern. Med.*2004. p. 920-928.
280. Fox, A., R. Ferber, N. Saunders, S. Osis, and J. Bonacci, *Gait Kinematics in Individuals with Acute and Chronic Patellofemoral Pain.* Med Sci Sports Exerc, 2018. **50**(3): p. 502-509.
281. Neal, B.S., C.J. Barton, A. Birn-Jeffrey, M. Daley, and D. Morrissey, *The effects & mechanisms of increasing running step rate: A feasibility study in a mixed-sex group of runners with patellofemoral pain.* Phys Ther Sport, 2018. **32**: p. 244-251.
282. Willy, R.W. and I.S. Davis, *The effect of a hip-strengthening program on mechanics during running and during a single-leg squat.*, in *J Orthop Sports Phys Ther*2011. p. 625-632.
283. Lack, S., *The interaction of hip and foot biomechanics in the presentation and management of patellofemoral pain.* Br J Sports Med, 2017.
284. Cook, C.E., S.Z. George, and F. Keefe, *Different interventions, same outcomes? Here are four good reasons.* British Journal of Sports Medicine, 2018. **52**(15): p. 951-952.
285. Smith, B.E., M.S. Rathleff, and J. Selfe, *Patellofemoral pain: is it time for a rethink?*, in *With Tide; Off UK …*2015.
286. Arendt-Nielsen, L., S.T. Skou, T.A. Nielsen, and K.K. Petersen, *Altered Central Sensitization and Pain Modulation in the CNS in Chronic Joint Pain.* Curr Osteoporos Rep, 2015. **13**(4): p. 225-34.
287. Pazzinatto, M.F., D. de Oliveira Silva, J. Pradela, M.B. Coura, C. Barton, and F.M. de Azevedo, *Local and widespread hyperalgesia in female runners with patellofemoral pain are influenced by running volume.* J Sci Med Sport, 2017. **20**(4): p. 362-367.
288. Maclachlan, L.R., M. Matthews, P.W. Hodges, N.J. Collins, and B. Vicenzino, *The psychological features of patellofemoral pain: a cross-sectional study.* Scand J Pain, 2018. **18**(2): p. 261-271.
289. Esculier, J.F., L.J. Bouyer, B. Dubois, P. Fremont, L. Moore, B. McFadyen, and J.S. Roy, *Is combining gait retraining or an exercise programme with education better than education alone in treating runners with patellofemoral pain?A randomised clinical trial.* Br J Sports Med, 2017.

290. Earl-Boehm, J.E., L.A. Bolgla, C. Emory, K.L. Hamstra-Wright, S. Tarima, and R. Ferber, *Treatment Success of Hip and Core or Knee Strengthening for Patellofemoral Pain: Development of Clinical Prediction Rules.* J Athl Train, 2018. **53**(6): p. 545-552.
291. Esculier, J.F., L.J. Bouyer, B. Dubois, J. Leblond, M. Brisson, L. Chau, and J.S. Roy, *Predictors of clinical success in runners with patellofemoral pain: Secondary analyses of a randomized clinical trial.* J Sci Med Sport, 2018. **21**(8): p. 777-782.
292. Franettovich, M., A. Chapman, P. Blanch, and B. Vicenzino, *A physiological and psychological basis for anti-pronation taping from a critical review of the literature.* Sports Med, 2008. **38**(8): p. 617-31.
293. Neal, B.S., C.J. Barton, R. Gallie, P. O'Halloran, and D. Morrissey, *Runners with patellofemoral pain have altered biomechanics which targeted interventions can modify: A systematic review and meta-analysis.* Gait & Posture, 2016. **45**: p. 69-82.
294. American College of Sports, M., *American College of Sports Medicine position stand. Progression models in resistance training for healthy adults.* Med Sci Sports Exerc, 2009. **41**(3): p. 687-708.
295. Barton, C.J., H.B. Menz, and K.M. Crossley, *Clinical predictors of foot orthoses efficacy in individuals with patellofemoral pain.* Medicine and science in sports and exercise, 2011. **43**(9): p. 1603-1610.
296. Iverson, C.A., T.G. Sutlive, M.S. Crowell, R.L. Morrell, M.W. Perkins, M.B. Garber, J.H. Moore, and R.S. Wainner, *Lumbopelvic Manipulation for the Treatment of Patients With Patellofemoral Pain Syndrome: Development of a Clinical Prediction Rule.* dx.doi.org, 2008.
297. Lankhorst, N.E., M. van Middelkoop, Y.D.M. van Trier, R. van Linschoten, B.W. Koes, J.A.N. Verhaar, and S.M. Bierma-Zeinstra, *Can We Predict Which Patients With Patellofemoral Pain Are More Likely to Benefit From Exercise Therapy? A Secondary Exploratory Analysis of a Randomized Controlled Trial.* The Journal of orthopaedic and sports physical therapy, 2015. **45**(3): p. 183-189.
298. Natri, A., P. Kannus, and M. Jarvinen, *Which factors predict outcome in the nonoperative treatment of patellofemoral pain syndrome? A prospective follow-up study.* Medicine and science in sports and exercise, 1998. **30**(11): p. 1572-1577.
299. Kannus, P. and S. Niittymaki, *Which factors predict outcome in the nonoperative treatment of patellofemoral pain syndrome? A prospective*

follow-up study. Medicine and science in sports and exercise, 1994. **26**(3): p. 289-296.

300. Wittstein, J.R., S.D. O'Brien, E.N. Vinson, and W.E. Garrett, *MRI evaluation of anterior knee pain: predicting response to nonoperative treatment.* Skeletal Radiology, 2009. **38**(9): p. 895-901.
301. Collins, N.J., K.M. Crossley, R. Darnell, and B. Vicenzino, *Predictors of short and long term outcome in patellofemoral pain syndrome: a prospective longitudinal study.* BMC musculoskeletal disorders, 2010. **11**: p. 11.
302. Kettunen, J.A., A. Harilainen, J. Sandelin, D. Schlenzka, K. Hietaniemi, S. Seitsalo, A. Malmivaara, and U.M. Kujala, *Knee arthroscopy and exercise versus exercise only for chronic patellofemoral pain syndrome: 5-year follow-up.* British Journal of Sports Medicine, 2012. **46**(4): p. 243-246.
303. Witvrouw, E., R. Lysens, J. Bellemans, D. Cambier, A. Cools, L. Danneels, and J. Bourgois, *Which factors predict outcome in the treatment program of anterior knee pain?* Scandinavian journal of medicine & science in sports, 2002. **12**(1): p. 40-46.
304. Karlsson, J., R. Thomeé, and L. Swärd, *Eleven year follow-up of patello-femoral pain syndrome.* Clinical Journal of Sport Medicine, 1996. **6**(1): p. 22-26.
305. Nimon, G., D. Murray, M. Sandow, and J. Goodfellow, *Natural History of Anterior Knee Pain: A 14- to 20-Year Follow-up of Nonoperative Management.* Journal of Pediatric Orthopaedics, 1998. **18**(1): p. 118.
306. Crowell, M.S. and N.H. Wofford, *Lumbopelvic manipulation in patients with patellofemoral pain syndrome.* The Journal of manual & manipulative therapy, 2012. **20**(3): p. 113-120.
307. Peng, H.-T. and C.-Y. Song, *Predictors of treatment response to strengthening and stretching exercises for patellofemoral pain: An examination of patellar alignment.* The Knee, 2015: p. 1-5.
308. Rathleff, M.S., E.M. Roos, J.L. Olesen, S. Rasmussen, and L. Arendt-Nielsen, *Self-reported Recovery is Associated with Improvement in Localised Hyperalgesia Among Adolescent Females with Patellofemoral Pain - Results from a Cluster Randomised Trial.* The Clinical journal of pain, 2015.
310. Fukuda, T.Y., F.M. Rossetto, E. Magalhães, F.F. Bryk, P.R.G. Lucareli, and N. de Almeida Aparecida Carvalho, *Short-term effects of hip abductors and lateral rotators strengthening in females with patellofemoral pain syndrome: a randomized controlled clinical trial.*, in *J Orthop Sports Phys Ther*2010. p. 736-742.

311. Austin, P.C., *Absolute risk reductions, relative risks, relative risk reductions, and numbers needed to treat can be obtained from a logistic regression model.* J Clin Epidemiol, 2010. **63**(1): p. 2-6.

Appendix 1 Search strategy and results

	Search terms	MEDLINE	EMBASE	CINAHL	SPORTDiscus	Web of Science	Scopus
1	Arthralgia	13099	46401	1310	64	4495	42568
2	Knee Joint OR Knee OR Patella	137304	181740	30204	39252	118874	180553
3	#1 AND #2	2020	4157	250	16	219	4496
4	anterior knee pain	3296	4931	392	666	3142	4570
5	femoropatell* OR femoro-patell* OR retropatell* OR ”patellofemoral pain syndrome” OR ”patellofemoral pain”	2043	1636	1145	1224	2185	2787
6	”lateral compression syndrome” OR ”lateral facet syndrome” OR ”lateral pressure syndrome” OR ”facet syndrome”	138	239	25	21	118	237
7	chondromalac* or chondropath*	1252	230	141	411	1185	6225
8	#3 OR #4 OR #5 OR #6 OR #7	7675	10261	3230	2025	5963	16470
9	Success*	866281	327494	90406	76371	1123969	349693
10	Factor*	4528431	3032546	669098	106100	3446802	7141735
11	Predict*	1214973	421916	137305	43884	1894723	2982535
12	Charact*	2401783	169595	137915	55024	3992407	6553192
13	Prognos*	652826	54789	57054	4194	443798	827108
14	#9 OR #10 OR #11 OR #12 OR #13	7835734	3756532	888981	248457	9141006	16466975
15	#8 AND #14	2636	1665	600	491	1774	6013
16	Limit to human only studies	2196	1555	600	491	1774	5013

Appendix 2 Details and patient characteristics evaluated in retrieved studies

Number	Patient Characteristic	Specified treatment studies (n)	Prognostic studies (n)	Successful outcome to a specified treatment	Poor outcome, regardless of treatment
1.	Age	7 [95, 141, 152, 155, 299-301]	7 [146, 147, 302-306]	>25 yrs to foot orthoses treatment [95]	Older [303]
2.	Sex	7 [95, 141, 152, 155, 299-301]	7 [146, 147, 302, 303, 305-307]		At 3 months: Female [146]
3.	Knee pain duration	6 [95, 152, 155, 299-301]	7 [146, 147, 302, 303, 305-307]		At 6 weeks: Longer duration [305] At 3 months: >6 months, >4 months [146], At 12 months: Longer duration [305, 307]
4.	Q- Angle	4 [141, 152, 155, 300]	4 [121, 146, 303, 308, 309]	Larger Q angle to patella taping treatment [141]	
5.	Body mass index	5 [95, 112, 141, 155, 301]	3 [147, 303, 305, 306]	Lower BMI to patella taping treatment[141]	
6.	Weight	5 [95, 112, 141, 155, 299]	3 [302, 303, 306]		
7.	Height	5 [95, 112, 141, 155, 299]	3 [302, 303, 306]		
8.	Sports participation	2 [299, 301]	4 [147, 302, 303, 307]		
9.	Navicular Drop	5 [144, 152, 155, 299, 300]		<3mm to foot orthoses treatment [152], >3mm to lumbopelvic manipulation [300]	
10.	Baseline worst pain score	2 [95, 299]	3 [147, 148, 305]	<53.25mm (VAS) to foot orthoses treatment [95]	
11.	Hamstring muscle length	3 [152, 155, 300]	1 [307]		

12.	Anterior Knee Pain Scale (Kujala)	1 [95]	3 [148, 305]		Low baseline score [305]
13.	Step-downs	1 [299]	3 [148, 305, 307]		
14.	Bilateral symptoms	2 [95, 300]	2 [147, 307]		Bilateral symptoms [147]
15.	Effusion	1 [300]	3 [121, 146, 147, 309]		Self-reported swelling [147]
16.	Tibial torsion	3 [152, 155, 300]			
17.	Craig's test	3 [152, 155, 300]			
18.	Obers test	3 [152, 155, 300]			
19.	Thomas test	3 [152, 155, 300]			
20.	Ankle dorsiflexion (Bent knee)	3 [144, 152, 300, 310]		<41.3deg to foot orthoses treatment [299], >16deg to lumbopelvic manipulation [300]	
21.	Arch height weight bearing	2 [95, 112]	1 [305]		
22.	X-ray: Lateral Patellofemoral Angle	2 [141, 155]	1 [303]	Smaller lateral patellofemoral angle to patella taping treatment[141]	
23.	X-ray: Sulcus angle	1 [155]	2 [121, 303, 309]		
24.	Functional index questionnaire	1 [95]	2 [305, 307]		
25.	Pain when ascending stairs (VAS)		3 [148, 307]		
26.	Pain when descending stairs (VAS)		3 [148, 307]		
27.	Grating		3 [146, 147, 307]		
28.	Hypermobile patella		3 [121, 146, 303, 309]		Hypermobile Patella [146]
29.	Baseline usual pain score	2 [95, 299]		<22/100mm usual pain to foot orthoses treatment [299]	

30.	Ankle dorsiflexion (Straight knee)	2 [152]			
31.	Rearfoot in subtalar neutral	2 [152, 300]			
32.	Forefoot to rearfoot alignment	2 [152, 300]		≥2deg valgus forefoot alignment to foot orthoses treatment [152]	
33.	Relaxed calcaneal stance	2 [152, 300]			
34.	Tibial varus/valgus	2 [152, 300]			
35.	Hip extension strength – Dynamometer	2 [144, 155, 310]			
36.	Hip abduction strength- Dynamometer	2 [144, 155, 310]			
37.	Knee extension strength- Dynamometer	2 [144, 155, 310]			
38.	Midfoot width weight bearing	2 [95, 112]			
39.	Midfoot width non-weight bearing	2 [95, 112]			
40.	Midfoot width difference	2 [95, 112]		>10.96mm [95] and >11.25mm [112] to foot orthoses treatment	
41.	Arch height non-weight bearing	2 [95, 112]			
42.	Arch height difference	2 [95, 112]			
43.	Arch height ratio	2 [95, 112]			
44.	Left knee pain	2 [155, 300]			
45.	Right knee pain	2 [155, 300]			
46.	First metatarsal phalangeal extension ROM	2 [152, 300]		<78deg to foot orthoses treatment [152]	

47.	PFP affects ability to squat	2 [144, 300, 310]		Squatting reported as most painful activity to lumbopelvic manipulation [300]	
48.	Hip internal rotation ROM	2 [144, 300, 310]		>14deg side to side difference [300]	
49.	Stiff after prolonged sitting	2 [144, 300, 310]		No stiffness with sitting >20mins to lumbopelvic manipulation treatment [300]	
50.	Beighton Hypermobility Scale	1 [155]	1 [303]		
51.	X-ray Patella congruence angle	1 [155]	1 [121]		
52.	Leg Length discrepancy	1 [152]	1 [303]		
53.	X-ray: Lateral Patellofemoral Displacement	1 [141]	1 [303]		
54.	Clicking	1 [300]	1 [307]		
55.	Step-ups	1 [299]	1 [148]		
56.	Patella alta		2 [121, 146, 309]		
57.	Vastus Medialis Atrophy		2 [121, 146, 309]		
58.	Peripatellar tenderness		2 [121, 146, 307]		
59.	Pain at rest		2 [148, 307]		
60.	Triple hop (cm)		2 [148, 307]		
61.	Pain when Squatting/ kneeling (VAS)		2 [148, 307]		
62.	Pain during prolonged sitting (VAS)		2 [148, 307]		
63.	Pain during daily activities (VAS)		2 [148, 307]		

64.	Triple hop limb symmetry index		2 [148, 307]		
65.	Single limb hop symmetry index		2 [148, 307]		
66.	Pain at rest		2 [148, 307]		
67.	Quadriceps muscle torque at 60deg/s (concentric)		2 [148, 307]		
68.	Frequency of pain (how often)		2 [148, 307]		Higher frequency [148]
69.	Patella grind test (Clarke sign)		2 [146, 302]		
70.	Patellar glide	1 [300]	1 [307]		
71.	Patellar orientation	1 [152]			
72.	Pelvic obliquity	1[300]			
73.	McConnell test	1 [300]			
74.	Patellar tilt	1 [300]			
75.	Patella tilt angle difference	1[311]		Greater patella tilt angle difference [311]	
76.	Peak Medial-lateral foot loading during drop jump	1 [153]		Immediate decrease in medial – lateral peak foot force after fitting orthoses [153]	
77.	Peak Medial-lateral foot loading during drop jump	1 [153]			
78.	Peak Medial-lateral foot loading during drop jump	1 [153]			
79.	Peak Medial-lateral foot loading during drop jump	1 [153]			
80.	Ely Test	1 [155]			
81.	Femoral Slump test	1 [155]			

82.	History of low back pain	1 [155]			
83.	Leg Dominance	1 [155]			
84.	Bilateral difference in hip extension angle	1 [155]		After 6 sessions (2weeks): ≥3deg difference [155]	
85.	Significant immediate efficacy	1 [155]		After 6 sessions (2weeks): positive significant immediate response [155]	
86.	forefoot relative to rearfoot dorsiflexion	1 [77]			
87.	Forefoot relative to rearfoot Abduction	1 [77]			
88.	Rearfoot relative to laboratory floor eversion	1 [77]		Greater peak rearfoot eversion with foot orthoses treatment [77]	
89.	Rearfoot relative to tibia eversion	1 [77]			
90.	Previous knee pain history	1 [300]			
91.	Knee locking	1 [300]			
92.	Knee giving way	1 [300]			
93.	PFP affects ability to run	1 [300]			
94.	PFP affects ability to lift	1 [300]			
95.	PFP affects ability to go up stairs	1 [300]			
96.	PFP affects ability to go downstairs	1 [300]			
97.	Crepitus	1 [300]			
98.	Stiffness	1 [300]			
99.	Hip flexion strength –	1 [300]			

	Manual muscle test				
100.	Hip extension strength– Manual muscle test	1 [300]			
101.	Hip abduction strength– Manual muscle test	1 [300]			
102.	Hamstrings strength– Manual muscle test	1 [300]			
103.	Quadriceps strength – Manual muscle test	1 [300]			
104.	Sitting flexion test	1 [300]			
105.	Stork test.	1 [300]			
106.	Hip external rotation strength- Dynamometer	1 [144]			
107.	Foot length	1 [112]			
108.	Single leg rises	1 [299]			
109.	Footwear motion control characteristics	1 [299]		>5.0 (weighted mean) to foot orthoses treatment [299]	
110.	Foot posture index	1 [299]			
111.	Change in functional performance	1 [299]		Reduced pain during single leg squat with foot orthoses in place [299]	
112.	change in footwear comfort	1 [299]			
113.	MRI tibial tubercle lateral deviation		1 [304]		

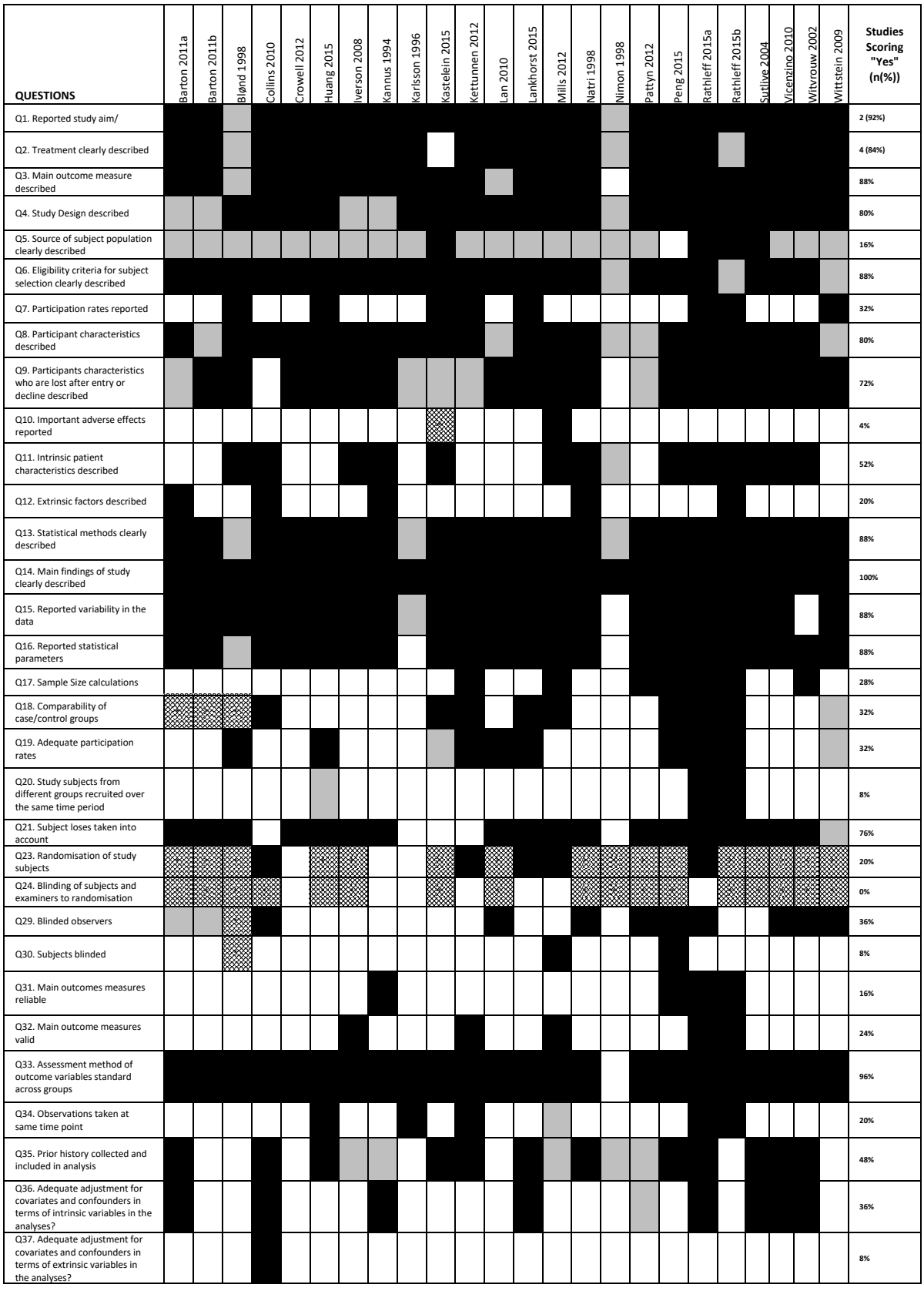
114.	MRI Patellar cartilage surface		1 [304]		
115.	MRI Trochlear cartilage surface		1 [304]		Evidence of chondromalacia patella [304]
116.	Patella Squinting		1 [303]		
117.	Rearfoot eversion – Squatting test		1 [303]		
118.	Knee range of motion		1 [303]		
119.	Knee hyperextension		1 [303]		
120.	Insall-Salvati Index		1 [303]		
121.	Blackburne-Peel index		1 [303]		
122.	Patellofemoral Index		1 [303]		
123.	Knee angle (X-ray)		1 [303]		
124.	Tight lateral retinaculum		1 [146]		
125.	MRI Cross-sectional area VMO (patella)		1 [148]		
126.	MRI Cross-sectional area VL (patella)		1 [148]		
127.	MRI Cross-sectional area VM & VI (thigh)		1 [148]		
128.	MRI Cross-sectional area VL (thigh)		1 [148]		
129.	MRI Cross-sectional area Rectus femoris (thigh)		1 [148]		
130.	MRI Cross-sectional area		1 [148]		Smaller quadriceps muscle size [148]

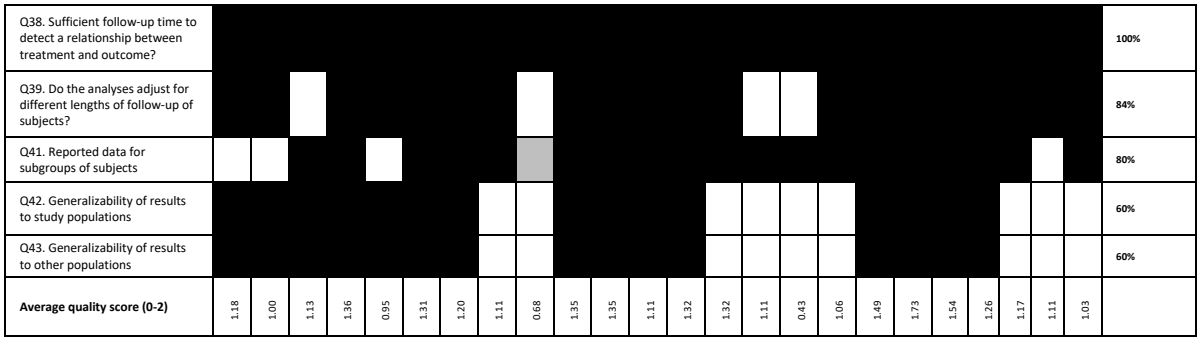
	total quadriceps (thigh)				
131.	Quadriceps muscle torque at 60deg/s (eccentric)		1 [148]		larger eccentric peak torque at 60deg/sec [148]
132.	Quadriceps muscle torque at 240deg/s (concentric)		1 [148]		
133.	Quadriceps muscle torque at 240deg/s (eccentric)		1 [148]		
134.	Retro-patellar cartilage damage		1 [308]		
135.	Age at symptom onset		1 [308]		
136.	Feeling of giving way		1 [307]		
137.	Length quadriceps		1 [307]		
138.	Length m. gastrocnemius		1 [307]		
139.	Step test ascending (Maximum height pain free)		1 [307]		
140.	Step test descending (Maximum height pain free)		1 [307]		
141.	Unilateral squat test (°pain free)		1 [307]		
142.	Pain during triple jump test		1 [307]		
143.	Reflex response time VMO		1 [307]		Slower reflex response time [307]
144.	Reflex response time VL		1 [307]		

145.	Quadriceps muscle torque at 180deg/s,		1 [307]		
146.	Quadriceps muscle torque at 300deg/s		1 [307]		
147.	Hamstring muscle torque at 60deg/s		1 [307]		
148.	Hamstring muscle torque at 180deg/s		1 [307]		
149.	Hamstring muscle torque at 300deg/s		1 [307]		
150.	Pain during work		1 [307]		
151.	Pain during walking		1 [307]		
152.	Presence of crepitations		1 [307]		
153.	Pain during ascending stairs		1 [307]		
154.	Pain during descending stairs		1 [307]		
155.	Pain during running		1 [307]		
156.	Pain during jumping		1 [307]		
157.	Pain during sports activities		1 [307]		
158.	Nightly pain		1 [307]		
159.	Pain during squatting		1 [307]		
160.	Movie sign symptoms		1 [307]		
161.	Pain daily activity		1 [307]		
162.	Pain during isokinetic testing		1 [307]		

163.	Pain with patella apprehension test		1 [302]		
164.	Isometric quadriceps muscle strength side-to-side difference		1 [302]		Larger side to side isometric quadriceps muscle strength difference [302]
165.	X-ray malalignment		1 [302]		
166.	Pain score (VAS) during functional test		1 [155]		
167.	Pressure pain threshold localized		1 [312]		
168.	Pressure pain threshold distal		1 [312]		
169.	Education level		1[147]		Low/middle education level [147]
170.	Comorbidity skeletal system		1[147]		
171.	Non-skeletal comorbidity		1[147]		
172.	Poor health		1[147]		Poor health [147]
173.	History of knee symptoms		1[147]		
174.	Recurrence of symptoms		1[147]		
175.	Self-reported warm knee		1[147]		
176.	Locking of the knee (Lysholm)		1[147]		
177.	Instability of the knee (Lysholm)		1[147]		
178.	WOMAC function		1[147]		
179.	WOMAC Pain		1[147]		
180.	WOMAC Stiffness		1[147]		

Appendix 3 Study quality of all included studies assessed using the Epidemiological Appraisal Instrument



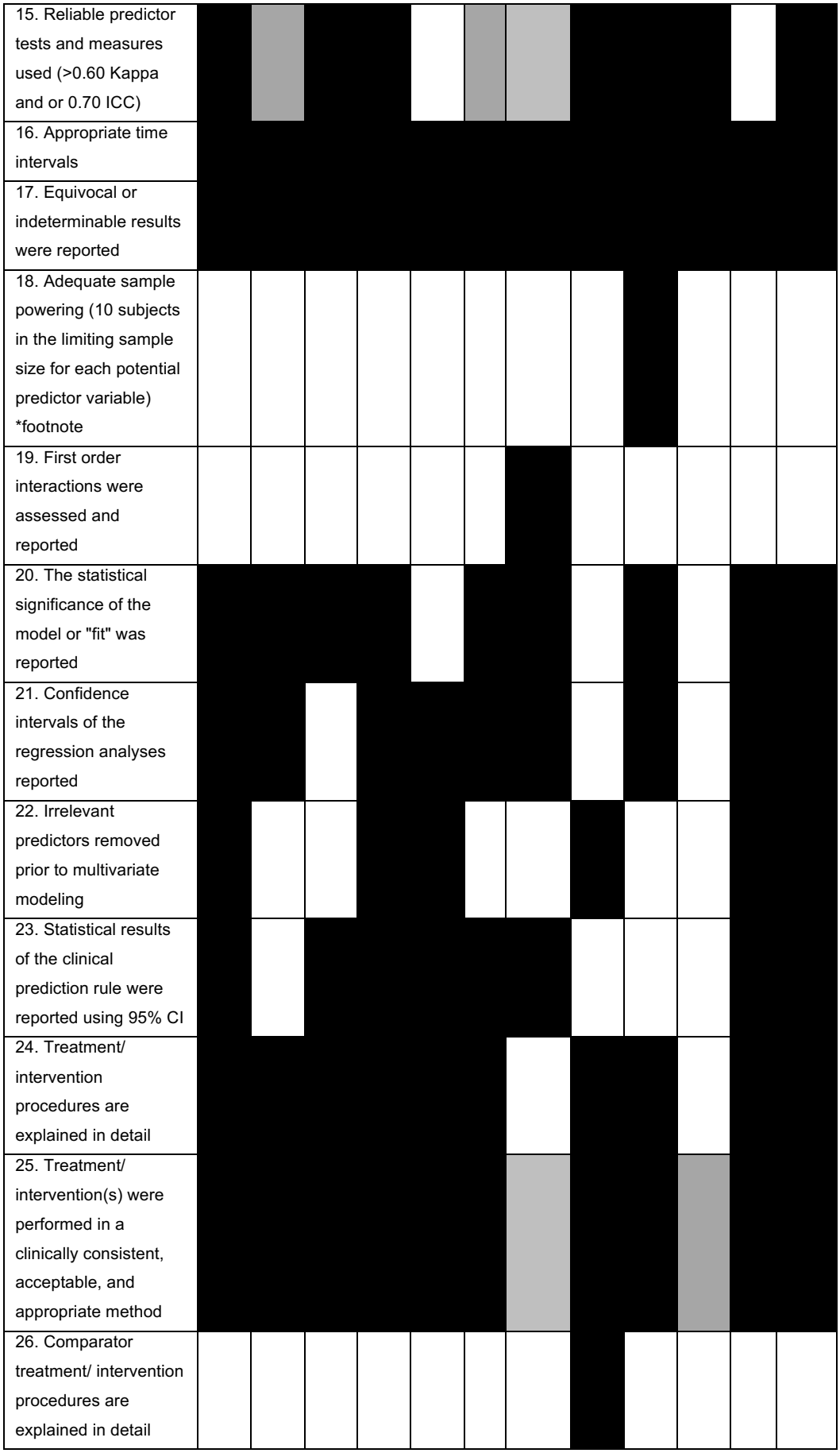


Black shading (2) = “Yes”; Grey shading (1)= “Partial”; White (0) = “No” or “Unable to determine”; ‘shaded with a * ’= “Not applicable”, items removed from scoring and not included in calculations.

Question 22, 25, 26, 27, 28 & 40 were removed as they are not applicable to intervention studies
Inter-rater agreement between the quality assessors was 87%

Appendix 4 Quality appraisal using a checklist for prescriptive, derivation-based clinical prediction rules (QUADCPR)

Questions	Barton 2011a	Barton 2011b	Crowell 2012	Huang 2015	Iverson 2008	Lan 2010	Lankhorst 2015	Mills 2012	Peng 2015	Rathleff 2015	Sutlive 2004	Vicenzino 2010
1. Setting and location reflective												
2. Inclusion and exclusion criteria												
3. Sample characteristics												
4. Prospective and consecutive sampling												
5. Outcome measure(s) defined												
6. Outcome measure reliability, validity and sensitivity to change												
7. Blinded outcome measure(s)												
8. Outcome measure defined (positive/ negative)												
9. Logical rationale for predictor test												
10. Predictor test was performed pre-treatment												
11. Predictor test and measures were explained in detail												
12. Predictor tests/ measures performed in a clinically consistent, acceptable, and appropriate method												
13. Examining clinicians blinded to the outcome measures												
14. Treating clinicians blinded to outcome measures												


15. Reliable predictor tests and measures used (>0.60 Kappa and or 0.70 ICC)
16. Appropriate time intervals
17. Equivocal or indeterminable results were reported
18. Adequate sample powering (10 subjects in the limiting sample size for each potential predictor variable) *footnote
19. First order interactions were assessed and reported
20. The statistical significance of the model or "fit" was reported
21. Confidence intervals of the regression analyses reported
22. Irrelevant predictors removed prior to multivariate modeling
23. Statistical results of the clinical prediction rule were reported using 95% CI
24. Treatment/ intervention procedures are explained in detail
25. Treatment/ intervention(s) were performed in a clinically consistent, acceptable, and appropriate method
26. Comparator treatment/ intervention procedures are explained in detail

27. Comparator treatment/ intervention(s) were performed in a clinically consistent, acceptable, and appropriate method												

Black shading = "Yes", Grey shading = "Unclear", White (no shading) = "No"
Inter-rater agreement between the quality assessors was 92% across all 13 papers.
*footnote: Modified in accordance with the TRIPOD statement [134] recommendation for a minimum of 10 subjects in the limiting sample size (i.e. those who experienced the least frequent outcome) for each potential predictor variable.

Appendix 5 Patient characteristics associated with a poor outcome (prognosis)

Author	Sample size (n)	Variables assessed (n)	Outcome measures	Univariate (p) or Multivariate (p)	Follow up	Prognostic variables for a poor outcome	Explained Variance (R^2)	Covariate	Intervention(s)	Trial Type
Blond and Hansen 1998 [146]	250	12	Pain resolution	Univariate ($p<0.05$)	5.7 yrs	Hypermobile patella >4month duration of symptoms Female	-	None specified	Advised to wear knee brace and VMO exercises: open and closed kinetic chain (Phase 1: non-loaded, phase 2: loaded exercises, phase 3: return to main athletic activity)	Retrospective case study
Collins et al 2010 [138]	179	11	1. Pain (VAS) 2. Kujala Scale 3. Functional Index Questionnaire	Univariate ($p<0.01$) then multivariate ($p<0.01$)	6 wks	1. High pain severity 2. Longer duration of symptoms, lower baseline Kujala score 3.Longer duration of symptoms, lower baseline Functional Index Questionnaire score	1. R^2 = 23% 2. R^2 = 40.1% 3. R^2 = 38.6%	Treatment group	Flat inserts - versus - foot orthoses – versus - physio exercises (patellar mobilization, patellar taping, VMO retraining, Hip ER retaining and hip and hamstring stretches) – versus - foot orthoses and physio exercises	Randomized Controlled Trial
					12 wks	1. Nil 2. Lower baseline Kujala score 3. Lower baseline kujala score	1. - 2. R^2 = 28% 3. R^2 = 22%			
					52 wks	1.Nil 2. Long duration of symptoms, lower baseline Kujala 3. Long duration of symptoms	1. - 2. R^2 = 29.5% 3. R^2 = 26.6%			

Kannus and Nittymaki 1994 [149]	49	22	1. Pain (VAS) 2. Lysholm scale 3. Tegner scale	Univariate (p<0.05) then multivariate (p<0.05)	6 wks 26 wks	1. Older age 2. Older age 3. Older age 1. Nil 2. Older age 3. Older age	-	None specified	Rest, quadriceps strength, quadriceps stretch, cold pack (10mins) non-steroidal anti-inflammatory medication and intra-articular injections (n=33, 5x - 1x/week) of physiologic saline (n=17) or glucosamine (n=16)	Prospective cohort study
Karlsson et al 1996 [308]	48	3	Patellofemoral joint evaluation scale	Univariate (p≤0.001)	11 yrs	No variables found	-	None specified	Quadriceps isometric activation. Straight leg rises with angle weights and inner range quad with ankle weights (30-0°)	Retrospective case-control study
Kastelein et al 2015 [147]	48	21	GROC - 7 point	Univariate (p<0.20) then multivariate (p<0.10)	52 wks	Low/middle education level Poor health Bilateral symptoms Self-report of a swollen knee	-	None specified	None	Prospective cohort study
Kettunen et al 2012 [306]	56	6	Kujala Knee Pain score	Univariate (p value not specified)	5 yrs	No variables found	-	None specified	Arthroscopic surgery – versus - home exercise program (8weeks)	Randomized Controlled Trial
Natri et al 1998 [150]	49	11	1. Pain severity (VAS) 2. Lysholm scale 3. Tegner Scale	Univariate (p<0.05) then multivariate (p<0.05)	7 yrs	Greater side to side isometric quadriceps muscle strength difference	-	None specified	Rest, quadriceps strength , quadriceps stretch, Non-steroidal anti-inflammatory medication & intra-articular injections (n=33, 5x - 1x/week) of physiologic saline (n=17) or glucosamine (n=16)	7 year Prospective cohort study

Nimon et al 1998 [121]	63	6	1. Pain resent 2. Pain severity 3. Analgesic use 4. Pain frequency 5. Sport restriction 6. Pain associated activities 5. Other symptoms	Univariate (p not specified)	16 yrs	No variables found	-	None specified	Physiotherapy and laster immobilization	Prospective cohort study
Pattyn et al 2012 [148]	40	21	1. Kujala Knee pain Scale 2. GROC – 5-point Likert scale	Univariate ($p<0.05$)	7 wks	Higher frequency of pain at baseline Smaller quadriceps muscle size Greater average eccentric peak torque at 60°/sec	$R^2 = 0.46$	None specified	Mobilization, neuromuscular coordination exercises, stabilization exercises, strengthening exercises, stretching, cardiovascular and home exercise program of neuromuscular coordination exercises	Prospective cohort study
Rathleff et al 2015 [	39	2	1. PPT localised 2. PPT distal 3. GROC – 7-point Likert scale	Univariate ($p<0.05$)	12 and 52 wks	No variables found	-	None specified	Patient education – versus - patient education and exercises therapy	Randomized controlled trial
Wittstein et al	30	4	PT Responders: resolution of		8 wks	Evidence of chondromalacia patella on MR imaging Tibial tubercle deviation	-	None specified	Strengthening, stretching, footwear modification and	Retrospective case-control

2009 [151]			symptoms to the point that they required no further treatment PT Non-responders: continued to have PFP severe enough that they sought further treatment		>14.6mm			Non-steroidal anti-inflammatory medication	(comparative) study
Witvrouw et al 2002 [145]	30	39	1. Kujala Knee Pain Scale 2. Manual test (Q-angle, muscle length, patellar glide) 3. Subjective assessments 4. Functional assessments	5 wks	Slower reflex response time (VMO) Longer duration of symptoms	-	None specified	No sports participation, no medication prescribed, no brace or tape, stretching exercises, strength exercises (Seated leg press, double or single one-third knee bend, stationary bike (10-15min @ 100W), rowing machine, step up and down (at pain free height), progressive jumping (3x1min)) and home exercise program to maintain strength	Prospective cohort study
				12 wks	Slower reflex response time (VMO) Longer duration of symptoms				

GROC = global rating of change, PPT= pressure pain threshold, VMO = Vastus medialis obliquus, VAS = visual analogue scale, *foot note: all variables are listed in appendix 2

Appendix 6 Patient characteristics associated with a successful outcome from a specific treatment

Author	Intervention	Comparator	Outcome measure	Sample (n)	Success (n)	Predictors to a successful outcome	Significance level (p)	Positive Likelihood Ratio (95% CI)	Odds Ratio (95% CI)
Barton 2011a [143]	Foot orthoses	Nil	5-pt GROC	60	14	Footwear motion control properties (weighted mean) >5.0 Usual pain <22.0/100mm (VAS) Ankle Dorsiflexion (knee flexed) <41.3° Reduced pain during single leg squat	0.05	1.9 (1.1–3.1) 2.5 (1.3–4.8) 1.5 (0.71–3.3) 3.0 (1.8–4.9)	
Barton 2011b [77]	Foot orthoses	Nil	5-pt GROC	26	7	Greater rearfoot eversion relative to the laboratory floor	0.05	-	-
Crowell & Wofford 2012 [144]	Lumbo-pelvic manipulation	Nil	11-pt NPRS 15-pt GROC.	44	25	Hip IR side to side difference >14° Ankle dorsiflexion (knee flexed) >16° Navicular drop >3mm No self-reported stiffness sitting >20 min Squatting (most painful activity)	0.05	0.76 (0.05, 11.39) 0.93 (0.78, 1.11) 1.52 (0.54, 4.31) 0.74 (0.46, 1.19) 0.82 (0.49, 1.37)	
Huang 2015 [155]	Femoral nerve mobilization	Nil	10cm VAS 15-pt GROC	51	28	Significant immediate efficacy Bilateral difference in hip extension angle of femoral slump test (>3°)	0.05	NA 5.11 (1.28-20.30)	
Iverson 2008 [154]	Lumbo-pelvic manipulation	Nil	11-pt NPRS 15-pt GROC.	49	22	Hip IR side to side difference >14° Ankle dorsiflexion (knee flexed) >16° Navicular drop >3mm No self-reported stiffness sitting >20 min Squatting (most painful activity)	0.05	4.9 (1.2, 20.8) 2.0 (1.0, 3.9) 1.91 (1.0, 3.6) 2.0 (1.1, 3.4) 2.3 (1.1, 4.7)	
Lan 2010 [141]	Patella taping	Nil	100mm VAS	100	66	Smaller Lateral Patellofemoral Angle Larger Q Angle Lower BMI	0.05	-	0.81 (0.70-0.95) 1.14 (1.03-1.26)

									0.85 (0.75-0.98)
Lankhorst 2015 [156]	Exercise therapy (ET)	Usual care (UC)	Kujala scale 11-pt NPRS	131	At 3mth 26(ET) 21(UC) At 12 mth 36(ET) 30(UC)	Nil significant [a]	0.01	-	-
Mills 2012 [142]	Foot orthoses	Wait-and-see	6-pt GROC	40	9(FO) 1(W-S)	Foot orthoses: Mid-foot width difference >11.25mm [b]	0.05	3.9 (1.07-14.1)	
Peng 2015 [138]	Leg press and stretching	Nil	10cm VAS	43	24	Difference in patella tilt angle between maximal quadriceps contraction and quadriceps relaxed (measured on axial CT)	0.05	-	0.84
Rathleff 2015b [153]	Foot orthoses	Nil	PFP Severity Scale	23	12	Immediate decrease in the medial-to-lateral peak force after fitting the orthoses during drop jump task	0.05	-	-
Sutlive 2004 [152]	Foot orthoses and activity modification	Nil	15-pt GROC	50	27	Forefoot alignment ≥2° valgus Great toe extension <78° Navicular drop test ≤3mm	Uncertain	4.0 (0.7–21.9) 4.0 (0.7–21.9) 2.3 (1.3–4.3)	-
Vicenzino 2010 [140]	Foot orthoses		5-pt Likert GROC	42	17	Age >25 years Mid-foot width difference >10.96mm Height <165cm Worst pain <53.25/ 100mm (VAS)	0.05	1.9 (1.1 to 3.1) 3.0 (0.91 to 9.6) 4.9 (1.2 to 20.9) 1.5 (0.74 to 2.9)	-

GROC = global rating of change, PPT= pressure pain threshold, VMO = Vastus medialis obliquus, VAS = visual analogue scale, NPRS = Numerical Pain Rating Scale, a: Analysis of interaction used was a classification and regression tree approach, b: Analysis of interaction used was a liner regression modeling.

Appendix 7 Derived Clinical Prediction Rules for a specific treatment

Study	Intervention	Follow-up (weeks)	Predictors within the rule	n of predictors	Success/ non-success (n)	Sensitivity (95%CI)	Specificity (95%CI)	Positive Likelihood Ratio (95% CI)	Posttest Success (%)
Barton 2011a [143]	Foot orthoses	12	Footwear motion control properties >5.0	≥1	11/25	1.00 (0.74-1.00)	0.26 (0.14 - 0.42)	1.3 (1.1 - 1.6)	24
			Usual pain <22.0/100mm (VAS)	≥2	11/16	1.00 (0.74-1.00)	0.54 (0.38 - 0.70)	2.2 (1.5 - 3.1)	41
			Ankle Dorsiflexion (knee flexed) <41.3°	≥3	7/2	0.64 (0.35-0.85)	0.94 (0.81 - 0.98)	11.1 (2.7 - 46.9)	78
			Reduced pain during single leg squat	All 4	0/0	0	0	0	0
Crowell & Wofford 2012 [144]	Lumbo-pelvic manipulation	1	Hip IR side to side difference >14°	≥2	-	0.72 (0.54–0.90)	0.11 (0–0.24)	0.8 (0.6–1.1)	-
			Ankle dorsiflexion (knee flexed) >16°	≥3	-	0.45 (0.23–0.67)	0.33 (0.14–0.52)	0.7 (0.4–1.2)	-
			Navicular drop >3mm	≥4	-	0.16 (0.02–0.30)	0.84 (0.68–1.01)	1.0 (0.3–4.0)	-
			No self-reported stiffness sitting >20 min	≥5	-	0.02 (0–0.07)	0.95 (0.85–1.0)	0.4 (0–10.5)	-
			Squatting (most painful activity)						
Iverson 2008 [154]	Lumbo-pelvic manipulation	1	Hip IR side to side difference >14°	≥1	0/11	0.91 (0.71, 0.99)	0.15 (0.04, 0.35)	1.1 (0.87, 1.3)	47
			Ankle dorsiflexion (knee flexed) >16°	≥2	5/11	0.91 (0.71, 0.99)	0.56 (0.35, 0.75)	2.05 (1.3, 2.9)	63
			Navicular drop >3mm	≥3	8/1	0.68 (0.45, 0.86)	0.96 (0.81, 1.00)	18.4 (3.6, 105.3)	94
			No self-reported stiffness sitting >20 min	≥4	5/0	0.32 (0.15, 0.55)	1.00 (0.84, 1.00)	Infinite (0.90, infinite)	100
			Squatting (most painful activity)	all 5	2/0	0.09 (0.02, 0.31)	1.00 (0.84, 1.00)	Infinite (0.31, infinite)	100
Vicenzino 2010 [140]	Foot orthoses	12	Age >25 years	≥1	17/16	1 (0.77 to 1.0)	0.36 (0.19 to 0.57)	1.6 (1.2 to 2.1)	52.7
			Mid-foot width difference >10.96mm	≥2	12/8	0.71 (0.44 to 0.89)	0.68 (0.46 to 0.84)	2.2 (1.1 to 4.2)	59.5
			Height <165cm	≥3	6/1	0.35 (0.15 to 0.61)	0.96 (0.78 to 0.99)	8.8 (1.2 to 66.9)	85.4
			Worst pain <53.25/ 100mm (VAS)	All 4	0/0	-	-	-	-

IR = internal rotation; (VAS) = visual analogue scale

Appendix 8 Prognostic factors and potential treatment effect modifiers identified in this review

		Modifiable with non-operative treatment	Potentially modifiable	Unable to modify with non-operative treatment
Factors associated with a poor outcome				
Prognosis	Clinically measurable	Swelling of knee (self-reported) [147] Lower Kujala score [137] Higher frequency of pain [148] Bilateral symptoms [147] Lower eccentric knee strength [148] Larger asymmetry in side-to-side isometric quads strength [150]	Low/middle education [147] Poor health [147]	Longer duration [137, 145, 146])] Older age [149] Female gender [146] Patellar hypermobility [146]
	Not standard clinical measurement	Smaller quads cross sectional area [148]	Slower VMO reflex response [145]	Tibial tubercle lateral deviation >14.6mm[151] Chondromalacia patella [151]
Factors reported to be associated with a successful outcome to a specific treatment				
Foot orthoses	Clinically measurable	Midfoot width difference > 11mm [140, 142] Ankle dorsiflexion (knee flexed) <41° [143] Usual pain < 22/100mm (VAS) [143] Worst pain <53/100mm (VAS) [140] Reduced pain during single leg squat with orthoses fitted[143] Footwear motion control properties (weighted mean) <5[143]	-	Height < 165cm [140] Age > 25 yrs [140]
	Not standard clinical measurement	Greater rearfoot eversion relative to floor [77] Reduced medial-lateral peak force during drop-jump [153]		
Patellar Taping	Clinically measurable	Lower Body Mass Index [141]		Larger Q-angle [141]
	Not standard clinical measurement		Smaller lateral patellofemoral angle [141]	

Leg press & stretching lower limb muscles	Not standard clinical measurement		Difference in patellar tilt angle between maximum quadriceps contraction and quadriceps relaxed [138]	-

Appendix 9 Hip exercise descriptors

	Hip abduction (side lying) (Fig 3A)	Hip external rotation (Fig 3B)	Hip abduction (standing) (Fig 3C)	Hip extension (Fig 3D)
Load magnitude	Approximately 10-12RM	Approximately 10-12RM	Approximately 10-12RM	Approximately 10-12RM
Number of repetitions	10	10	10	10
Number of sets	3	3	3	3
Rest in-between set (s)	Approx. 90s	Approx. 90s	Approx. 90s	Approx. 90s
Number of exercise interventions (per week)	3/week	3/week	3/week	3/week
Duration of the experimental period (weeks)	4 weeks	4 weeks	4 weeks	4 weeks
Fractional and temporal distribution of the contraction	2s concentric 1s isometric 2s concentric	2s concentric 1s isometric 2s concentric	2s concentric 1s isometric 2s concentric	2s concentric 1s isometric 2s concentric

modes per repetition and duration (s) of one repetition				
Rest in-between repetitions (s)	1s	1s	1s	1s
Time under tension (s)	5s/ rep 50s/ set 150s/ exercise session 1800s/ total intervention	5s/ rep 50s/ set 150s/ exercise session 1800s/ total intervention	5s/ rep 50s/ set 150s/ exercise session 1800s/ total intervention	5s/ rep 50s/ set 150s/ exercise session 1800s/ total intervention
Volitional muscular failure	No	No	No	No
Perceived exertion (/11) (appendix 1)	5-7/11 (‘Hard’ to ‘very hard’)	5-7/11 (‘Hard’ to ‘very hard’)	5-7/11 (‘Hard’ to ‘very hard’)	5-7/11 (‘Hard’ to ‘very hard’)
Range of motion (degrees)	0° to approx. 30°	0° to approx. half of available external rotation range°	0° to approx. 30°	45° hip flexion to approx 0°

Recovery time in-between exercise sessions ((hr)	48hr	48hr	48hr	48hr
Anatomical definition of the exercise (exercise form)	Side lying with the symptomatic leg top-most. Elastic band is placed around the ankle of the symptomatic leg and attached to the end of plinth. Participants abduct the leg up to 30° hip abduction and return back from the bed.	With the participant supine, and hips in 30° flexion over a wedge. Elastic band is placed around the ankle of the symptomatic leg and held by the therapist. Participants externally rotate the hip against resistance to mid-range of available external rotation.	The participant will stand with the elastic band looped around both ankles, superior to lateral malleoli. Prior to the exercise, the target hip will be in slight internal rotation (to minimize incorrect compensatory action of external rotation during abduction). Hip abduction will then be performed to approximately 45°.	The participant will stand with target hip in 45°hip flexion. One end of the elastic band fixated (or held by the therapist) at knee height and looped around the back of the knee. The hip is then extended whilst maintaining a neutral lumbo-pelvic position.

Appendix 10 SPIRIT figure. Schedule of enrolment, interventions and assessments

		TRIAL PERIOD								
	Enrolment	Allocation	Intervention period						Follow up	Close out
	May 2014-November 2016	May 2014-November 2016	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 6	August 2014 – Feb 2017
ENROLMENT										
Eligibility screening	X									
Informed Consent	X									
Allocation		X								
INTERVENTION										
Foot orthoses			X	X	X	X	X	X		
Hip exercises			X	X	X	X				
ASSESSMENT										
Diagnosis	X									
Midfoot width mobility	X									
Demographics		X								
Global rating of change									X	X
Rate of recovery									X	X

Patient acceptable symptom state									X	X
Numerical pain rating		X							X	X
PSFS		X							X	X
Kujala		X							X	X
KOOS		X							X	X
HADS		X							X	X
Euro-QoL		X							X	X
TSK		X							X	X
PCS		X							X	X
Functional tests: step up, step down, squat		X							X	X
Navicular height		X								X
Midfoot height mobility		X								X
Isometric hip strength testing		X							X	X
Range of motion measures		X							X	X

Kujala – Kujala patellofemoral pain scale; PSFS – Patient specific functional scale; KOOS - Knee injury and osteoarthritis outcome scale; HADS – Hospital anxiety and depression scale; TSK – Tampa scale for kinesophobia; PCS - Pain catastrophising scale

Appendix 11 Research Ethics Approval

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Comparing Foot Orthoses And Hip Exercises For Patellofemoral Pain: Predicting Those Who Will Benefit Most From Foot Orthoses
Chief Investigator:	Prof Bill Vicenzino
Supervisor:	None
Co-Investigator(s):	Mr Mark Matthews, Dr Andrew Claus, A/Prof Kay Crossley, Prof Tom McPoil, A/Prof Robert Nee
School(s):	UQ School of Health and Rehabilitations Sciences; Physical Therapy Faculty, Regis University USA; Arizona School of Health Science, A.T. Still University, USA
Approval Number:	2013000981
Granting Agency/Degree:	NHMRC
Duration:	31st August 2018

Comments:

Note: If this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Associate Professor Stephan Riek
Deputy Chairperson
Medical Research Ethics Committee

Signature _____ Date 05-8-13

Appendix 12 Participant information sheet

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Sports Injury Rehabilitation & Prevention for Health research unit (SIRPH)
School of Health and Rehabilitation Sciences
Division of Physiotherapy

The University of Queensland
Brisbane Qld 4072
Australia
Telephone (07) 3365 2008
International +61 7 3365 2275
Facsimile (07) 3365 2775

PARTICIPANT INFORMATION SHEET

TITLE: **Comparing foot orthoses and hip exercises for patellofemoral pain: predicting those who will benefit most from foot orthoses.**

LAY TITLE: **Predicting which people with knee pain improve more by using foot orthoses.**

INVESTIGATORS: **Mr Mark Matthews**
Dr Andrew Claus
Professor Bill Vicenzino
Associate Professor Kay Crossley
Professor Tom McPoil
Associate Professor Robert Nee

You have been invited to participate in this trial of interventions for knee pain. It is important for you to read and understand the following information about the trial, which contains details about your role and rights in the trial.

1. Purpose of study

This study will examine current treatments that are commonly used to treat people, similar to you with pain around the front of the knee. The treatments are foot orthoses and hip exercises. Previous studies have shown that these treatments reduce pain and improve the ability to do move about and exercise. There have been no studies that have directly compared the two treatments against each other. The main purpose of this study is to compare the two treatments in the same study. The study will also evaluate if there are any measures of your foot or hip taken before you start the treatments that predict how your knee responds to treatment.

2. Description and duration of the study

If you are willing to participate, you will be required to attend a preliminary session at the School of Physiotherapy at the University of Queensland for a screening exam to ensure that it is safe and appropriate to treat you with either of the two treatments (foot orthoses or hip exercises). In addition to this you will undergo a number of tests (e.g., physical measures and functional movement analysis involving tasks like walking up and down a step) and completion of questionnaires. These tests are commonly used in physiotherapy clinics and if it brings on it should usually be mild and short lasting (i.e., settle within minutes of doing the test). Functional movement analysis will involve measuring knee and thigh posture from a digital video recording of a single leg small squat (approximately one third squat). The questionnaires will cover a wide range of factors related to your knee pain. For example, the questionnaires will get your description of the pain and how it impacts on you, your physical activity levels and other pain related impacts.

Prior to commencing the trial, you will be randomly assigned to one of the two treatments. That is, much like a flip of a coin, you will have a 50/50 chance of being treated either by foot orthoses or hip exercises. The study investigators who will be working with you will not know what you are going to be assigned before you know yourself. Most importantly nor will they be able to change your treatment once you have been assigned. So before you agree to enroll in the study, it is extremely important that you are comfortable with being treated with either the foot orthoses or the hip exercises. Remember, both treatments have been shown to help relieve pain and improve movement, but we do not know which one of these treatments is better. It is important for you to understand that once you have been assigned to either foot orthoses or hip exercise, there will be no possibility of this being changed by yourself or the investigators. It is also important to avoid other treatments for your knee during the 12 week study period.

You will be assigned to either of the two following treatments:

1. Foot orthoses

Foot orthoses are a device that is inserted inside of your footwear. An experienced and trained physiotherapist will fit these into your footwear. The orthoses will be fitted and modified to ensure that they fit you well. It is essential that the orthoses are comfortable for you to wear. You will also do a simple home exercise program of daily calf stretching and foot exercises, which will be taught to you by the physiotherapist. You will be required to attend 6 physiotherapy sessions (each will take approximately 30-45 minutes) over a time frame of 6 weeks. As well as fitting the orthoses and teaching you the exercises during these sessions, the physiotherapist will also monitor your treatment and make modifications as required.

2. Hip exercises

The hip exercises have previously been shown to help pain at the front of the knee. The exercises will strengthen muscles around the hip that have been shown in previous studies on knee pain to be weak. The strengthening exercises will use strong elastic bands under the direct instruction and supervision of an experienced and trained physiotherapist in the clinic, That is, you will not have to do a home exercise program. As your hip muscles strengthen, stronger elastic bands will be used to progressively increase muscle strength, so that you gain maximum benefit from these exercises. The exercise program will require you to attend 3 exercises sessions (each will take approximately 30-45 minutes) per week for 4 weeks. That is, you will be required to attend a physiotherapy clinic for a total of 12 sessions over 4 consecutive weeks.

In addition to the treatments at the physiotherapy clinics, you will be required to attend two follow-up testing sessions at the School of physiotherapy at the University of Queensland. At these testing sessions you will undergo the tests mentioned above as well as some questions regarding how your condition has changed since treatment. These sessions will occur 6 and 12 weeks after starting treatment.

This current informed consent process seeks your involvement in the 12 week study described herein as well as an option to be followed up over an extended period. There is some evidence that patients with pain at the front of the knee continue to experience symptoms well into the future. So in addition to following you up at 12 weeks to determine the effects of the two treatments in the short term, we would like to follow you up long term, over an extended period of 10 years. If you do not wish to be followed up over this extended period, please mark where indicated on the consent form. This is entirely at your discretion and will not impact upon your involvement in this 12 week study. You are free to change your mind and withdraw your consent at any time without any consequences.

You will not have to pay for your treatments (physiotherapy sessions or foot orthoses etc), because we will pay the therapists directly once they have completed all of your treatment sessions.

4. Location of the study

Baseline measurements will be conducted at the School of Health and Rehabilitative Science, Division of Physiotherapy at the St Lucia campus of The University of Queensland. We will provide you with parking vouchers if you come to St Lucia in a car or we will be able to provide up to $20 to cover some of the costs for bus or taxi for travel to and from St Lucia campus of The University of Queensland.

Treatment sessions will be conducted locally at participating physiotherapy clinics. The physiotherapy clinics are spread around the greater Brisbane area so that it should be reasonably easy to attend a clinic that is near your work or residence, thereby reducing any time required to get to and from the clinics.

5. Benefits and risks

It is important to understand this treatment trial may or may not be of benefit to you and your symptoms. While treatments used in this study have been shown to improve pain and movement for the majority of patients, it is important to understand that not all patients would have improved.

It is very important to be aware of the very low risk of being involved in this trial. A small number of people involved in previous studies have experienced some discomfort at foot or at the hip. They did not experience any worsening of their knee symptoms because of the treatment.

The risk involved if you do the hip strength treatment is that you may feel some delayed muscle soreness. This sometimes happens when you are doing a new exercise and the muscle aches the next day. You have probably felt this after a long walk or climbing a lot of stairs. It is a low temporary stiffness and or muscle ache that can last 1-2days and should not limit you in anyway. The elastic bands used in the trial may contain latex products so please inform your physiotherapist if you have any known allergies.

If you receive the foot orthoses, they will be fitted to you with the main goal of being comfortable. However there is a small chance you may feel some rubbing and discomfort on your foot and toes with a chance of a small blister. This usually happens at the very start of wearing orthoses and can be improved with small adjustments made by the physiotherapist at one of the six treatment sessions.

Generally these minor discomforts do not stop you from continuing to participate in the trial. If you do experience any discomfort, please report it immediately to your treating physiotherapist who will advise you on what to do. Your treating physiotherapist will let us know about any complications you report to them. In addition to contacting your physiotherapist during the four or six week treatment period please contact a member of the research team (details below) for any complications or adverse reaction at any stage during the 12 weeks of the study or thereafter.

Feedback on individual assessment results will be provided on request and a summary of the overall outcomes of the study will be available at the completion of the research project. Should you have any questions regarding the nature of the research, please feel free to contact Professor Bill Vicenzino (b.vicenzino@uq.edu.au or 3365 2781) who will be happy to provide you with more information.

Your privacy while participating in this study will be maintained at all times. Any publications or presentations will not identify you or any individual in the study., We will use a numerical code, not your name, in our databases. All information provided by yourself and data collected will be kept securely in a locked filing cabinet and password protected computer files at the School of Health and Rehabilitative Sciences, Division of Physiotherapy at the University of Queensland. All information will only be accessed by the research team at the School of Health and Rehabilitative Sciences, University of Queensland.

This study has been cleared by one of the human ethics committees of the University of Queensland in accordance with the National Health and Medical Research Council's guidelines. Whilst you are free to discuss your participation in this study with the project staff, if you would rather speak to an officer of the University not involved in the study, you may contact Michael Tsu, the Ethics Officer on 3365 3924.

Whilst we have invited you to be involved in this trial, your participation in this trial is completely at your discretion. Your involvement is completely voluntary and you are free to withdraw from the trial at any stage without providing a reason, without any penalty, and this will not affect in any way future management of your condition.

Thank you for your interest in this research project.

Professor Bill Vicenzino
Ph: 07 3365 2781
Email: b.vicenzino@uq.edu.au

Dr Andrew Claus
Ph: (07) 3365 2095
Email: a.claus1@uq.edu.au

Appendix 13 Consent form

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

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School of Health and Rehabilitation Sciences
Division of Physiotherapy

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Brisbane Qld 4072 Australia
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CONSENT FORM

TITLE: **Comparing foot orthoses and hip exercises for patellofemoral pain: predicting those who will benefit most from foot orthoses.**

LAY TITLE: **Predicting which people with knee pain may improve their symptoms by using foot orthoses.**

INVESTIGATORS: **Mark Matthews** – PhD Candidate, University of Queensland
Dr Andrew Claus – University of Queensland
Professor Bill Vicenzino – University of Queensland
Associate Professor Kay Crossley – University of Queensland
Professor Tom McPoil - Regis University, USA
Associate Professor Robert Nee - A.T Still University, USA

1. I, _____(PLEASE PRINT YOUR NAME) hereby consent to take part in this research project.
2. I understand that this project is a trial of two treatments.
3. The details of the treatments have been explained to me, including the frequency and duration of the treatment sessions,as well as an indication of any discomfort or possible risks that may occur.
4. I understand that my involvement in this project requires me to attend regular physiotherapy sessions, and may require me to comply with a prescribed home exercise program.
5. I understand that measurements will be taken prior to commencing and also after completing the intervention protocol. These will include questionnaires, repeated movements (i.e. Step-ups), joint movement, foot posture, muscle length and muscle strength measurements.
6. I acknowledge that I have read the information sheet provided, and that I have had the project, so far as it affects me, fully explained to my satisfaction by the investigators. I freely consent to my participation in the project.
7. I understand I will be randomly assigned to an intervention protocol, which cannot be changed. I also acknowledge that the treatment will involve some of the following: hip or foot exercises, and foot orthoses.
8. I am informed that the results of any tests involving me will be published so as to not reveal my identity, and that my privacy will be maintained at all times.
9. I understand that I am free to withdraw from the project at any stage without penalty and that this will not affect in any way the ongoing management of my condition.
10. I understand that the trial has a follow-up period after completion of the treatment. Please select ([X]) one of the two follow up options below to indicate the follow up period you consent to:
    [ ] I wish to participate in ONLY the 12 week trial
    [ ] I wish to participate in the 12 week trial AND consent to being followed up over a 10 year period

Signed: _____ Name: _____ Date: _____
(participant) (Print)

Signed: _____ Name: _____ Date: _____
(witness) (Print)

Appendix 14 FOHX trial Statistical Analysis plan

Study: Foot Orthoses versus Hip eXercises for patellofemoral pain

1. EXECUTIVE SUMMARY

Trial registration:

Australian New Zealand Clinical Trial Registry : ACTRN12614000260628

Background:

Current best practice guidelines for optimally managing patellofemoral pain lists tailoring of treatment to the individual as first of four over-arching principles. [86] Foot orthoses and hip exercises are two such targeted treatments with supporting level II evidence (at least one RCT), but they have not been directly compared head to head in a trial. Preliminary evidence suggests that a more mobile foot (measured as midfoot width change from non-weight bearing to weight bearing) is predictive of superior outcomes with foot orthoses. [140, 142]

The FOHX trial is a randomised controlled trial that directly compares the efficacy of foot orthoses versus hip exercises, as well as investigating the utility of a midfoot width mobility measure to predict success with foot orthoses.

Primary objectives:

1. To determine if those with greater midfoot width mobility are more likely to report better outcomes from foot orthoses when compared to hip exercises
2. To conduct a head to head comparison between foot orthoses and hip exercises in the treatment of patellofemoral pain.

Possible treatment effect modifier

A reliable method of measuring midfoot width in weight bearing and non-weight bearing postures will be used to calculate the index of midfoot width mobility. [76] Preliminary studies have shown that a midfoot width mobility

index of approximately 11mm is a cut point, above which there is a far higher probability of success with foot orthoses. [140, 142]
An investigator will take this measurement before participants are allocated to a treatment. Participants will be stratified on this index ('*high*' ≥11mm midfoot width mobility; '*low*' <11mm) to ensure there are approximately equal amounts of those in *high* subgroup in each of the treatment groups.
The investigator responsible for screening participants for study inclusion and collecting outcome measures, as well as the treating physiotherapists, will be blind to the midfoot width mobility measurements.

Primary outcome

The primary outcome measure will be a 7-point global rating of change scale, with following categories: much better, better, a little better, no change, a little worse, worse, and much worse. The scale categories will be dichotomized for analysis, with much better and better representing a success with treatment. Participants will be assessed at 6 and 12 weeks follow up, with 12 weeks being the primary endpoint.

2. INTRODUCTION

Current best practice guidelines for managing PFP suggests tailoring treatment to the individual as the first of four over-arching principles to optimize treatment outcome. [86] One method to do this is by using clinically assessable patient characteristics to match the right treatment to the right patient.

Distal to the patellofemoral joint, greater mobility of the midfoot width has previously been suggested as a patient characteristic associated with better outcomes to foot orthoses. [140, 142] Proximal to the patellofemoral joint, weaknesses in the hip abductor and external rotator muscle groups have been associated with PFP. [213] Hip muscle strengthening exercises targeting these muscle groups have been shown to be efficacious [180, 310][310] but to date no characteristic has been reported to suggest those that would have better outcome over other treatments.

The FOHX trial: Foot Orthoses versus Hip eXercises for PFP is a randomised controlled trial comparing the efficacy of two common forms of treatment for

PFP at 12 weeks, and if a foot mobility measure will identify those who will be successfully treated with a foot orthosis.

3 STUDY OBJECTIVES

3.1 Primary objectives

The primary objectives are to:

3.1.1 Determine if greater mobility of the midfoot width (≥11 mm) is associated with better self-reported outcome with foot orthoses compared to hip exercises at 12 weeks.

[Note: midfoot determined to be at half the total foot length; mobility determined as the difference in midfoot width between 50% weight bearing (i.e. bipedal stance) and non-weight bearing]

3.1.2 Assess the efficacy of foot orthoses compared to hip exercises on self-reported global perceived effect of treatment pain at 12 weeks

3.2 Secondary objectives

The secondary objectives are to:

3.2.1 To explore the moderation of the treatment group-outcome relationship by midfoot mobility, where midfoot mobility is included in the model as a continuous variable

3.2.2. Determine the effects of foot orthoses compared to hip strengthening exercises on a range of secondary outcomes (pain (usual and worst pain), self-reported knee pain scores, self-reported functional and physical activity, functional tasks (step up, step down, squats), health-related quality of life and psychological well-being domains (fear of movement, anxiety and depression, and pain catastrophising), at 6 and 12 weeks.

3.2.3 Identify patient characteristics that could identify those who will be likely benefit from hip strengthening exercises compared to foot orthoses; at 6 and 12weeks.

4. STUDY DESIGN

4.1 Experimental design and procedures

The trial is a two-arm parallel-group randomised controlled trial in which participants will be randomly assigned to the foot orthoses or hip exercises treatment group. The trial and measurements taken are designed to be clinically relevant/applicable so as to help inform clinicians on optimizing treatment outcomes.

An off-site clinical trials centre will provide the randomisation sequence. Concealed randomisation will occur after the completion of the baseline assessment.

Midfoot width mobility of the target knee (left or right, as some are bilateral, so we treat the most symptomatic) will be measured as a potential treatment effect modifier. An independent investigator who is not involved in participants screening for study inclusion, or any other baseline or any outcome measures will be measuring midfoot width mobility. Midfoot width mobility is defined as the difference in width of the midfoot between the bipedal stance position (50% body weight) and the non-weight bearing sitting position (0% body weight, as in feet not in contact with floor). Based on preliminary evidence that suggests midfoot width mobility of ≥11mm seems to predict success with foot orthoses, we will stratify participant into 'high' (≥11mm) and 'low' (<11mm)' subgroups.

The trial will be conducted across two sites; Brisbane, Australia and Aalborg, Denmark.

4.2 Study population

Participants will be recruited from advertisements and undergo a screening procedure to ensure they meet the following selection criteria.

4.2.1 Inclusion criteria:

- Aged from 18 to 40years at the time of study inclusion
- Reporting a history of anterior, retro or peri-patellar knee pain of non-traumatic origin
- Greater than 6 weeks duration of symptoms

- Self-reported worst pain over the previous week will be required to be greater than 3/10 on a numerical pain scale (0 = no pain, 10 = worst pain imaginable)
- Self-reported symptoms provoked by at ≥2 of the following activities: squatting, running, prolonged sitting, stair ascending or descending.
- On physical examination, pain should be provoked by clinical palpation of the patella borders, stepping down from a 25 cm step, during a double-leg squat and present on clinical compression of the patella into the trochlear groove.
- Have basic comprehension of written and spoken English (Brisbane, Australia) or Danish (Aalborg, Denmark)
- Provide informed consent

4.2.2 Exclusion criteria:

- Prior treatment for PFP that included targeted hip exercises or foot orthoses.
- Concomitant injuries or pathologies affecting other knee structures (e.g. ligamentous, meniscal, tendon, iliotibial band, pes anserinus)
- A history of knee surgery, patellofemoral dislocation or subluxation, Osgood-Schlatter's disease, Siding-Larsen-Johanssen syndrome,
- On physical examination a positive patellar apprehension test, evidence of knee joint effusion, a foot condition that may preclude the use of foot orthoses, pain in and/or referred from the hip, pelvis or lumbar spine
- Current use of anti-inflammatory or corticosteroid medication
- Pregnant at the time of study inclusion

4.3 Study blinding

Participants will not be informed of the primary objective of the study pertaining to midfoot width mobility as a possible treatment effect modifier. Participants will be blind to the physical measurements taken at baseline and follow-up, including midfoot width measurements.

Treating physiotherapists will be blind to the baseline and follow-up questionnaires and physical measurements taken, including midfoot width measurements. The physiotherapists will be aware that there are the two treatment arms of the study, so blinding to treatment will not occur.
The investigator responsible for screening participants for study inclusions, collecting all baseline data (demographic and physical measurements, and baseline questionnaires) and outcome measures will be blind to treatment allocation and midfoot width mobility measurements.
The investigator responsible for collecting midfoot measurements will be blind to all baseline data and outcome measures.

5. INTERVENTIONS

All participants will receive an education sheet about PFP, how their allocated treatment is associated with addressing the condition and the advice to keep active as long as symptoms cease as soon as activity ceases and there are no residual symptoms immediately after exercise or later.

5.1 Foot orthoses

Participants in the foot orthoses group will be prescribed foot orthoses following a protocol established in a previous randomised control trial. [92] Registered physiotherapists will be provided with a range of commercially available prefabricated foot orthoses (Vionic Group LLC, Labrador, Australia). Physiotherapists will follow a standardised systematic fitting procedure that prioritises comfort of the orthoses, with the scope during the fitting procedure to re-review the length, size and hardness of the device and various modifications until the participant deems the device fits comfortably. Participants will also be asked to perform a home foot and ankle exercise program, to be repeated twice per day consisting of i) stretches for the triceps surae/tendo-achilles complex (3 x 30 sec weight-bearing), and ii) foot exercises for active anti-pronation. Participants will attend a total of six 30min sessions over six weeks.

5.2 Hip exercises

Participants in the hip exercise group will receive a hip muscle strengthening exercise program that has previously been reported. [180] Participants will complete a 30min exercise session with the physiotherapist, consisting of four

exercises to be done bilaterally. The four exercises will be: hip abduction in side-lying, hip external rotation in supine with the hips in 30degrees of flexion, hip abduction in standing and hip extension in standing. Resistance will be provided by Theraband™ elastic bands of predetermined lengths and strengths (red, green, blue, black, grey). These exercises are prescribed routinely in clinical practice. Participants will attend three sessions per week for four weeks. There are exercises to be conducted at home.

5.3 Intervention recording

- In the hip exercise group the physiotherapist will record such information as: number of exercises, repetitions and sets per exercise, strength and pre-determined length of Theraband™ used per exercise, level of difficulty on a scale of perceived exertion.
- In the foot orthoses group the physiotherapist will record the size and type of orthoses used, any modifications to the orthoses, comfort rating on a scale of 0-10 (0 'too uncomfortable to wear'; 10 'very comfortable'), and exercises taught (calf stretching, arch forming.
- Adherence to treatment will be calculated using a treatment diary completed by the treating physiotherapists.

6. OUTCOMES

One primary outcome, a number of secondary outcomes be collected at two follow up sessions at 6 and 12 weeks, by an investigator blinded to treatment allocation and midfoot width measurement.

6.1 Primary outcome

The primary outcome measure will be a global rating of change scale for participants to rate their perception of the overall effect of their treatment. The scale will consist of a 7-point vertical scale (much better, better, a little better, no change, a little worse, worse, much worse).

6.2 Secondary outcomes

- *Single assessment numerical evaluations:* Participants will be asked to rate their symptoms with a numerical evaluations (0-100):

- *Self reported rate of recovery*: participants will self-report a percentage on how they feel they have recovered from their knee pain on a scale where 0% is ‘not at all’ and 100% is ‘totally recovered’.
- *Self reported scale of normality*: participants will be asked to rate their knee on the day of assessment as a percentage of normal on a scale of 0% to 100% (no problems at all).
- *Usual pain in the last seven days:* participants will self-report their worst pain experience in the last seven days using a 11-point numerical rating scale (0 to 10), where 0 is ‘no pain’ and 10 is ‘worst pain imaginable’, This will be measured at baseline, 6 and 12 week follow up. An improvement of two or more on the NPS indicates clinically meaningful change.
- *Worst pain in the last seven days*: participants will self-report their worst pain experience in the last seven days using an 11-point numerical rating scale (0 to 10), where 0 is ‘no pain’ and 10 is ‘worst pain imaginable’. This will be measured at baseline, 6 and 12 week follow up. An improvement of two or more on the NPS indicates clinically meaningful change.
- *Knee pain score*: participants will complete the Kujala patellofemoral scale which comprises of 13 items, each weigh differently, to give a total score out of 100 (0 represents total incapacity, 100 represents full pain free function).
- *Physical activity (level):* physical activity will be self-reported using the International Physical Activity Questionnaire-Short Form [11]. Participants will be classified into one of the three activity levels (low, moderate or high). For secondary analysis Physical activity (level) will then be dichotomised as having low physical activity (yes/no).
- *Knee injury scale*: participants will complete the Knee injury and Osteoarthritis Outcome Scale (KOOS) that comprises of five separate subscales (pain, symptoms, activities of daily living function, sporting and recreation function and quality of life) designed to assess the patient’s opinion of their knee and symptoms. Each subscale is scored separately.

- *Health-related problems and quality of life*: will be measured using the Euro-Qol-5 Dimensions instrument that comprises of five questions about mobility, usual activities, self care, pain and discomfort, and anxiety and depression.
  Fear of movement: will be measured using the 13-item Tampa scale of kinesiophobia.
- *Health-related anxiety and depression*: will be measured using the 14-item Hospital Anxiety and Depression Scale
- *Pain catastrophising*: will be measured using the 13-item pain catastrophising scale that comprises of three subscale scores for ruminations, magnification and helplessness respectively.
- *Functional abilities*: participants will complete three physical tasks (step-up and step-down respectively on a 25cm step, and full depth squats) to first onset of pain, increase in existing symptoms or a maximum of 25 repetitions.
- *Participant acceptable symptom state*: participants will be asked to respond yes or no to a question: "*Is your **current** condition satisfactory, when you take your general functioning and your current pain into consideration?*"
- *Participant perception of success:* Participants will be asked to answer yes or no to (a) Overall, if they agreed their treatment has been successful, and (b) if they would recommend the same treatment to a good friend.
- *Participant satisfaction:* participant's statisfaction will be assessed on a five-point satisfaction scale (very satisfied, somewhat satisfied, neither satisfied not dissatisfied, somewhat dissatisfied, very dissatisfied). Participants will be asked how they felt overall about (a) their treatment, and (b) if they had to live with their current symptoms.

7. STUDY SAFETY

A safety committee will be established when the need arises. It is not anticipated that a safety committee will need to convene much or at all, because the treatments have been previously studied with no reported serious adverse events, are common to everyday practice for this condition

and there is low perceived risk to participants. Participants and the treating physiotherapists are instructed to report any adverse effects. Adverse effects reported by participants or documented by the physiotherapists during the treatment phases of the trial will be managed and reported (to ethics and relevant institutional unit) as per appropriate policies and procedures at the relevant site.

8. SAMPLE SIZE

Sample size was based on proportions of patients rating themselves as "better" or "much better" on the Global Rating of Change (GROC) score in the foot orthoses and hip exercise treatment groups. A sample of 30 participants (15 per group) provides 80% power using a two-sided significance level of 0.05 to detect a difference between the proportions of participants with improvement of 30% in the hip exercises group compared to 80% in the foot orthoses group. Of primary interest is the detection of an interaction between randomised treatment group and foot mobility group, where foot mobility is dichotomised as high (≥11mm) versus low mobility (<11mm). To ensure adequate power to detect an interaction effect of 50% (the difference in the difference in outcomes between the randomised groups in the high versus low mobility groups), assuming 20% of participants would be in the high mobility group, we inflated the sample size to 94 per group. [222] To allow loss to follow-up of up to 15%, the final sample size was 220 participants (110 per group).

We decided to power the study on an interaction effect of 50% on the basis of our previous findings that have indicated a strong effect of foot orthoses in patients with PFP who had a midfoot mobility ≥11mm. [142] In that study we found 78% (7/9) of those with high midfoot mobility responded to an orthosis compared to only 20% (2/10) assigned to a control group. [142] The success rate had improved substantially from 47% (9/19) in the group assigned foot orthoses. [142]

9. DATA ANALYSIS

9.1 Data collection quality

To ensure all data collected during the trial maintains quality, the following procedures will be employed:

- All investigators will have standardized data collection forms with pre-determined set-up and verbal instructions to give, and will ensure all applicable outcomes at each assessment time point have been appropriately completed.
- All relevant participant variable and outcome data collected during the trial will be entered into a password protected online database (OpenClinica™) that is maintained by an external offsite party. The database will incorporate range limits for each variable entered to minimize input error. Once data from all participants have been entered, the database will be locked and data extracted in file formats appropriate to statistical analysis package(s) used.

To maintain investigator blinding, participants' data will be coded and documents that can disclose treatment allocation and midfoot width mobility measurements will be stored in locked filing cabinet accessible only to the appropriate investigator. Related online files will be password protected

9.2 Data analysis principles

All analysis of data will be conducted on a intention-to-treat basis. All statistical tests will be at a significance level of $p<0.05$ with no adjustment for number of comparisons.

9.3 Blinding of data

All data will be entered in a coded fashion and all analyses will be undertaken in a blind method. The statistician will be blind to group allocation by coding the treatment and the participants. Revealing of the coding to treatment allocation will only occur once the final statistical analyses have been conducted.

9.5 Missing data handling

Once all data has been collected, missing data will be reviewed. Should the proportion of missing data be greater than 5%, multiple imputed methods will be applied where necessary prior the analysis of the primary trial objectives.

9.6 Statistical analysis

A biostatistician blinded to treatment group allocation will conduct the trial analyses. All participants who have missing data and did not fully comply with the treatment protocol will be included in analyses. Demographic

characteristics will be inspected to assess baseline comparability of treatment groups and compare those participants who remain in the study and those who withdraw. If the proportion of missing data for endpoints exceeds 5%, multiple imputation methodology will be applied. To test the hypothesis of interaction between randomised group and foot mobility, terms for randomised group and foot mobility group, together with an interaction between the two, will be included in models. For the primary outcome (dichotomised GROC) and other binary secondary outcomes, binary regression models with a logarithmic link will be fit. Odds ratios will be presented, as will risk differences calculated from marginal probabilities. [311] For continuous outcomes, linear regression models will be fit, and assumptions assessed using standard diagnostic plots. To test for an overall treatment effect, the regression models described above will be interrogated to yield a marginal treatment effect estimate and 95% confidence interval. Similar models will be fit to determine the effects of treatment on secondary outcomes.

We will also undertake a secondary analysis to further explore the relationship between foot mobility and the effect of treatment, whereby foot mobility will be included in the model as a continuous variable, together with an interaction term with randomised group. Relationships will be investigated using fractional polynomials. [223] Further exploratory analyses to assess effect modification will be conducted including interaction terms between treatment group and potential effect modifiers.

Appendix 15 Baseline demographics by randomised treatment group.

	Foot Mobility Strata	Total	Hip Exercises	Foot Orthoses
Site				
Both (n (%))	High	49 (22.5)	25 (22.9)	24 (22.0)
	Low	169 (77.5)	84 (77.1)	85 (78.0)
	All	218	109	109
Australia (n (%))	High	28 (12.8)	14 (12.8)	14 (12.8)
	Low	110 (50.1)	55 (50.1)	55 (50.1)
	All	138 (63.3)	69 (63.3)	69 (63.3)
Denmark (n (%))	High	21 (9.6)	11 (10.1)	10 (9.2)
	Low	59 (27.1)	29 (26.6)	30 (27.5)
	All	80 (36.7)	40 (36.7)	40 (36.7)
Sex	High	32 (65.3)	16 (64.0)	16 (66.7)
Female (n (%))	Low	119 (70.4)	54 (64.3)	65 (76.5)
	All	151 (69.3)	70 (64.2)	81 (74.3)
Bilateral symptoms	High	37 (78.7)	17 (73.9)	20 (83.3)
Yes (n (%))	Low	109 (66.1)	52 (63.4)	57 (68.7)
	All	146 (68.9)	69 (65.7)	77 (72.0)
Study Knee (most problematic)	High	30 (63.8)	16 (69.6)	14 (58.3)
Right (n (%))	Low	81 (49.4)	43 (52.4)	38 (46.3)
	All	111 (52.6)	59 (56.2)	52 (49.1)
Age (years mean (SD))	High	27.8 (5.8)	29.2 (4.9)	26.4 (6.3)
	Low	28.2 (6.1)	28.0 (6.3)	28.3 (5.9)
	All	28.1 (6.0)	28.3 (6.0)	27.9 (6.0)
Height (cm mean (SD))	High	170.0 (10.5)	169.1 (10.1)	170.9 (11.1)
	Low	171.5 (9.3)	172.1 (9.7)	171.0 (8.9)
	All	171.2 (9.6)	171.4 (9.8)	171.0 (9.4)
Weight (kg mean (SD))	High	76.0 (14.9)	80.7 (15.5)	71.0 (12.7)
	Low	73.3 (17.0)	73.7 (17.0)	72.9 (17.1)
	All	73.9 (16.5)	75.3 (16.9)	72.5 (16.2)
BMI (kg/m^2 mean (SD))	High	26.3 (4.8)	28.3 (5.3)	24.3 (3.4)
	Low	24.8 (4.8)	24.7 (4.5)	24.9 (5.1)
	All	25.1 (4.8)	25.5 (4.9)	24.7 (4.8)
Duration of Symptoms	High	62.6 (69.0)	67.6 (67.0)	57.7 (72.1)
(months mean (SD))	Low	51.3 (58.8)	47.9 (60.1)	54.8 (57.7)

	All	53.8 (61.2)	52.3 (61.9)	55.4 (60.8)
Self-reported measures				
Worst Pain	High	6.4 (2.0)	6.4 (2.4)	6.2 (1.9)
(NRS mean (SD))	Low	6.25 (2.0)	6.2 (2.0)	6.1 (2.3)
	All	6.3 (2.0)	6.3 (2.0)	6.3 (2.0)
Tampa	High	39.3 (6.7)	39.3 (6.5)	39.2 (7.0)
(mean (SD))	Low	39.5 (5.5)	38.9 (5.4)	40.0 (5.5)
	All	39.4 (5.7)	39.0 (5.6)	39.9 (5.8)
HADS Anxiety	High	6.4 (3.1)	6.2 (3.1)	6.2 (3.4)
(mean (SD))	Low	5.8 (3.9)	5.6 (3.8)	6.0 (3.9)
	All	5.9 (3.7)	5.8 (3.6)	6.0 (3.8)
HADS Depression	High	2.9 (2.5)	3.0 (2.7)	2.8 (2.2)
(mean (SD))	Low	3.0 (2.6)	3.0 (2.7)	3.0 (2.6)
	All	3.0 (2.6)	3.0 (2.7)	3.0 (2.5)
Pain Catastrophising Scale	High	13.4 (8.3)	12.6 (7.5)	13.7 (9.5)
(mean (SD))	Low	12.5 (9.5)	11.9 (8.5)	13.0 (10.5)
	All	12.7 (9.3)	12.2 (8.2)	13.3 (10.2)
Percentage of normal	High	59.7 (19.1)	54.0 (25.5)	55.6 (24.2)
(0-100% mean (SD))	Low	59.6 (21.5)	55.8 (25.8)	52.1 (28.0)
	All	59.6 (20.9)	60.3 (20.3)	58.8 (21.6)
KOOS (mean (SD))	High	65.6 (16.0)	66.1 (15.8)	65.2 (16.4)
Symptoms	Low	68.1 (15.3)	69.3 (16.2)	66.9 (14.4)
	All	67.6 (15.4)	68.6 (16.1)	66.5 (14.8)
Pain	High	69.1 (12.1)	67.2 (12.4)	70.9 (11.7)
	Low	69.0 (12.9)	69.5 (13.0)	68.5 (12.9)
	All	69.0 (12.7)	69.0 (12.9)	69.0 (12.6)
Activities of daily living	High	78.9 (13.4)	79.4 (14.5)	78.4 (12.5)
	Low	79.3 (13.0)	79.7 (12.7)	78.9 (13.4)
	All	79.2 (13.1)	79.6 (13.1)	78.8 (13.1)
Sporting and recreation	High	52.5 (22.9)	49.2 (23.4)	55.8 (22.3)
	Low	52.4 (21.6)	55.5 (20.9)	49.2 (22.0)
	All	52.2 (21.6)	54.1 (21.5)	50.7 (22.1)
Quality of Life	High	48.4 (16.7)	48.4 (13.9)	48.4 (19.4)
	Low	44.9 (15.8)	45.9 (16.9)	43.9 (14.6)
	All	45.7 (16.0)	46.5 (16.3)	44.69 (15.8)

KOOS Patellofemoral	High	52.9 (19.1)	51.1 (19.0)	54.9 (19.5)
(mean (SD))	Low	52.3 (16.1)	52.5 (15.2)	50.0 (17.7)
	All	52.3 (16.1)	52.2 (16.1)	51.0 (18.1)
Physical measurements				
Functional tests study knee	High	13.5 (8.3)	13.6 (8.4)	13.5 (8.4)
Step-up (n mean (SD))	Low	13.1 (8.6)	13.1 (8.6)	13.2 (8.6)
	All	13.2 (8.5)	13.2 (8.5)	13.3 (8.6)
Step-down (n mean (SD))	High	8.7 (8.5)	8.4 (8.6)	9.0 (8.6)
	Low	7.7 (7.5)	7.5 (7.3)	8.0 (7.7)
	All	7.9 (7.7)	7.7 (7.6)	8.2 (7.9)
Squats (n mean (SD))	High	9.9 (7.3)	10.7 (7.5)	9.0 (7.1)
	Low	9.2 (7.7)	8.5 (7.5)	9.9 (7.9)
	All	9.4 (7.6)	9.0 (7.5)	9.7 (7.7)
Beighton Joint Mobility	High	2.3 (2.3)	1.9 (2.4)	2.6 (2.3)
(mean (SD))	Low	2.2 (2.3)	1.9 (2.3)	2.4 (2.2)
	All	2.2 (2.3)	1.9 (2.3)	2.5 (2.2)
Hip Strength study knee	High	1.39 (0.33)	1.35 (0.29)	1.44 (0.38)
Abduction	Low	1.43 (0.41)	1.47 (0.42)	1.39 (0.39)
($Nmkg^{-1}$ mean (SD))	All	1.42 (0.39)	1.44 (0.40)	1.40 (0.39)
Adduction	High	1.45 (0.40)	1.44 (0.43)	1.46 (0.37)
($Nmkg^{-1}$ mean (SD))	Low	1.43 (0.47)	1.49 (0.49)	1.38 (0.44)
	All	1.44 (0.45)	1.48 (0.48)	1.40 (0.43)
External rotation	High	0.48 (0.12)	0.49 (0.13)	0.47 (0.11)
($Nmkg^{-1}$ mean (SD))	Low	0.45 (0.12)	0.46 (0.12)	0.44 (0.13)
	All	0.46 (0.12)	0.46 (0.12)	0.45 (0.12)
Hip ROM study knee	High	25.3 (7.6)	23.4 (8.4)	26.2 (8.3)
Internal rotation	Low	26.9 (8.0)	26.5 (7.6)	27.3 (8.3)
(degrees mean (SD))	All	26.5 (7.9)	26.0 (7.5)	27.0 (8.3)
External rotation	High	32.8 (7.7)	32.0 (9.8)	32.2 (8.2)
(degrees mean (SD))	Low	32.8 (7.4)	33.1 (8.0)	32.5 (6.8)
	All	32.7 (7.4)	33.1 (7.8)	32.4 (7.1)
Midfoot width Mobility study side	High	12.6 (1.5)	12.7 (1.4)	12.5 (1.7)
(mean (SD))	Low	7.4 (2.3)	7.9 (2.0)	6.9 (2.6)
	All	8.5 (3.1)	9.0 (2.7)	8.1 (3.4)
Foot Posture Index study side	High	6.0 (4.0)	6.0 (4.6)	5.8 (3.5)
(mean (SD))	Low	3.3 (4.0)	3.6 (3.9)	2.9 (4.1)

	All	3.9 (4.2)	4.2 (4.2)	3.6 (4.2)
Navicular Drop study side	High	8.3 (4.3)	8.4 (4.9)	8.0 (3.8)
(mm mean (SD))	Low	5.5 (3.8)	5.6 (3.5)	5.3 (4.1)
	All	6.1 (4.1)	6.3 (4.0)	5.9 (4.1)
Ankle Dorsiflexion study side	High	126.0 (35.9)	116.2 (32.3)	135.8 (37.4)
Bent knee	Low	118.1 (33.4)	112.1	121.4 (31.0)
(mm mean (SD))	All	119.9 (34.1)	115.2 (34.7)	124.6 (32.9)
Straight knee	High	36.9 (5.4)	35.0 (5.1)	38.7 (5.2)
(degrees mean (SD))	Low	37.0 (5.5)	36.2 (5.8)	37.9 (5.1)
	All	37.0 (5.5)	35.9 (5.7)	38.1 (5.1)

BMI: Body Mass Index; NRS: Numerical pain Rating Scale

Appendix 16 Secondary analysis including midfoot width mobility as a continuous interval measure.

Relative risk of Global rating of Change associated with a one-unit increase in midfoot width mobility in each treatment group at each time point. P-value for the three-way interaction between time, treatment group and midfoot width mobility was 0.097.

	Hip exercises		Foot orthoses		Treatment-by-MFW interaction
Time	RR (95% CI)	P-value	RR (95% CI)	P-value	P-value
6	1.00 (0.92, 1.08)	0.956	0.97 (0.91, 1.05)	0.477	
12	0.93 (0.88, 0.99)	0.025	0.99 (0.93, 1.05)	0.715	
					0.66

Appendix 17 Secondary outcomes for Foot orthoses versus Hip exercises, for each visit and each foot-mobility subgroup

Time (wk)	Strata	Hip Exercises Count (successful/total)(%)	Foot orthoses Count (successful/total)(%)	Foot orthoses - Hip exercises		Treatment by strata interaction
				RR (95% CI)	P-value	P value
Global rating of change outcome based on treatment allocation and stratification on midfoot width mobility at 6 weeks						
6	High	10/21 (47.62)	6/23 (26.09)	0.52 (0.23, 1.20)	0.12	
6	Low	35/75 (46.67)	35/78 (44.87)	0.95 (0.68, 1.34)	0.78	
6	All	45/96 (46.88)	41/101 (40.59)	0.87 (0.63, 1.19)	0.37	
“Is your current condition satisfactory?” (y/n)						
6	High	10/21 (47.62)	15/23 (65.22)	1.26 (0.78, 2.06)	0.35	
6	Low	47/75 (62.67)	47/77 (61.04)	1.01 (0.80, 1.27)	0.95	
6	All	57/96 (59.38)	62/100 (62.00)	1.05 (0.85, 1.29)	0.66	
12	High	11/20 (55.00)	14/21 (66.67)	1.17 (0.72, 1.88)	0.53	
12	Low	47/72 (65.28)	48/78 (61.54)	0.96 (0.78, 1.19)	0.72	
12	All	58/92 (63.04)	62/99 (62.63)	1.00 (0.82, 1.21)	0.97	
12						0.41
“Overall, has treatment been successful?” (y/n)						
6	High	12/21 (57.14)	15/23 (65.22)	1.09 (0.66, 1.80)	0.72	
6	Low	49/74 (66.22)	48/74 (64.86)	1.01 (0.80, 1.28)	0.94	
6	All	61/95 (64.21)	63/97 (64.95)	1.02 (0.82, 1.27)	0.83	
12	High	12/20 (60.00)	10/20 (50.00)	0.81 (0.46, 1.45)	0.48	
12	Low	42/71 (59.15)	46/77 (59.74)	1.00 (0.77, 1.29)	0.99	
12	All	54/91 (59.34)	56/97 (57.73)	0.96 (0.75, 1.21)	0.72	
12						0.77

EQ-5D – Mobility (no problem/ problems)						
6	High	4/21 (19.05)	5/23 (21.74)	1.11 (0.37, 3.35)	0.85	
6	Low	16/73 (21.92)	24/76 (31.58)	1.29 (0.76, 2.17)	0.35	
6	All	20/94 (21.28)	29/99 (29.29)	1.25 (0.78, 2.01)	0.36	
12	High	2/20 (10.00)	2/21 (9.52)	0.97 (0.15, 6.14)	0.97	
12	Low	11/72 (15.28)	23/79 (29.11)	1.73 (0.92, 3.24)	0.089	
12	All	13/92 (14.13)	25/100 (25.00)	1.62 (0.89, 2.92)	0.11	
12						0.81
EQ-5D: Usual activities (no problem/ problems)						
6	High	7/21 (33.33)	12/23 (52.17)	1.52 (0.80, 2.86)	0.20	
6	Low	26/73 (35.62)	30/76 (39.47)	1.13 (0.75, 1.70)	0.57	
6	All	33/94 (35.11)	42/99 (42.42)	1.23 (0.88, 1.73)	0.23	
12	High	7/20 (35.00)	6/21 (28.57)	0.81 (0.38, 1.74)	0.59	
12	Low	18/72 (25.00)	27/79 (34.18)	1.40 (0.86, 2.26)	0.17	
12	All	25/92 (27.17)	33/100 (33.00)	1.19 (0.79, 1.78)	0.40	
12						0.44
EQ-5D: Pain/ discomfort (no problem/ problems)						
6	High	17/21 (80.95)	19/23 (82.61)	1.00 (0.76, 1.30)	0.98	
6	Low	49/73 (67.12)	58/76 (76.32)	1.14 (0.93, 1.41)	0.21	
6	All	66/94 (70.21)	77/99 (77.78)	1.10 (0.93, 1.30)	0.28	
12	High	14/20 (70.00)	14/21 (66.67)	1.05 (0.67, 1.62)	0.84	
12	Low	51/72 (70.83)	51/79 (64.56)	0.93 (0.74, 1.16)	0.51	
12	All	65/92 (70.65)	65/100 (65.00)	0.96 (0.79, 1.17)	0.67	
12						0.43
EQ-5D: Anxiety/ Depression (no problem/ problems)						
6	High	4/20 (20.00)	2/23 (8.70)	0.35 (0.08, 1.62)	0.18	
6	Low	11/73 (15.07)	12/76 (15.79)	1.01 (0.50, 2.06)	0.98	
6	All	15/93 (16.13)	14/99 (14.14)	0.81 (0.43, 1.53)	0.51	
12	High	3/20 (15.00)	2/21 (9.52)	0.45 (0.09, 2.17)	0.32	
12	Low	10/72 (13.89)	10/78 (12.82)	0.74 (0.35, 1.57)	0.43	
12	All	13/92 (14.13)	12/99 (12.12)	0.66 (0.33, 1.32)	0.24	
12						0.21

		Hip Exercises mean(SD)	Foot orthoses mean(SD)	Foot orthoses - Hip exercises		
				Coefficient (95% CI)	P-value	
Rating knee as % of normal (0-100%)						
6	High	67.1 (18.4)	67.3 (21.1)	-1.66 (-12.98, 9.67)	0.77	
6	Low	73.5 (18.3)	67.5 (18.8)	-4.89 (-10.73, 0.95)	0.10	
6	All	72.2 (18.4)	67.4 (19.3)	-4.16 (-9.46, 1.14)	0.12	
12	High	71.8 (22.7)	73.8 (21.5)	-0.89 (-13.96, 12.19)	0.89	
12	Low	75.9 (18.5)	73.0 (18.9)	-2.75 (-8.56, 3.05)	0.35	
12	All	75.0 (19.4)	73.2 (19.4)	-2.34 (-7.78, 3.10)	0.40	
12						0.61
Recovery scale score (0-100%)						
6	High	56.0 (26.8)	50.0 (28.9)	-8.34 (-24.70, 8.02)	0.32	
6	Low	57.9 (29.2)	51.0 (27.7)	-7.43 (-16.21, 1.36)	0.098	
6	All	57.5 (28.6)	50.8 (27.8)	-7.67 (-15.38, 0.04)	0.051	
12	High	51.8 (34.9)	47.1 (33.6)	-6.28 (-26.59, 14.03)	0.55	
12	Low	58.7 (31.2)	60.4 (30.3)	1.31 (-8.60, 11.22)	0.80	
12	All	57.2 (32.0)	57.6 (31.3)	-0.36 (-9.32, 8.60)	0.94	
12						0.92
Kujala Patellofemoral scale (0-100)						
6	High	75.9 (12.2)	77.5 (12.3)	0.90 (-4.67, 6.47)	0.75	
6	Low	77.8 (9.8)	74.9 (11.8)	-1.71 (-4.70, 1.27)	0.26	
6	All	77.4 (10.3)	75.5 (11.9)	-1.13 (-3.78, 1.51)	0.40	
12	High	77.5 (9.3)	79.0 (13.1)	-0.02 (-5.92, 5.87)	0.99	
12	Low	79.8 (9.0)	78.5 (13.6)	0.39 (-2.84, 3.63)	0.81	
12	All	79.3 (9.0)	78.6 (13.4)	0.31 (-2.50, 3.11)	0.83	
12						0.42
KOOS: Symptoms subscale						
6	High	70.4 (15.7)	69.6 (16.0)	-0.83 (-5.55, 3.89)	0.73	

6	Low	76.2 (14.1)	69.9 (15.7)	-3.86 (-6.85, -0.87)	0.011*	
6	All	74.9 (14.6)	69.8 (15.7)	-3.17 (-5.73, -0.62)	0.015*	
12	High	72.7 (13.6)	71.1 (16.3)	-2.21 (-7.18, 2.76)	0.38	
12	Low	76.7 (14.6)	71.9 (17.5)	-3.12 (-6.19, -0.04)	0.047*	
12	All	75.8 (14.4)	71.7 (17.2)	-2.92 (-5.52, -0.32)	0.028*	
12						0.29
KOOS: Pain subscale						
6	High	75.7 (13.8)	78.0 (11.6)	-0.31 (-6.22, 5.60)	0.92	
6	Low	78.8 (10.6)	74.6 (13.2)	-3.43 (-6.64, -0.21)	0.037*	
6	All	78.1 (11.4)	75.4 (12.9)	-2.73 (-5.57, 0.11)	0.060	
12	High	79.4 (12.3)	77.8 (14.8)	-3.88 (-11.42, 3.65)	0.31	
12	Low	81.1 (10.9)	76.0 (16.2)	-4.15 (-8.16, -0.14)	0.042*	
12	All	80.7 (11.2)	76.4 (15.9)	-4.09 (-7.63, -0.55)	0.023*	
12						0.36
KOOS: Daily living subscale						
6	High	83.0 (14.7)	87.0 (10.4)	3.18 (-2.64, 9.00)	0.28	
6	Low	86.8 (9.7)	83.0 (14.9)	-2.98 (-6.24, 0.28)	0.07	
6	All	86.0 (11.0)	84.0 (14.0)	-1.59 (-4.45, 1.26)	0.27	
12	High	87.4 (10.9)	87.7 (11.1)	0.35 (-6.10, 6.81)	0.91	
12	Low	89.0 (9.1)	84.2 (15.8)	-4.44 (-8.09, -0.80)	0.017*	
12	All	88.6 (9.5)	84.9 (14.9)	-3.37 (-6.54, -0.20)	0.037*	
12						0.072
KOOS: Sports & recreational subscale						
6	High	65.5 (22.9)	70.0 (22.1)	1.00 (-9.58, 11.58)	0.85	
6	Low	66.0 (20.9)	60.2 (23.7)	-3.12 (-9.60, 3.36)	0.34	
6	All	65.9 (21.2)	62.5 (23.6)	-2.20 (-7.74, 3.33)	0.43	
12	High	70.0 (18.6)	71.9 (23.3)	-3.20 (-13.84, 7.45)	0.56	
12	Low	69.6 (20.7)	67.8 (22.4)	0.51 (-5.88, 6.89)	0.88	
12	All	69.7 (20.2)	68.7 (22.5)	-0.31 (-5.81, 5.18)	0.91	
12						0.52
KOOS: Quality of life Subscale						
6	High	57.7 (16.6)	53.3 (19.4)	-5.79 (-14.67, 3.09)	0.20	

6	Low	51.7 (17.3)	50.8 (19.9)	-0.62 (-5.93, 4.69)	0.82	
6	All	53.1 (17.3)	51.4 (19.7)	-1.80 (-6.35, 2.75)	0.44	
12	High	55.9 (16.8)	58.6 (16.6)	-0.65 (-10.45, 9.15)	0.90	
12	Low	59.9 (17.3)	55.1 (19.9)	-4.16 (-9.70, 1.37)	0.14	
12	All	59.1 (17.2)	55.8 (19.2)	-3.35 (-8.24, 1.53)	0.18	
12						0.33
Worst pain past week (NPRS; 0-10)						
6	High	5.2 (2.2)	4.9 (2.6)	-0.17 (-1.53, 1.19)	0.81	
6	Low	4.4 (2.4)	4.9 (2.5)	0.35 (-0.35, 1.05)	0.33	
6	All	4.6 (2.4)	4.9 (2.5)	0.23 (-0.40, 0.86)	0.47	
12	High	4.7 (2.6)	4.6 (3.1)	0.33 (-1.28, 1.93)	0.69	
12	Low	4.0 (2.4)	4.6 (2.9)	0.64 (-0.17, 1.45)	0.12	
12	All	4.1 (2.5)	4.6 (2.9)	0.57 (-0.16, 1.30)	0.13	
12						0.50
Average pain past week (NPRS; 0-10)						
6	High	3.5 (1.8)	2.7 (1.6)	-0.43 (-1.38, 0.52)	0.38	
6	Low	2.8 (1.9)	3.1 (2.0)	0.21 (-0.36, 0.77)	0.47	
6	All	2.9 (1.9)	3.0 (1.9)	0.06 (-0.43, 0.55)	0.80	
12	High	2.9 (1.8)	3.0 (2.2)	0.43 (-0.79, 1.65)	0.49	
12	Low	2.5 (1.8)	2.9 (2.2)	0.40 (-0.20, 1.00)	0.19	
12	All	2.6 (1.8)	2.9 (2.2)	0.40 (-0.13, 0.94)	0.14	
12						0.26
Step-up most-problematic knee (Pain free reps: 0-25)						
6	High	21.1 (6.2)	18.1 (8.0)	-2.06 (-6.12, 2.00)	0.32	
6	Low	19.3 (7.3)	16.7 (7.8)	-2.42 (-4.74, -0.10)	0.040*	
6	All	19.7 (7.1)	17.0 (7.8)	-2.34 (-4.38, -0.30)	0.025*	
12	High	20.2 (7.2)	18.9 (8.0)	-1.31 (-5.48, 2.86)	0.54	
12	Low	18.0 (8.3)	17.2 (8.6)	-0.90 (-3.56, 1.76)	0.51	
12	All	18.5 (8.1)	17.6 (8.5)	-0.99 (-3.28, 1.29)	0.39	
12						0.88
Step-down most-problematic knee (Pain free reps: 0-25)						
6	High	15.1 (9.6)	10.2 (10.4)	-5.23 (-9.97, -0.48)	0.031*	
6	Low	14.5 (9.2)	12.5 (8.7)	-1.82 (-4.35, 0.70)	0.16	
6	All	14.6 (9.2)	12.0 (9.0)	-2.58 (-4.82, -0.34)	0.024*	

12	High	14.2 (9.1)	15.4 (10.0)	0.35 (-4.69, 5.40)	0.89	
12	Low	14.1 (9.2)	12.7 (9.4)	-1.42 (-4.35, 1.51)	0.34	
12	All	14.1 (9.2)	13.3 (9.6)	-1.03 (-3.59, 1.52)	0.43	
12						0.22
Squats (Pain free reps: 0-25)						
6	High	13.9 (8.3)	12.4 (9.6)	-0.60 (-4.58, 3.39)	0.77	
6	Low	15.8 (9.1)	12.2 (8.5)	-3.71 (-6.22, -1.20)	0.004*	
6	All	15.4 (8.9)	12.2 (8.7)	-3.00 (-5.18, -0.82)	0.007*	
12	High	17.5 (8.4)	13.8 (8.6)	-3.29 (-7.88, 1.30)	0.16	
12	Low	15.2 (9.0)	13.1 (9.0)	-2.73 (-5.43, -0.03)	0.047*	
12	All	15.7 (8.9)	13.3 (8.9)	-2.86 (-5.14, -0.59)	0.014*	
12						0.19
Hip Abduction strength ($Nmkg^{-1}$)						
6	High	1.44 (0.33)	1.45 (0.37)	-0.05 (-0.17, 0.06)	0.37	
6	Low	1.53 (0.38)	1.44 (0.38)	-0.04 (-0.10, 0.03)	0.25	
6	All	1.51 (0.37)	1.44 (0.37)	-0.04 (-0.10, 0.01)	0.15	
12	High	1.46 (0.25)	1.49 (0.35)	-0.02 (-0.15, 0.10)	0.71	
12	Low	1.54 (0.39)	1.43 (0.34)	-0.03 (-0.10, 0.04)	0.35	
12	All	1.52 (0.36)	1.44 (0.34)	-0.03 (-0.09, 0.03)	0.32	
12						0.81
Hip Adduction strength ($Nmkg^{-1}$)						
6	High	1.57 (0.53)	1.46 (0.42)	-0.12 (-0.25, 0.02)	0.10	
6	Low	1.49 (0.48)	1.38 (0.39)	-0.02 (-0.09, 0.05)	0.55	
6	All	1.51 (0.49)	1.40 (0.39)	-0.04 (-0.10, 0.02)	0.18	
12	High	1.52 (0.57)	1.51 (0.44)	-0.04 (-0.21, 0.13)	0.67	
12	Low	1.49 (0.45)	1.37 (0.40)	-0.01 (-0.08, 0.06)	0.79	
12	All	1.50 (0.48)	1.40 (0.41)	-0.01 (-0.08, 0.05)	0.65	
12						0.22
Hip External rotation strength ($Nmkg^{-1}$)						
6	High	0.53 (0.18)	0.46 (0.10)	-0.06 (-0.12, -0.01)	0.028	
6	Low	0.51 (0.13)	0.47 (0.14)	-0.04 (-0.06, -0.01)	0.013	
6	All	0.52 (0.14)	0.47 (0.13)	-0.04 (-0.07, -0.02)	0.001*	

12	High	0.51 (0.15)	0.49 (0.12)	-0.01 (-0.06, 0.04)	0.70	
12	Low	0.52 (0.10)	0.48 (0.14)	-0.01 (-0.04, 0.02)	0.36	
12	All	0.51 (0.12)	0.48 (0.13)	-0.01 (-0.04, 0.01)	0.33	
12						0.41
Tampa Scale of Kinesiophobia score						
6	High	36.1 (7.6)	37.8 (6.8)	1.83 (-1.35, 5.01)	0.26	
6	Low	36.3 (7.2)	37.7 (6.1)	0.55 (-1.17, 2.27)	0.53	
6	All	36.3 (7.3)	37.8 (6.2)	0.84 (-0.68, 2.35)	0.28	
12	High	35.6 (7.7)	34.2 (6.9)	-0.17 (-3.67, 3.33)	0.93	
12	Low	35.5 (7.5)	36.2 (6.5)	0.09 (-1.74, 1.93)	0.92	
12	All	35.6 (7.5)	35.8 (6.6)	0.04 (-1.55, 1.63)	0.96	
12						0.49
Hospital Anxiety and Depression Scale: Anxiety subscale						
6	High	5.5 (3.2)	4.3 (3.0)	-1.08 (-2.81, 0.65)	0.22	
6	Low	5.3 (3.6)	4.9 (3.3)	-0.86 (-1.58, -0.13)	0.020*	
6	All	5.3 (3.5)	4.8 (3.3)	-0.91 (-1.60, -0.22)	0.010*	
12	High	4.7 (3.2)	4.0 (3.7)	-0.45 (-2.18, 1.28)	0.61	
12	Low	4.8 (3.8)	4.6 (3.5)	-0.65 (-1.50, 0.20)	0.13	
12	All	4.8 (3.7)	4.5 (3.5)	-0.61 (-1.38, 0.16)	0.12	
12						0.81
Hospital Anxiety and Depression Scale: Depression subscale						
6	High	2.5 (2.1)	2.2 (2.7)	0.06 (-1.09, 1.21)	0.92	
6	Low	2.5 (2.3)	2.6 (2.6)	0.04 (-0.56, 0.63)	0.91	
6	All	2.5 (2.3)	2.5 (2.6)	0.04 (-0.49, 0.57)	0.88	
12	High	2.5 (2.3)	2.1 (2.4)	-0.39 (-1.77, 0.98)	0.58	
12	Low	2.3 (2.4)	2.2 (2.4)	-0.31 (-0.92, 0.31)	0.33	
12	All	2.4 (2.4)	2.1 (2.4)	-0.33 (-0.90, 0.25)	0.26	
12						0.97
Pain Catastrophising Scale (total)						
6	High	10.2 (7.8)	10.9 (11.7)	0.54 (-3.71, 4.79)	0.80	
6	Low	9.4 (8.0)	10.8 (9.0)	0.32 (-1.75, 2.38)	0.76	
6	All	9.6 (7.9)	10.8 (9.6)	0.37 (-1.49, 2.22)	0.70	
12	High	8.3 (8.2)	8.9 (10.3)	1.25 (-3.08, 5.58)	0.57	
12	Low	8.8 (9.0)	8.5 (8.1)	-0.78 (-3.02, 1.46)	0.50	
12	All	8.7 (8.8)	8.6 (8.5)	-0.32 (-2.31, 1.67)	0.75	

12						0.93

No model was fit for EQ-5D Personal care due to almost all participants reporting no problems with personal care.

+ The model for “Pain or discomfort” failed to converge.

* $p<0.05$

EQ-5D: The personal care, problems with usual activities, pain/discomfort, and anxiety/depression outcomes were dichotomised due to very few participants reporting the most extreme values of these variables

Appendix 18 Treatment outcomes for hip exercises versus foot orthoses at 6 and 12 weeks, grouped according to midfoot width mobility stratification

(treatment by foot mobility strata interaction p value = 0.53).

Midfoot Width Mobility	Hip Exercises (successful[+]/total (%))*	Foot orthoses (successful[+]/total (%))*	Foot orthoses vs Hip exercises^	
			Relative Risk (95% CI)	*P*-value
Week 6				
High (≥11 mm)	13/20 (65.00)	14/23 (60.87)	1.00 (0.63, 1.61)	0.99
Low (<11 mm)	51/75 (68.00)	42/76 (55.26)	0.85 (0.66, 1.08)	0.18
All	64/95 (67.37)	56/99 (56.57)	0.88 (0.70, 1.09)	0.23
Week 12				
High (≥11 mm)	13/19 (68.42)	13/21 (61.90)	0.88 (0.57, 1.37)	0.58
Low (<11 mm)	52/72 (72.22)	55/79 (69.62)	0.96 (0.79, 1.17)	0.70
All	65/91 (71.43)	68/100 (68.00)	0.95 (0.79, 1.13)	0.55

[+] successful defined as a decrease of at least 2 units in worst pain experienced in the past week, and/or an increase in the Kujala patellofemoral scale of at least 8 units, * frequency counts are complete-cases, ^ point estimates (Relative Risk) are based on multiply imputed data