A loaded self-managed exercise programme for patellofemoral pain:

a mixed methods feasibility study

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Abstract

Patellofemoral pain (PFP) is a common musculoskeletal disorder, with one in five young adults suffering at any one time. The main symptoms include pain behind or around the patella (kneecap) during activities that load the joint, such as climbing stairs and exercise.

Despite the implementation of evidence based physiotherapy, long-term outcomes are poor; 91% of patients still report pain and dysfunction four years post-diagnosis and treatment.

It is not known whether patient outcomes are better with physiotherapy prescribed exercises designed around contemporary pain models (where exercises are designed to load and temporarily aggravate patients' symptoms) and self-management strategies, compared with usual physiotherapy. In relation to terminology, in the context of this thesis, the intervention has been referred to as a loaded self-managed exercise programme. This thesis presents a programme of work with the primary aim to establish the feasibility and acceptability of conducting a definitive randomised controlled trial (RCT) on the new intervention. Secondary aims build towards this, with refinement and development of the intervention, comprising: two systematic reviews; a cross-sectional online questionnaire survey; a qualitative interview study; and a feasibility RCT, with a further embedded qualitative study.

The first systematic review aimed to identify the incidence and prevalence data for this condition, which should inform clinical decision-making and the allocation of healthcare and research funding. The review demonstrated high incidence and prevalence levels for PFP, across adolescent, adult, military and athletic populations.

The second systematic review aimed to establish the effectiveness of loaded painful exercises for musculoskeletal (MSK) pain in general and identify the important components of such an exercise programme. The review concluded that pain during exercise need not be a barrier to successful outcomes and was able to offer some preliminary guidance in relation to the contextual factors of pain and exercise prescription.

A cross-sectional online questionnaire survey was designed to understand the current management strategies undertaken by UK physiotherapists. The survey concluded there was no standardised management approach for PFP in the UK, and there was large variability in response to pain with exercise and physical activity.

Semi-structured qualitative interviews were completed to gain a detailed account of the experience of people living with PFP. A convenience sample of ten participants were recruited. The five major themes that emerged from the data were: (1) impact on self; (2) uncertainty, confusion and sense-

making; (3) exercise and activity beliefs; (4) behavioural coping strategies and (5) expectations of the future. The study suggested that current best-evidence treatments alone may not be adequate to address the fears and beliefs identified.

The findings of this work were used to refine the proposed loaded self-managed exercise programme and inform the design of a feasibility RCT.

Following this, a feasibility RCT was conducted to establish the feasibility and acceptability of conducting a definitive RCT which will evaluate the clinical and cost-effectiveness of the new intervention. Sixty patients with PFP were randomised to receive either a loaded self-managed exercise programme (intervention) (*n*=30) or usual physiotherapy (control) (*n*=30). Baseline assessment included demographic data, average pain within the last week, fear-avoidance behaviours, catastrophising, self-efficacy, sport and leisure activity participation, and general quality of life (Euro-QOL); follow-up was at three and six months and included the global rating of change scale. Feasibility indicators of process, resources, and management were collected. Participants in both groups showed improvements from baseline. The results of the study confirmed that it was feasible and acceptable to deliver a loaded self-managed exercise programme to adults with PFP in an NHS physiotherapy setting. However, there remained uncertainty on some feasibility aspects of study design, with between-group differences in loss to follow-up and poor exercise diary completion.

To explore the possible implementation barriers and facilitators embedded semi-structured qualitative interviews were completed. The intervention was acceptable to patients and physiotherapists; contrary to popular concerns relating to painful exercises, all participants in the intervention group reported positive engagement. Implementation, delivery and evaluation of the intervention in clinical settings may be challenging, but feasible with the appropriate training for physiotherapists.

The principal conclusions from this programme of work were that there is some preliminary evidence that interventions designed to load and temporarily aggravate patients' symptoms, combined with pain education and self-management strategies, may be beneficial to people with PFP. Additionally, that it is feasible and acceptable to deliver a loaded self-managed exercise programme to adults with PFP. However, there remained uncertainty on some feasibility aspects of the trial design.

This research is the first RCT incorporating pain science in treatment strategies for people with PFP in the UK and is, therefore, an important and novel development of the evidence-base.

This PhD has thus offered new insights and expanded the evidence-base into the understanding and management of PFP, and more broadly the public health priorities of all MSK pain and physical activity.

Publications arising from this study

Smith BE, Hendrick P, Bateman M, et al. Musculoskeletal pain and exercise - challenging existing paradigms and introducing new. Br J Sports Med 2018. doi:10.1136/bjsports-2017-098983.

Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis. PLoS One 2018;13(1). doi:10.1371/journal.pone.0190892.

Smith BE, Moffatt F, Hendrick P, et al. The experience of living with patellofemoral pain—loss, confusion and fear-avoidance: a UK qualitative study. BMJ Open 2018;8:e018624. doi:10.1136/bmjopen-2017-018624.

Smith BE, Hendrick P, Smith TO, et al. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. Br J Sports Med 2017;51:1679–87. doi:10.1136/bjsports-2016-097383.

Smith BE, Hendrick P, Bateman M, et al. Current Management Strategies for Patellofemoral Pain: An online survey of 99 practising UK physiotherapists. BMC Musculoskelet Disord 2017;18. doi:10.1186/s12891-017-1539-8.

Smith BE, Hendrick P, Bateman M, et al. Study protocol: a mixed methods feasibility study for a loaded self-managed exercise programme for patellofemoral pain. Pilot Feasibility Stud 2017;4. doi:10.1186/s40814-017-0167-2.

Smith BE, Hendrick P, Logan P. Patellofemoral pain: Challenging current practice - A case report. Man Ther 2016;22:216–9. doi:10.1016/j.math.2015.09.002.

Publications currently under review

Smith BE, Moffatt F, Hendrick P, et al. Barriers and facilitators of loaded self-managed exercises and physical activity in people with patellofemoral pain: understanding the feasibility of delivering a multi-centred randomised controlled trial – A UK qualitative study.

Smith BE, Hendrick P, Bateman M, et al. A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study.

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List of Abbreviations

AMED	The Allied and Complimentary Medicine Database
APA2011	Adolescent Pain in Aalborg
CI	Confidence interval
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
CKRS	Cincinnati Knee Rating System
CONSORT	Consolidate Standard of Reporting Trials
COREQ	COnsolidated criteria for REporting Qualitative research
COS	Core Outcome Sets
CPM	Conditioned pain modulation
CSP	Chartered Society of Physiotherapy, UK
DASH	Disabilities of the Arm Shoulder and Hand score
DNA	Did not attend
DNIC	Diffuse noxious inhibitory control
EIH	Exercise-induced hypoalgesia
EQ-5D-5L	Euro-QOL
ES	Cohen's effect size
FFI	The Foot Function Index
fMRI	Functional Magnetic Resonance Imaging
GP	Primary care / General practitioner
GROC	Global rating of change
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSES	General self-efficacy scale
HEE	Health Education England
IASP	International Association for the Study of Pain
iCSP	Interactive CSP
IPRR	International Patellofemoral Research Retreat
KOOS	Knee Injury and Osteoarthritis Outcome Score
LSM	Loaded self-managed
MCID	Minimal clinically important difference
MOOSE	Meta-analyses in observational studies
mPFC	Medial prefrontal cortex
MRC	Medical Research Council

MRI	Magnetic Resonance Imaging
MSK	Musculoskeletal
NHS	National Health Service
NIHR	National Institute for Health Research
PAG	Periaqueductal gray
PCS	Pain catastrophising scale
PFJ	Patellofemoral joint
PFP	Patellofemoral pain
PPI	Patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRRs	Pattern-recognition receptors
PTSD	Posttraumatic stress disorder
RCT	Randomised controlled trial
RMDQ	Roland-Morris Disability Questionnaire
SD	Standard deviation
SMD	Standardised mean difference
SPADI	The Shoulder Pain & Disability Index
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TiDieR	Template for Intervention Description and Replication guidelines
TLRs	Toll-like receptors
TSK	Tampa Scale for Kinesiophobia
TSP	Temporal summation of pain
UP	Usual physiotherapy
VAS	Visual analogue scale
VL	Vastus lateralis
VM	Vastus medialis
VML	Vastus medialis longus
VMO	Vastus medialis obliquus

Chapter 1 – Introduction

Summary

This chapter provides the theoretical basis to this PhD thesis. It sets the scene, describes the patellofemoral joint, relevant terminology in relation to anatomy, physiotherapy assessment and management, and the burden and aetiology of patellofemoral pain. Justification for further research is explained, before the aims of the PhD are considered.

1.1 Setting the scene

Patellofemoral pain (PFP) is a common musculoskeletal (MSK) disorder and one of the most common reasons why young adults seek medical help [1]. The main symptoms include pain around the kneecap (patella) with activities that load the joint, such as climbing and descending stairs, squatting and sitting with prolonged knee flexion [2].

Despite the implementation of evidence-based treatment, including exercise therapy, the long-term prognosis for PFP is poor, with only one third being pain-free one year after the initial diagnosis [3].

This thesis presents a programme of work with the primary aim to establish the feasibility and acceptability of conducting a definitive randomised controlled trial (RCT) on an intervention based on pain science, self-management strategies and improvements in physical activity levels. The Medical Research Council (MRC) Complex Interventions Framework [4] has been used for the development of this programme of work, which is presented consecutively in this thesis, with each component of work informing the development of the succeeding component.

This introductory chapter describes the patellofemoral joint (PFJ); relevant terminology in relation to anatomy, physiotherapy assessment and management; and the burden and aetiology of PFP. It concludes with justification for further research before the main and secondary aims of the thesis are considered.

1.2 What is the patellofemoral joint?

The patella is the largest sesamoid bone in the body, located on the anterior aspect of the knee (Figure 1) [5]. The PFJ is the compartment of the knee formed between the patella and the femur, with the underlying surface of the patella articulating with a groove (femoral trochlea) at the distal end of the

femur [6,7].

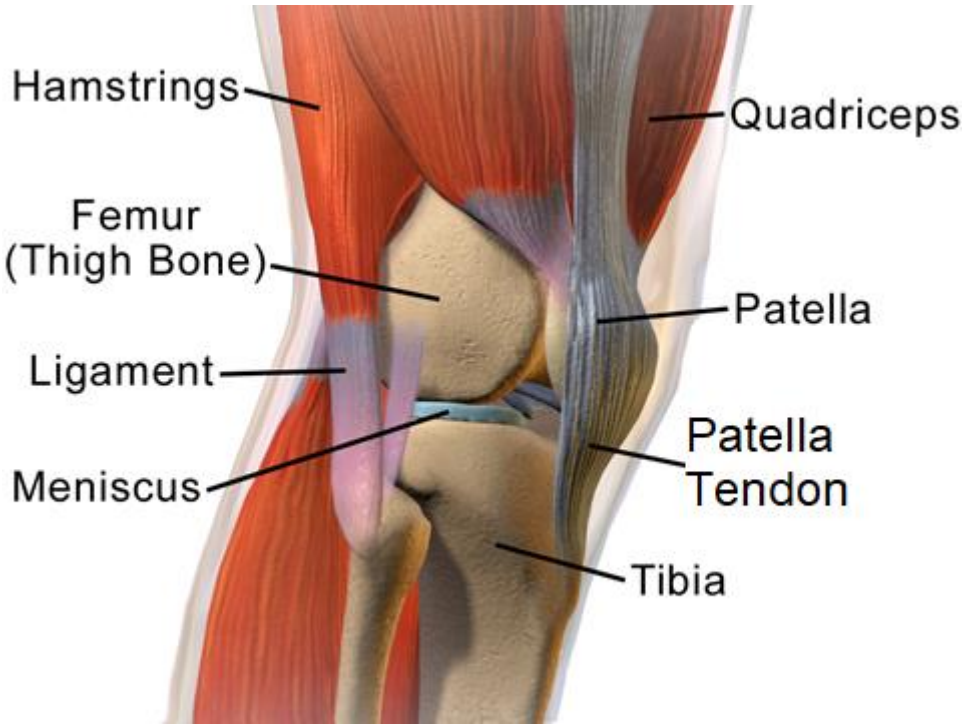

Figure 1 - The knee. Open source Blausen.com Staff. Medical gallery of Blausen Medical 2014. WikiJournal Med 2014;1.

The primary role of the patella is to act as a biomechanical lever arm, to improve the mechanical advantage and the effective extension capacity of the quadriceps muscle [6]. It achieves this by increasing the moment arm of the patellar tendon, centralising the divergent forces of the four quadriceps muscles around the femur onto the patellar tendon [6]. The four muscles which form the quadriceps are rectus femoris, vastus lateralis (VL), vastus intermedius and vastus medialis (VM) [7]. VM is often further subcategorised into two separate portions, the vastus medialis longus (VML) proximally, and the vastus medialis obliquus (VMO) distally [8]; although, a 2009 systematic review, that included 26 papers, with a total of 699 Magnetic Resonance Imaging (MRI) scans and 591 cadaveric specimens suggested there was little evidence to support this belief [8].

Based on a number of cadaveric studies using pressure-sensitive film, it is understood that at full knee extension the contact area between the trochlea and the patella is at a minimum [9,10]. This gradually increases as the patella descends into the trochlea during knee flexion. At 30° the patellofemoral contact area is approximately 2.0cm^2, increasing to a maximum of approximately 6.0cm^2 at 90° of knee flexion, demonstrating improved joint congruity from extension to 90° flexion [9,10]. During the final degrees of knee flexion, the contact area decreases again (Figure 2) [11,12].

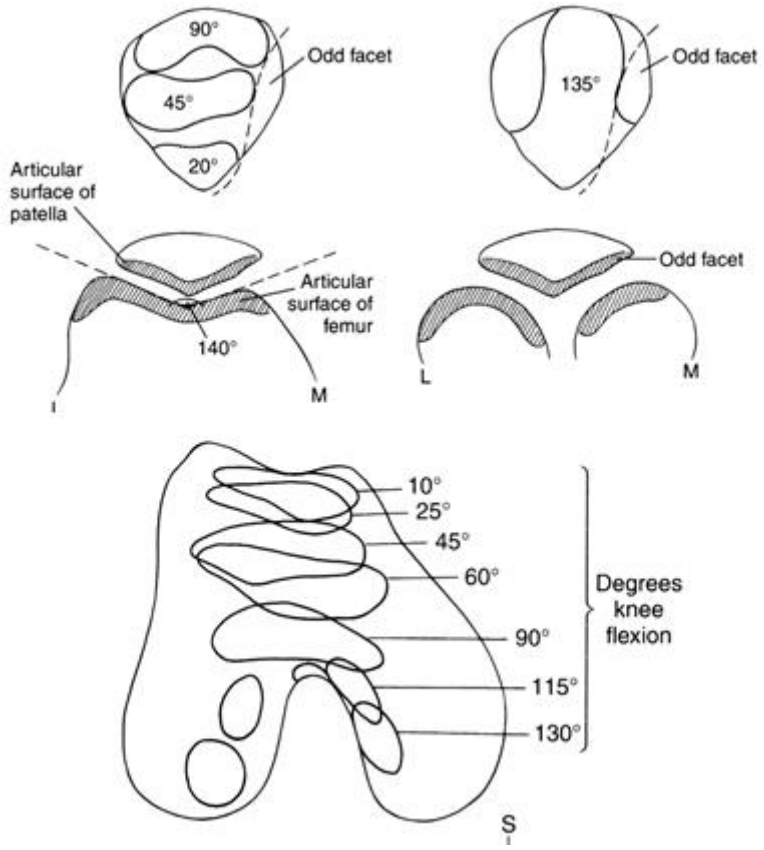

Figure 2 - Contact area between the patella and trochlea. With permission from https://mikereinold.com.

PFJ reaction forces are observed during all movements of the knee and are related to the size of the external moment arm, the contact area between the patella and trochlear groove, and the forces exerted by contraction of the quadriceps muscle [6,10]. For example, based on imaging cohorts in pain free-individuals (*n*=10), during an open-chain exercise (Figure 3) the PFJ reaction force increases as the knee extends from 90° flexion to full extension, and the contact area decreases [13]. During closed-chain exercises (activities such as squatting) the contact forces gradually increase over a concurrently increasing contact area; until the knee flexes past 45° [13], when the contact force increases at a greater rate than the contact area, resulting in a sudden rise in PFJ reaction forces [6,10].

Figure 3 - Open-chain knee exercise. Open source. From BruceBlaus, Wikimedia Commons.

The force produced by the quadriceps muscles is greatest at near terminal knee extension and exerts a considerable compressive force on the patella [10]. Although not based on rigorous and repeated findings from numerous studies, computational modelling on small samples of healthy subjects have been used to estimate PFJ joint reaction forces [14–18]. It was demonstrated how different activities could exert different PFJ joint reaction forces, depending on the type of movement, and compressive force exerted by the quadriceps, and can, in some cases, be substantial (Table 1).

Table 1 – Patellofemoral joint load with activity.

Activity	Patellofemoral Joint Reaction Force
Level walking	1.3 x body weight [14]
Stationary bike	1.3 x body weight [15]
Ascending/descending stairs	1.7 – 2.2 x body weight [16]
Running	4.5 – 7.6 x body weight [17]
Jumping	2.4 – 4.6 x body weight [18]

The term PFP refers to pain attributable to the anterior aspect of the knee, around the patella [2]. Systematic reviews have concluded that no definitive clinical test can diagnose PFP [19]. Expert consensus in diagnosis and terminology, as agreed at the International Patellofemoral Research Retreat (IPRR) in Manchester in 2015, defined symptoms as typically developing insidiously [2]. With retropatellar pain or diffuse peripatellar pain, aggravated by activities that "load the joint", such as climbing and descending stairs, squatting, running or jumping [2]. Additional, but not essential findings, include tenderness on palpation [2]. However, historically, some epidemiological research has diagnosed PFP through a detailed subjective and objective assessment, with the inclusion of objective findings of pain on a number of special tests, such as patellofemoral compression test, palpation of the patella and pain of resisted knee extension [20–23]. This will be discussed further in Chapter 2, part two. There has also been much debate around the most preferred terminology used, with a range of synonymous and overlapping terms proposed: patellofemoral pain syndrome; chondromalacia patella; anterior knee pain and runner's knee [2]. The IPRR 2015 consensus statement stated a preferred term of PFP, and in the context of this thesis, PFP will also be used as the preferred term.

A high-quality population-based cohort study, from the APA2011 (Adolescent Pain in Aalborg) cohort, has demonstrated that PFP is reasonably common in the adolescent population [24]. Symptoms have been shown to start between 11 and 13 years of age [24] and continue through adolescence [25]. However, RCTs have highlighted differences in success rates of exercise interventions between adults [26,27] and adolescents [28] with PFP, despite similar exercise compliance and exercise treatments; suggesting that despite similar presentations, the underlying condition and pain mechanism may be different and different treatments may be required [29]. Within the context of this, and the 2015 IPRR

consensus statement [2,30], that highlighted adolescents and adults as separate research priorities, this programme of work has focused on the adult population.

As will be discussed in the subsequent sections, PFP is a poorly understood and treated condition [31]. The complexity in joint anatomy and biomechanics, as discussed, has led to biomedical models of care dominating research interests [32]. There remains a lack of knowledge around what causes the pain, with limited evidence relating to risk and prognostic factors [33–36], and therefore, the most effective management strategies remain uncertain [31].

1.3 What is the burden of patellofemoral pain?

PFP is one of the most common forms of knee pain in adults under the age of 40 [1,37,38], with a UK based cross-sectional study estimating an annual prevalence of 23% in the general population [1].

From the perspective of the person suffering from PFP, a systematic review demonstrated people with PFP have a significant decrease in quality of life and high levels of pain, with difficulty performing everyday tasks, such as walking or using the stairs, when compared with pain-free individuals [39]. Patient-reported outcomes in pain, disability and function are similar to people on a waiting list for knee replacement surgery [28,40,41]. Seventy-five per cent of patients will typically withdraw from participation in sport and leisure activities [42], with the associated health risks of age-related illnesses, such as heart disease and diabetes [43]. Furthermore, associated psychological distress, such as fear-avoidance behaviours and catastrophising thoughts about knee pain, may be elevated in individuals with PFP, and correlates with pain and reduced physical function, when also compared with pain-free individuals [44]. This thesis explores further the experience of living with PFP qualitatively in Chapter 4.

From an economic perspective, there are over 100,000 primary care (GP) appointments a day in the UK for musculoskeletal (MSK) pain disorders [45], with associated work absenteeism costing the UK economy £7.4 billion annually [46]. Knee pain, as a whole is the second most common condition, with prevalence rates estimated at between 19% and 35% in the general population [1,37,38], with PFP reported as one of the most prevalent forms of knee pain [2]. Worryingly, the overall long-term prognosis for the majority of patients with PFP is poor [5]. Only one-third of patients are pain-free one year after the diagnosis [3], and 91% of patients still report pain and dysfunction four years post-diagnosis [47].

It is such a common, costly and poorly understood condition that the Chartered Society of Physiotherapy, UK (CSP) ranked PFP the 3rd most important topic out of 185 in their Musculoskeletal

Research Priority Project in 2012 [48].

1.4 Aetiology of patellofemoral pain

There remains scientific debate and uncertainty around the underlying aetiology of the condition [49]. It is thought most likely to be multifactorial in its origin [50]. There is currently little high-quality Level 1 evidence on which to base clinical physiotherapy treatments [51], with very low quality of evidence demonstrating that exercise may result in a clinically important reduction in pain and improvements in functional ability compared with no treatment at all [52]. Historically, models of clinical reasoning based on the pathoanatomical basis of tissue pathology and differential diagnosis have labelled one major cause of PFP as patella mal-tracking/mal-alignment [50,53–55], with the supposition that various tissue structures could be contributing, such as: lower limb muscle weakness [56], soft tissue tightness [57], lower limb structural abnormalities [58], movement dysfunction [59], imbalance of muscle activity between VL and VMO [60], or quadriceps mal-timing [61]. It is thought that these deviations from the "normal" affect patellar alignment, kinematics or joint loading, resulting in greater stress between the patella and femur and the development of pain and dysfunction [50,53–55]. Another commonly cited cause for the development of pain is "overuse" [62]; with periods of repeated "trauma" through increased physical activity believed to be a particular risk factor [34]. This biomedical model of pain establishes a direct relationship between tissue structure and pain [63]. Traditionally the focus of physiotherapy treatment has been aimed at reducing pain and improving function by addressing these biomedical tissue structures [53,54]. Treatments including taping, stretches, exercises, electrotherapy, joint mobilisations and foot orthoses have all been suggested [53,54]. However, systematic reviews consistently acknowledge the limitations in study design of included studies when drawing their conclusions on the effectiveness of these interventions [50–52,54,64,65]. Even in relation to exercise therapy, which has systematic review level evidence-base [51], there remains insufficient evidence on which to determine the best form or dose of exercise [52].

The biomedical model of pain with respect to persistent PFP has been recently challenged [63,66,67]. A systematic review including prospective and randomised trials has demonstrated that even with improvements in patients' pain and function, patients' kinematics and "alignment dysfunction" at the knee or patella remains unaffected following exercise therapy [35]. A 2016 cross-sectional, case-control study of 64 patients with PFP and 70 pain-free controls demonstrated that structural abnormalities of the PFJ on MRI were not associated with PFP [68,69]. In another study that included 25 patients with PFP, the authors found no significant correlation between pain and disability (pain was measured on a 0mm – 100mm visual analogue scale (VAS), and disability was measured on the Cincinnati Knee Rating System (CKRS)) [70]. Other studies have also failed to find a significant

correlation between pain and disability [71,72]. It may, therefore, be hypothesised that PFP results in pain and disability, but that these two constructs are independent and poorly correlated [63].

1.5 Rationale for further research

Recent research has acknowledged the importance of the foot, hip and trunk with PFP [73]. This led to sub-grouping, which has been highlighted as a research priority [73], to investigate the effectiveness of targeted treatments based upon a classification system [74]. To date, no large randomised controlled trial has been published on subgroup treatments for PFP, but currently, this approach is being investigated in three potential sub-groups [74]. However, now it appears that research should perhaps broaden the perspective even further and consider contemporary models of pain [75], and this will now be discussed further in the following sections.

Biomedical models of care dominate the literature for this pathology [32]. Best practice guidelines for conservative management published in 2015 included expert opinion (recruited from the 2009 and 2011 IPRR) that supported treatments aimed directly at tissue structures, for example, braces, orthotics, taping, stretching and joint mobilisations [51]. Furthermore, some experts advise patients to reduce or stop physical activity engagement if they experience pain [51], potentially indicating a biomedical bias in clinical reasoning for people with PFP [76–78]. Similarly, recent IPRRs have presented a relatively low proportion of submitted abstracts examining pain science, compared with biomechanical themes (6% (3/50; Manchester, UK, 2015) and 29% (15/52; Gold Coast, Australia, 2017) [2,30,32,79,80]. Indeed, one major publication arising from the 2015 IPRR consensus discussed purely biomechanical features associated with PFP, with an underlying assumption that PFP is primarily associated with abnormal loading of the PFJ [79].

There is a growing body of evidence that healthcare practitioners who diagnose and treat with a greater emphasis on the biomedical model of pain are less likely to follow evidence based guidelines [78], and underuse evidence based exercise interventions [81]. A 2012 mixed methods systematic review investigated the association between health care professional attitudes and beliefs and outcomes of patients with low back pain included 17 studies and measured the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [82]. It concluded that there is moderate evidence that healthcare practitioners with a biomedical orientation or high levels of fear-avoidance beliefs (measured on the Fear-Avoidance Beliefs Questionnaire [83]) are less likely to adhere to treatment guidelines [78]. Similarly, a 2010 systematic review exploring the attitudes, beliefs and behaviours of general practitioners (GP) regarding exercise for chronic knee pain included 20 studies [81]. Quality of included studies was assessed through the

Newcastle Critical Appraisal Worksheet [84], and the Critical Appraisal Skills Programme Qualitative Research Assessment Tool [85]. The review demonstrated limitations of the studies, including poor methodological quality and limited generalisability [81]; however, it concluded that GPs generally underused evidence based exercise, of any type, with up to 29% believing rest was optimal [81].

Attitudes, beliefs and the emotional response are reflected in the National Institute for Health and Care Excellence (NICE) definition of pain as, a complex biopsychosocial issue, associated with expectations, self-efficacy, mood and coping abilities [86]. Indeed, a systematic review of RCTs of self-management interventions for chronic MSK pain that included 16 studies (*n*=4,047), found self-efficacy and depression were the strongest prognostic factors for pain and disability (irrespective of the intervention) [87]. Improvements in pain catastrophising and physical activity were the strongest mediating factors [87]. This review provides a foundation that interventions should be aimed at reducing pain-related fear and increasing appropriate physical activity, and these could be primary targets in rehabilitation programmes and RCTs for persistent MSK pain [87].

This view is supported by findings from studies specifically examining PFP. A recent prospective cohort study recruited 47 patients with chronic PFP [49]. Data collected from this cohort included outcomes on anxiety, depression, pain coping strategies, catastrophising and fear of movement beliefs (kinesiophobia) before and six-months after a usual care intervention [49]. The results indicated that patients who improved on catastrophising, kinesiophobia, anxiety and depression, had the greatest improvements in pain and disability scores ($p < 0.001$) [49]. Similarly, a longitudinal study of 74 patients with PFP demonstrated fear-avoidance beliefs to be the strongest predictor of pain and disability outcomes ($p \leq 0.01$) [67,88]. This was a greater predictor than biomedical factors including muscle strength, length, and lower limb alignment and movement patterns [67,88].

Another complexity to the presentation of PFP is the consideration of the central nervous system. This is discussed further in Chapter 5. It has been suggested that interventions for chronic MSK conditions need to go beyond muscles and joints [89], to instead consider the concept of central pain mechanisms and in particular central sensitisation [90]. Pain does not provide a measure of the state of tissue and is thought to be modulated by many factors [75]. Nociceptive inputs, defined as specialised primary sensory neurons situated in various body tissues, such as skin, muscles and tendons, are involved in the transduction and transmission of information from the periphery to the central nervous system [91,92]. Nociceptors can be modulated centrally, which, in some people, can lead to an enhancement of pain output, resulting in heightened sensitivity to pain and touch [93,94]; revealing an important role in chronic pain states [93].

Catastrophising and kinesiophobia are thought to play an important role in shaping the physiological responses to pain, and therefore the development and maintenance of central sensitisation [95]. Altered central processing of pain may be present in patients presenting with long-standing PFP; for example, individuals with PFP have demonstrated lower pressure pain thresholds at sites around the knee, shin and elbow, suggesting widespread hyperalgesia [96–99], with a spreading of the sensation of pain beyond the patella [100]. For example, a study of 91 patients with unilateral PFP, with 23 pain-free controls, examined quantitative sensory testing, combining tactile and vibration sensation; warmth and cold thresholds [101]. The authors observed that patients with unilateral PFP pain had significantly increased tactile thresholds and altered thermal threshold on bilateral knees compared to pain-free controls; indicating altered central pain processing [102]. These findings are supported by other studies demonstrating thermal alterations in patients with PFP [103,104]. Additionally, a 2018 assessor blinded cross-sectional study, assessing cuff pain thresholds, not only demonstrated altered central processing of pain in people with PFP but also in people reporting symptom resolution (median of two years pain-free), suggesting pain processes may be influenced by "somatosensory pain memories" [105] (as seen with phantom limb pain).

Nijs et al. [90] have suggested that modern pain science indicates that contemporary treatment therapies should be aimed at desensitising strategies, and proposed that exercise prescription has the potential of decreasing the sensitivity of the central nervous system. Such an exercise prescription would involve an individually tailored approach so that exercises should target movements and activities patients find fearful and painful. This exposure, without the perceived danger, is considered key [106,107], when applying what they termed "cognition-targeted exercise therapy" [90].

However, it has been suggested that exercises that patients find painful may lead to an overall increase in central pain processes and result in deteriorating symptoms [108], the opposite of the desired effect. For example, a 2016 cross-sectional study that investigated the immediate pain response during pain inducing exercise in 38 patients with PFP, compared with 33 pain-free controls, demonstrated this phenomenon [109]. The authors measured pressure pain thresholds immediately before and after a "loading programme" designed as 15 repetitions of stair climbing with the addition of 35% body weight in a backpack, intended to aggravate the patients' symptoms. They showed a significant reduction in pressure pain thresholds (0.54kgf (95% CI = 0.33; 0.74; $P < 0.001$) at the quadriceps tendon) and a significant increase in pain VAS (−2.37cm (95% CI = −2.98; −1.76; $P < 0.001$)), indicating an increase in pain sensitivity. However, experimental data from two studies involving pain-free individuals (*n*=86), those with low-back pain (*n*=21), and those with depression (*n*=22) have demonstrated that paradoxically, repeated painful stimulation can decrease (habituation) over time

[110,111]. These studies used daily sessions of suprathreshold heat stimuli over eight days, with participants unaware of the number and strength of stimuli in each session. The authors established that all participants habituated (decreased) between sessions, despite within sessions sensitisation (increase) to pain [110,111].

Exercise therapies designed to load and temporarily aggravate patients' symptoms have demonstrated symptom improvements for patients with a range of MSK disorders including tendon pain [112], shoulder pain [113–115], low back pain [116,117] and plantar heel pain [118]. In agreement with Nijs et al. [90], Littlewood et al. [119] hypothesised that the positive response to the painful loaded exercise programme could be attributed to the therapeutic impact upon the central nervous system. Specifically, the exercise prescribed is aimed at addressing fear avoidance and catastrophising beliefs within a framework of "hurt not equalling harm", with pain rationalised as "de-conditioned" tissue. Thus, in time, reducing the overall sensitivity of the central nervous system, with a modified pain output. This proposed theoretical mechanism is discussed further in Chapter 5, part one.

Dose-response may be an important consideration for exercise prescription with people with PFP. A 2013 study in Norway (*n*=42) looked at a high-dose exercise regime versus a low-dose exercise regime for people with PFP and concluded that there was a significant benefit in the high-dose group over low dose regarding pain and function at 12-weeks [120]. Strikingly, the one-year follow-up showed that the high-dose group had continued to improve regarding pain and function, while the low-dose group had deteriorated, showing clinically important differences between groups across all outcomes measured [120,121]. However, with a lack of blinding and no intention-to-treat analysis, the results should be used with caution [120,121]. This finding is supported by a more recent study investigating supervised exercises and education versus education alone, for people with PFP [28]. In this high quality 2015 RCT, 121 participants were randomised into the two groups, with exercise adherence monitored through attendance and weekly text messages [28]. The authors demonstrated that successful outcome (defined as "completely recovered or strongly improved" on a seven-point Likert scale) was directly correlated to the amount of exercise a patient was prescribed; if patients completed the exercises once or less a week 21% recovered, compared with 55% who completed the exercises three or more times a week. Nonetheless, the optimal dose of exercise for the greatest improvements in PFP is still unknown [52] and warrants further investigation in relation to load, resistance and dosage.

Thus far, this thesis has argued that conventional biomedical models of care dominate PFP literature, and, when viewed in isolation, propose that PFP is peripherally-based nociception, which alone fails to explain the characteristic features associated with PFP (as described above), and has done little to

improve the prognosis of a large proportion of people who develop the condition. There is a growing body of evidence that recognises the uncertainty in the presentation and clinical management of PFP, and within the context of such a burdensome disorder, further research is warranted.

1.6 Aims of the thesis

Based on the uncertainties discussed in the above sections, high-quality research on exercise prescription with respect to pain mechanisms and dose-response (or response to load/resistance) in patients with PFP warrants further investigation. However, to ensure the success of a large multi-centred RCT, several feasibility questions need to be answered.

In relation to terminology, in the context of this thesis, the intervention has been referred to as a loaded self-managed exercise programme. A loaded self-managed exercise programme is considered a complex intervention because it is a combination of several components tailored to the individual patient, delivered by different therapists, and targeted at a diverse patient population. The Medical Research Council (MRC) Complex Interventions Framework [4] has been used for the development of this programme of work so that it could be reasonably expected to have an effect, be testable in a formal evaluation, and be suitable for subsequent implementation if found to be effective. The stages required to develop a complex intervention are:

- A background with theoretical underpinning to support the mechanisms through which it is intended that the intervention will produce the desired outcome. If there is no rational basis for applying the intervention, then the trial is not considered justifiable.

- The intervention should be defined sufficiently so that it is possible to demonstrate that it is deliverable in a trial or subsequent implementation (to enable assessments). It is important to know all the components of the intervention so that it can be replicated. It should be clear how the intervention differs from the usual practice and the control conditions used in a trial.

- The intervention should be acceptable to patients, clinicians and other stakeholders.

- The intervention should be demonstrated in the setting in which it is to be tested or implemented, with consequences that are compatible with the intended outcome and purpose.

The guidelines also recognised the importance of process evaluation in trials [4], with implementation into real-world environments thought an essential part of process evaluation [122]. For example,

despite a theoretical rationale supporting efficacy, combined with suitable preliminary research, if an intervention is not delivered as intended, or completed as intended in the real world and across different settings, treatment outcomes may be compromised. The guidelines further highlighted that the implementation of a complex intervention is likely to be more successful if stakeholders are involved in the stages of development [4]. Indeed, there is a need to fully understand fidelity, causal mechanisms, and any contextual factors associated with the intervention and trial design [4]. Therefore, whilst quantitative methods of research are currently accepted as the gold standard in the evaluation of medical interventions [123], a mixed-methods approach is appropriate to gain the perspectives of all stakeholders involved in the research.

The primary aim of this programme of work was to establish the feasibility and acceptability of conducting a definitive RCT. The definitive RCT will evaluate the clinical and cost-effectiveness of an intervention based on pain science (where exercises are designed to load and temporarily aggravate patients' symptoms), self-management strategies and improvements in physical activity levels for people with PFP compared with usual physiotherapy.

Secondary aims, with respect to the MRC Complex Interventions Framework [4], included establishing:

1. the scale of the problem of PFP in the UK, and the evidence-base of loaded painful exercise programmes, and identify key components of the programmes in order to refine and develop the intervention;
2. what "usual treatment" is before being able to design the feasibility RCT;
3. if the devised loaded self-managed exercise programme could be delivered in a UK National Health Service (NHS) physiotherapy outpatient clinic
4. if the outcome measures are feasible to use within an NHS setting
5. if reliable data can be collected
6. a sample size calculation for an RCT
7. if the intervention is acceptable and tolerable to participants and physiotherapists
8. if it is feasible to recruit and randomise participants

9. the potential barriers to recruitment and the training package delivered to physiotherapists.

There were three main components to this programme of research, which were based on the recommendations of the MRC Complex Interventions Framework [4], and were designed to meet the aims described above. These were:

1. Systematic reviews that explored the epidemiology of PFP in the UK; the evidence-base of loaded/painful exercises on all MSK disorders; and a survey of current physiotherapy practice.

2. A qualitative investigation that explored the lived experience of people suffering from PFP.

The first two components of this programme were used to inform the development of the intervention and protocol for the final component of this programme. This included a review on the understanding of the mechanisms behind therapeutic exercise, and to build on this into discussing the additional theoretical mechanisms of painful exercises (Chapter 5, part one).

3. A feasibility study with a controlled trial component was undertaken to examine the acceptability, feasibility and tolerability of the intervention within an NHS outpatient setting. This contained another qualitative component, embedded within it.

Each of these components will be presented consecutively in this thesis, with each one informing the development of the succeeding component (Figure 4). With this in mind and the overall strategy for this body of research as outlined above, the next chapter presents two systematic reviews. The first is to identify the incidence and prevalence data for this condition, which should inform clinical decision-making and the allocation of healthcare and research funding. The second is to establish the effectiveness of loaded exercises for MSK pain in general and identify the important components of such an exercise programme.

MRC Framework	Development phase					Feasibility / Piloting			
	Identify theory	Identify the evidence-base	Modelling process and outcomes			Testing research procedure	Recruitment and adherence	Testing intervention procedure and acceptability	
Thesis Chapters	Chapter 1	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6		Chapter 7	Chapter 8
	Introduction	Systematic reviews	Survey of current practice	Qualitative interviews	Development of the intervention	Feasibility RCT		Interviews	Discussion
Protocol's Mixed Methods Phases (Appendix C)				**Phase One Qualitative Interviews**		**Phase Two Feasibility RCT**		**Phase Three Qualitative interviews**	

Figure 4 - MRC Framework, the thesis and the protocol mixed methods phases.

Chapter 2 - Literature Review
Part one: incidence and prevalence of patellofemoral pain: a systematic review and meta-analysis

Summary

This chapter section presents a systematic review investigating the epidemiological data of PFP. Inconsistencies in reported incidence and prevalence exist and in relation to the allocation of healthcare and research funding, there is a clear need to accurately understand the epidemiology of patellofemoral pain.

2.1 Introduction

PFP prevalence has been cited as between 15% to 45% [124], and incidence between 9.7 and 1080.5 cases per 1,000 person-years [125,126]. Variations in reported incidence and prevalence may be due to differing populations assessed, inconsistencies in the diagnosis and lack of high-quality evidence on which to base assessment [127,128]. PFP is thought to affect the general population [129], and more specifically adolescents [130], active young adults [131], elite athletes [132], and military recruits [21]; with higher incidence and prevalence rates often cited among females [21,29]. Diagnosis has historically been based on detailed subjective and objective assessments, with pain on a number of special tests, as mentioned in Chapter 1 [20–23]. It is possible that this method of diagnosis could under-estimate the true incidence or prevalence rates, since many people with PFP reduce or withdraw from their aggravating activity [42], and consequently pain on palpation may only identify those with higher levels of pain, or still participating in activities. In contrast, due to the high sensitivity of historical tests, it may be that this approach results in an over-estimation of incidence or prevalence rates [133].

To date, no systematic reviews have been published on the incidence and prevalence of PFP; with publications often employing an indirect course of secondary and even tertiary referencing when citing incidence or prevalence data for PFP [128]. In relation to clinical decision-making and the allocation of healthcare and research funding, there is a clear need to understand the epidemiology of this problem accurately. Therefore, in the context of the current uncertainty regarding PFP, this

systematic review synthesises epidemiological data using a contemporary case definition and clear population classifications [2], to gain an understanding of incidence and prevalence data for this condition.

2.2 Method

This systematic review followed the recommendations of the meta-analyses in observational studies (MOOSE) guidance statement [134], the recommendations of the PRISMA statement where relevant [135], and was registered with the International Prospective Register of Systematic Reviews (PROSPERO reference CRD42016038870).

2.2.1 Data sources and search strategy

An electronic database search was conducted on titles and abstracts from inception to June 2017 using the following databases: Medline via PubMed, EMBASE, CINAHL), and Web of Science. For the keywords search strategy used see Table 2. The database searches were accompanied by hand searches of the reference list of included articles, as well as contacting authors for all included and potentially included studies. The grey literature and ongoing studies were searched using the following databases: OpenGrey, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov and the NIHR portfolio.

Table 2 - Search strategy (systematic review 1).

	Search Term
1	”anterior knee pain” or “AKP” or “patellofemoral pain syndrome” or “PFPS” or “ patellofemoral pain” or “PFP”
2	Inciden$ or prevalen$ or cohort$ or prospective or epidemiolog$ or trial
3	1 and 2 limited to English language

Inclusion criteria was study population of any age and any setting with signs and symptoms of PFP, defined as; anterior or retropatella pain reported on at least two of the following activities; prolonged sitting, ascending or descending stairs, squatting, jumping and running [2]. There was no restriction on the study setting for potentially included papers.

Exclusion criteria included: if the study population was selected from a specific disease area (e.g. diabetes, rheumatoid arthritis, osteoarthritis); if the study population comprised of participants with other knee pathology (e.g. knee ligamentous instability, history of patella dislocations, true knee

locking or giving way, patella or iliotibial tract tendinopathy, osteoarthritis).

Included studies were required to report incidence or prevalence data and had to be published in English or where an English translation was available.

2.2.2 Study selection

One reviewer (BES) undertook the searches. Titles and abstracts were screened by one reviewer (BES), with potential eligible papers retrieved and independently screened by two reviewers (BES & JS). Initial inclusion agreement was 83%. Five disagreements were due to case definition [130,132,136–138] and were discussed and resolved through consensus. Seven further case definition disagreements not resolved through consensus were resolved through a third reviewer (PH) [125,139–144].

2.2.3 Data extraction

One reviewer (BES) extracted data relating to study design, population and setting, case definition, incidence and prevalence data, which was independently verified by a second reviewer (DT).

2.7.4 Quality appraisal

In the absence of any validated quality assessment tools [145], two reviewers (BES & JS) independently appraised methodological quality using a tool developed by Hayden et al. [146] for the evaluation of the quality of prognostic studies in systematic reviews, and adapted by Luime et al. [147] for evaluation of the quality of epidemiological studies in systematic reviews. This assessed appropriateness and reporting of the study population, case definition, and the response rate and follow-up of the cohort. To be judged as “high quality”, all three criteria had to be met; with male and females represented, a clear, reproducible case definition relevant to the inclusion criteria and a response rate above 75%. Percentage agreement between the two reviewers was 94%, all disagreements were discussed and resolved through consensus.

2.2.5 Data synthesis

Study heterogeneity was assessed through visual examination of the data extraction table on details related to participant characteristics, case definition, study design and the process of the included studies. If heterogeneous, data were analysed narratively to assess trends in prevalence and incidence across the studies. When data allowed, incidence rates were converted to cases per 1,000 person-years, with associated 95% confidence intervals (CI) [148]. Where studies were homogeneous, data were pooled through a meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic where 0% to 25% was low, 26% to 74% moderate and 75% and over high statistical heterogeneity

[149]. When outcomes presented with low statistical heterogeneity, data were pooled using a fixed-effects model, and with moderate or high statistical heterogeneity a random-effects model was adopted. All data analyses were performed using Stata version 14.0 (College Station, TX, USA) [150].

2.3 Results

2.3.1 Study selection

The search results are presented in Figure 5. From a total of 7,746 titles, 66 papers were potentially eligible. One unpublished trial was identified. However the author declined to share the details. 43 full-text articles were excluded; 37 due to case definition not meeting criteria [131,138,151–185], three due to no prevalence or incidence data being recorded [24,136,186], and two because they were a replication of another included study [187,188]. In one study participants were tested longitudinally over multiple years, with participants being eligible to enrol multiple times, and therefore was excluded [189]. 23 studies met the eligibility criteria and were included in the final review, 12 reporting incidence data [20–23,125,126,139,141,143,190–192], and 13 reporting prevalence data [1,20,21,28,124,130,132,137,140,142,144,193,194]. Of the included 23 papers, 12 authors were contacted for clarification on: raw data extraction [28,139,141,142,190,192,193], and participant information [21,23,124,132,144]. Eight responded and gave further details where available [21,28,124,132,141,142,144,190]**.** The authors that were uncontactable or did not have available information account for the "unknown" items in the characteristics tables (Table 3 and Table 4).

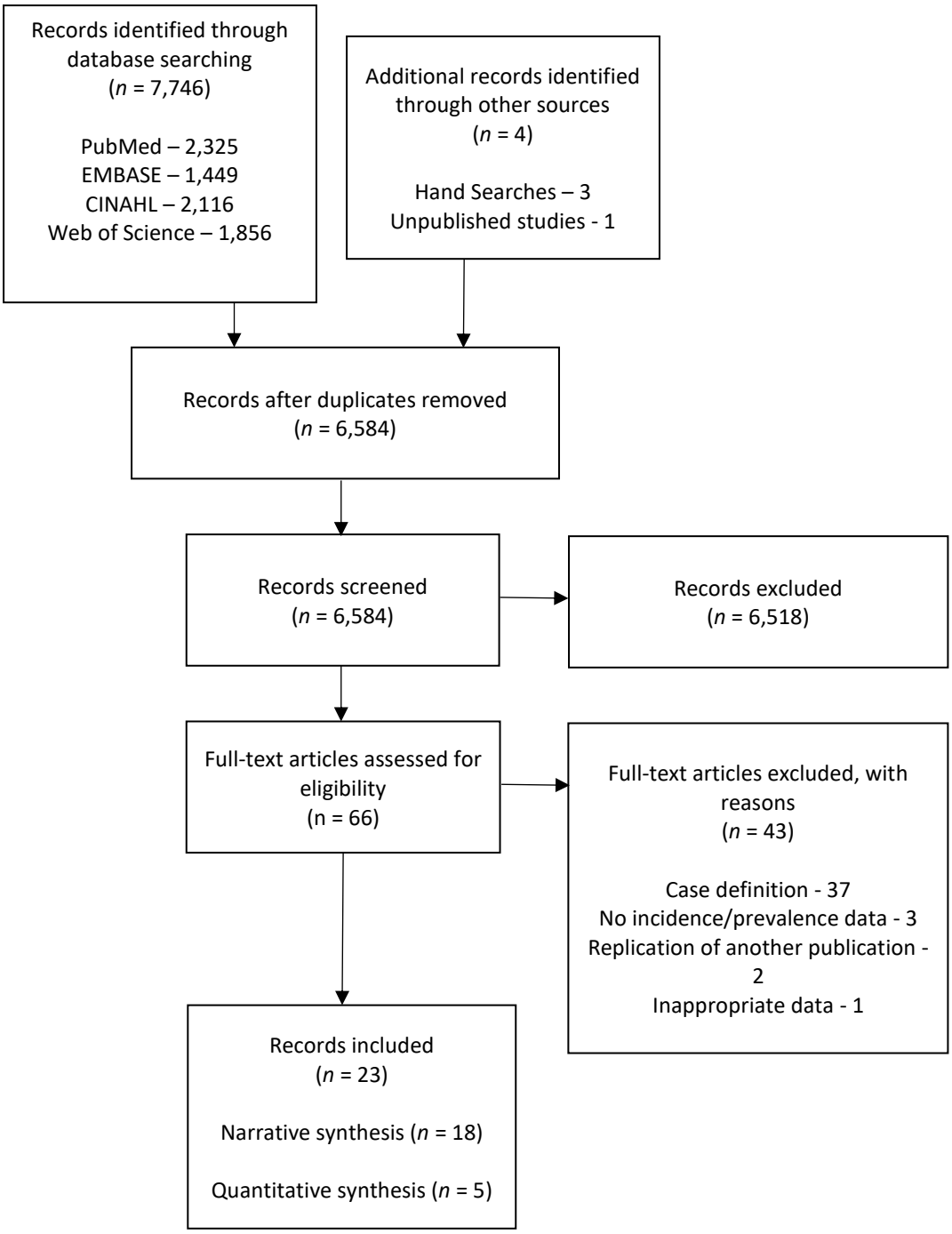

Figure 5 – PRISMA 2009 flow diagram (systematic review 1).

2.3.2 Study characteristics

A summary of the main characteristics of the included studies, with the main results can be found in Table 3 for incidence and Table 4 for prevalence. Six papers within the military setting (*n* = 4,199) reported incidence data [21,22,125,190–192], two papers reported incidence data within the general adult population setting (*n* = 140) [126,139], and four papers reported incidence data within the general adolescent population (*n* = 985) [20,23,141,143]. One paper within the military setting (*n* = 1,525) reported prevalence data [21], three papers reported prevalence data within the general adult population setting (*n* = 1,1011) [1,124,137], six papers reported prevalence data within the general adolescent population setting (*n* = 5,090) [20,28,130,140,142,144], and three papers reported prevalence data within the elite athlete setting (*n* = 568) [132,193,194].

As a result of study heterogeneity, with the exception of five studies that reported prevalence data in the adolescent population, a narrative synthesis was conducted.

Table 3 – Incidence (systematic review 1).

Study	Quality score	Study population	Sample Size	Case definition	Response rate	Results
Military						
Boling (2010) [21]	3/3	United States Naval Academy (USNA) (39.8% female; mean age unknown, range 18 - 25*).	1,525	Retropatella pain of any duration with two of the following activities: ascending/descending stairs, hopping/jogging, prolonged sitting with flexed knees, kneeling, and squatting. Plus, one of the following: pain on palpation of medial or lateral patellar facets, or pain on palpation of the anterior portion of the medial or lateral femoral condyles.	1,319/1,525 (86.5%)	22/1,000 person-years (95% CI: 15/1,000, 29/1,000 person-years). Female incidence was 33/1,000 person-years (95% CI: 20/1,000, 45/1,000 person-years) and in males was 15/1,000 person-years (95% CI: 7/1,000, 22/1,000 person-years).
Coppack (2011) [192]	2/3	British Army recruits, United Kingdom (27.9% female, mean age 19.6).	743	Pain from at least 2 of the following: prolonged sitting, stair climbing, squatting, running, kneeling, and hopping/jumping; insidious onset of symptoms unrelated to a traumatic incident; and presence of pain on palpation of the patellar facets, on step down from a 25-cm step, or during a double-legged squat.	743/743 (100%)	14-week incidence 36 / 743 (4.8%; 95% CI, 3.5-6.7). 180/1,000 person-years (95% CI: 127.9/1,000, 246.5/1,000 person-years).
Kaufman (1999) [190]	2/3	United States Navy Recruits. (100% male; mean age 22.5 years)	449	Ill-defined ache of insidious onset localised to the peripatellar area, plus pain on palpation of the patella and peripatellar soft tissues.	449/449* (100%)	25-week incidence 35/449 (7.8%). 162.1/1,000 person-years (95% CI: 114.7/1,000, 223.0/1,000 person-years).
Milgrom (1991) [22]	1/3	Infantry recruits, Israel (100% male; age unknown).	390	Subjective complaint of anterior knee pain, non-traumatic, with objective finding of pain on patellofemoral compression test and palpation of patella borders.	390/390 (100%)	14-week incidence 60/390 (15.4%). 571.4/1,000 person-years (95% CI: 439.9/1,000, 730.5/1,000 person-years).
Thijs (2007) [125]	3/3	Belgian Royal Military Academy recruits (22.6% female; mean age 19).	84	Two of the following: pain on direct compression of the patella with the knee in full extension, tenderness of the posterior surface of the patella on palpation, pain on resisted knee extension, or pain with isometric quadriceps muscle contraction.	84/105 (80%)	6-week incidence 36/84 (42.9%). 9.7/1,000 person-years (95% CI: 6.9/1,000, 13.3/1000 person-years).
Wills (2004) [191]	3/3	British Army Recruits (95.2% male; median age 19.4)	1,008	Pain around the anterior aspect of the knee, insidious onset and no evidence of trauma	926/1,008 (91.9%)	12-week incidence 81/926 (8.7%). 379.1/1,000 person-years (95% CI: 303.0/1,000, 468.7/1,000 person-years).

General Adult Population						
Devan (2004) [139]	2/3	Female amateur collegiate hockey, basketball and athletic athletes, USA (mean age 19.4).	63	Pain in or under patella while running, going up or down stairs; with diffuse pain on palpation.	53/63 (84.1%)	1 athletic season incidence 1/53 (1.9%).
Thijs (2011) [126]	2/3	Female novice recreational runners on a 10 week start to run programme, Belgium (mean age 38.4)	77	Retropatella pain during and/or after activities such as running, squatting, kneeling, going up and down stairs, cycling, prolonged sitting with the knee in flexion, or rising from a seated position. And 2 of the following: pain while compressing the patella, tenderness of patella on palpation, painful resisted knee extension and pain when isometrically contracting the quadriceps 15^{o} flexion.	77/77 (100%)	10-week incidence 16/77 (20.8%). 1080.5/1,000 person-years (95% CI: 639.6/1,000, 1717.0/1,000 person-years).
General Adolescents Population						
Finnoff (2011) [141]	2/3	High School runners aged 14 – 18, USA (45.9% female; mean age 16)	98	Anterior knee pain that was exacerbated by deep knee bending and/or climbing stairs plus pain on one of the following: (1) pressure over the subject's distal quadriceps tendon combined with active contraction of his or her quadriceps muscle (patellar grind test) or (2) direct palpation of the medial or lateral patellar facets.	98/1500 (6.5%)	1 running season incidence 5/98 (5.1%).
Herbst (2015) [143]	1/3	Female adolescent basketball players in middle and high school, USA (mean age 12.7 years).	255	Anterior Knee Pain Scale score < 100; International Knee Documentation Committee (IKDC) form, standardised history and physician-administered physical examination.	255/329 (77.5%)	1 season incidence 38/255 (14.9%). 0.97 per 1,000 athletic exposures (1 game or training session).
Myer (2010) [20]	2/3	Female adolescent athletes in middle and high school, USA (mean age 13.4 years)	152	Anterior Knee Pain Scale score < 100; knee pain with or shortly following activity and also if anterior knee tenderness was recent.	145/152 (95.4%)	1 season incidence 14/145 (9.7%). 1.09 per 1,000 athletic exposures (1 game or training session).
Witvrouw (2000) [23]	1/3	Students taking physical education, aged 17 – 21 in Belgium (gender unknown; mean age 18.6)	480	Retropatella pain > 6 weeks during physical activities such as jumping, running, squatting, and going up or downstairs. Plus, two of the following; pain on direct compression of the patella, tenderness of the posterior surface of the patella, pain on resisted knee extension, and pain with isometric quadriceps contraction.	282/480 (58.8%)	2-year incidence 24/282 (8.5%). 42.6/1,000 person-years (95% CI: 27.9/1,000, 62.4/1,000 person-years). Female incidence was 13/131 (9.9%), 49.6/1,000 person-years (95% CI: 27.6/1,000, 82.7/1,000 person-years); male was 11/151 (7.3%), 36.4/1,000 person-years (96% CI: 19.2/1,000, 63.3/1,000 person-years).

*Information not within publication, authors contacted for clarification.

Table 4 – Prevalence (systematic review 1).

Study	Quality score	Study population	Sample Size	Case definition	Response rate	Results
Military						
Boling (2010) [21]	3/3	United States Naval Academy (USNA) (39.8% female; mean age unknown, range 18 - 25*).	1,525	Retropatella pain of any duration with two of the following activities: ascending/descending stairs, hopping/jogging, prolonged sitting with flexed knees, kneeling, and squatting. Plus one of the following: pain on palpation of medial or lateral patellar facets, or pain on palpation of the anterior portion of the medial or lateral femoral condyles.	1,525/1,525 (100%)	Point prevalence of PFPS was 13.5% (95% confidence interval (CI): 11.7%, 15.3%]. For females and males, it was 15.3% (95% CI: 13.7%, 16.9%) and 12.3% (95% CI: 11.1%, 13.4%), respectively.
General Adult Population						
Dey (2016) [1]	3/3	Community within the UK. Convenience sample of attendance at a University science fair (53% female; mean age 30).	111	Anterior knee or retropatella pain, often bilateral, of insidious onset present for at least a month and associated with pain or difficulty with prolonged sitting or activities which load the patellofemoral joint, e.g., ascending or descending stairs, running and squatting. Positive diagnosis identified through a self-report questionnaire (SNAPPS- Survey instrument for Natural history, Aetiology and Prevalence of Patellofemoral pain Studies)	110/111 (99%)	Annual prevalence 25/110 (22.7%). Females 67%; males 33%.
Roush (2012) [124]	3/3	18-35 year old females, general population*, USA (mean age 24.7)	769	Anterior Knee Pain Scale score < 83	724/769 (94.1%)	Point prevalence was 12-13%*.
Weiss (1985) [137]	3/3	Amateur multi-day cyclist in USA (69% male; mean age 41.4).	132	Self-reported complaint of patella pain during a cycling event. Tenderness of posterior aspect of the patella during flexion and extension.	113/132 (86%)	Point prevalence was 35%.

General Adolescents Population						
Fairbank (1984) [140]	1/3	13 – 17-year-old students, randomly selected from a comprehensive school in the United Kingdom (49% female, mean age 14.7)	446	11-point questionnaire, including: Do you like playing sport? Have you had painful knees in the last year? Do your knees hurt climbing stairs? Do your knees hurt coming downstairs? Where do you feel the pain in your knees? Does your knee hurt after sitting for a long time? Does your knee hurt only after a lot of exercise?	446/1850 (24.1%)	Annual prevalence 129/446 (28.9%).
Hall (2015) [142]	2/3	Female adolescent athletes in middle and high school, USA (mean age 14.0).	546*	Assessment included the Anterior Knee Pain Scale (AKPS), International Knee Documentation Committee (IKDC) form, standardised history and physician-administered physical examination.	546/546*	Point prevalence 151/546* (28%).
Molgaard (2011) [130]	3/3	16 – 18-year-old students at one local high school in Denmark (mixed gender; mean age 16.9)	299	Anterior knee pain during physical activity for at least 1 month and pain in at least two of the following four tests: isometric contraction of quads, concentric extension against resistance, palpation of joint line, and compression of the patella	227/299 (76%)	Point prevalence 13/227 (5.7%). Females 69%; males 31%.
Myer (2010) [20]	2/3	Female adolescent athletes in middle and high school, USA (mean age 13.4 years).	240	Anterior Knee Pain Scale score < 100; knee pain with or shortly following activity and also if anterior knee tenderness was recent.	240/240 (100%)	Point prevalence was 39/240 (16.3%).
Rathleff (2014) [28]	3/3	Population-based cohort of students from secondary schools, Denmark, aged 15-19 years (64.9% female; mean age 17.2).	2,200	Insidious onset of anterior knee or retropatella pain for at least the past 6 weeks; pain provoked by at least 2 of the following activities: prolonged sitting or kneeling, squatting, running, hopping, or stair walking and tenderness on palpation of the patella.	2,220/2846* (77.3%)	Point prevalence 153/2,062 (7.4%)*.
Steinberg (2012) [144]	1/3	Non-professional female dancers, aged 8–20, Israel (mean age 13.7 years*).	1,359	Pain reproduced during clinical examination; knee swelling was evident, or a positive grinding sign and/or a positive Patella Inhibition Test (PIT) was obtained when the knee and especially the patella were palpated, contracted and stretched.	1,359/1,359 (100%)	Point prevalence 321/1,359 (23.6%).

Elite Athletes						
Clarsen (2010) [132]	2/3	Professional cycling; 7 training camps (100% male*; mean age 26)	109	Cyclist reported complaint of anterior knee pain in the last 12 months, of any duration. Cyclist reported complaint of anterior knee pain in the last 12 months, >30 days	109/109 (100%)	Annual prevalence 39/109 (35.8%). Annual prevalence 7/109 (6.4%).
Nejati (2010) [193]	1/3	Female athletes participating in 3rd Iranian Sports Olympiad (mean age 21.6, range 15 – 35).	418	Non-traumatic anterior knee pain of at least 3 months duration that was felt retropatella or peripatellar and was aggravated by descending or ascending stairs, squatting or prolonged sitting.	418/unknown	Point prevalence was 70/418 (16.7%).
Winslow (1995) [194]	1/3	University female ballet dancers, USA (mean age unknown)	41	Pain in front of or under the patella with 3 out of 5: associated with kneeling; squatting; during stair climbing; sensations of cracking/grinding or with incidents of joint locking or "catching."	41/unknown	Point prevalence was 12/41 (29.3%).

*Information not within publication, authors contacted for clarification.

2.3.3 Quality appraisal

The results of the methodological quality appraisal can be found in Table 5. 43.5% (10/23) of the included studies were high quality (quality score = 3/3), according to the definition agreed *a priori*. 26.1% (6/23) recorded a quality score of 2/3, and seven studies (30.4%) recorded a score of 1/3. The main risk of bias and low methodological quality was due to ten studies having populations comprising only male or female participants, and one study not describing the participant's gender [20,22,23,126,139,142–144,190,193,194]. Three studies had a response rate of below 75% [23,140,141], two had an unknown response rate [193,194], and four studies had imprecise case definitions [22,140,143,144]; all were scored low accordingly.

Table 5 - Quality appraisal (systematic review 1).

	The study sample represents the population of interest on key characteristics	Was there an adequate response rate?	Was the case definition specified and is it reproducible?
Boling (2010) [21]	✓	✓	✓
Clarsen (2010) [132]	✓	✓	✓
Coppack (2011) [192]	✓	✓	✓
Devan (2004) [139]	X	✓	✓
Dey (2016) [1]	✓	✓	✓
Fairbank (1984) [140]	✓	X	X
Finnoff (2011) [141]	✓	X	✓
Hall (2015) [142]	X	✓	✓
Herbst (2015) [143]	X	✓	X
Kaufman (1999) [190]	X	✓	✓
Milgrom (1991) [22]	X	✓	X
Molgaard (2011) [130]	✓	✓	✓
Myer (2010) [20]	X	✓	✓
Nejati (2010) [193]	X	Unknown	✓
Rathleff (2014) [28]	✓	✓	✓
Roush (2012) [124]	✓	✓	✓
Steinberg (2012) [144]	X	✓	X
Thijs (2011) [126]	X	✓	✓
Thijs (2007) [125]	✓	✓	✓
Weiss (1985) [137]	✓	✓	✓
Wills (2004) [191]	✓	✓	✓
Winslow (1995) [194]	X	Unknown	✓
Witvrouw (2000) [23]	Unknown	X	✓

✓, yes; X, no

2.3.4 Military

2.3.4.1 Incidence

Five studies reported incidence rates for military recruits, with a predominantly male population, that ranged from 9.7 – 571.4 cases per 1,000 person-years [22,125,190–192]. One study, with a mixed female and male military population, reported an incidence rate of 22 cases per 1,000 person-years, with female recruits being reported as 33 and males as 15, cases per 1,000 person-years [21].

2.3.4.2 Prevalence

One study with a mixed female and male military recruit population reported a point prevalence of 13.5%, females 15.3% and males 12.3% [21].

2.3.5 General Adult Population

2.3.5.1 Incidence

One study with novice recreational female runners recorded a 10-week incidence rate of 1080.5 cases per 1,000 person-years [126]. One study with female amateur collegiate athletes (mean age 19.4) reported an athletic season incidence rate of 1.9%.

2.3.5.2 Prevalence

Annual prevalence in the general population was reported as 22.7%, with the annual prevalence in females 29.2% and males 15.5% [1]. Point prevalence in females was reported as 12% to 13% [124]. Point prevalence during a multi-day amateur cycling event for mixed male and female was reported as 35% [137].

2.3.6 General Adolescents Population

2.3.6.1 Incidence

Two studies recorded the incidence rate over one season for female adolescent athletes as 9.7% - 14.9%, or 0.97 - 1.09 per 1,000 athletic exposures [20,143], and one study recorded the incidence rate over two seasons with adolescents participating in physical education (gender unknown) as 42.6 cases per 1,000 person-years [23]. One mixed gender study of high school runners reported the incidence rate over one running season as 5.1% [141].

2.3.6.2 Prevalence

Two studies reporting point prevalence (Molgaard [130] and Rathleff [28]) on mixed male and female adolescents were deemed suitably homogenous and accordingly were pooled in a meta-analysis. Statistical heterogeneity was negligible (I^2=5.4%), and the pooled estimate of point prevalence using a fixed effects model was 7.2% (95% CI 6.2% - 8.3%). Point prevalence in female-only adolescents was reported as 16.3% [20].

Three studies reporting point prevalence (Hall [142], Myer [20], and Steinberg [144]) on female only adolescent athletes were deemed suitably homogenous and accordingly were also pooled in a meta-analysis. Statistical heterogeneity was high (I^2=85.7%), and the pooled estimate of point prevalence using a random effects model was 22.7% (95% CI 17.4% - 28.0%).

One study of mixed gender adolescents reported an annual prevalence of 28.9% [140].

2.3.7 Elite Athletes

2.3.7.1 Prevalence

One study with professional male cyclists reported an annual prevalence of 35.8% with symptoms of any duration, and 6.4% with symptoms lasting greater than 30 days [132]. One study of female athletes (mean age 21.6) at the 3rd Iranian Sports Olympiad reported point prevalence of symptoms greater than three-months of 16.7% [193], and another with female university ballet dancers reported point prevalence (of unknown duration) as 29.3% [194].

2.4 Discussion

2.4.1 Summary of main findings

The results of this systematic review confirm that PFP is a relatively common pathology among adolescents, the general population, and those with high levels of activity, such as elite athletes and military populations. Point prevalence within military populations is reported as 13.5% [21]; female general populations 12% to 13% [124]; multi-day amateur cyclists 35% [137]; and female elite sports 16.7% to 29.3% [193,194]. It was calculated through meta-analysis to be 7.2% in mixed gender adolescents, and 22.7% in female amateur athletes. Annual prevalence in the general population is reported as 22.7% [1]; in professional cyclists, it is reported as 35.8% [132]; and in general adolescent population, it is reported as 28.9% [140]. No studies that were included within the review reported lifetime prevalence.

This research is the first review to systematically evaluate and synthesise incidence and prevalence data for PFP. Comparison between studies was fulfilled in relation to age, gender, and activity levels (general population, military and elite athletes).

2.4.2 Clinical implications

PFP is often cited as an overuse injury [62], with short periods of overuse or an increase in physical activity thought be a particular risk factor [34]. Within the military population, there was low agreement on incidence rate, with predominantly male recruits reported in five studies at 9.7 – 571.4 cases per 1,000 person-years [22,125,190–192]. Of note is the study with the highest reported incidence (571.4/1,000 person-years) originated from a country with military conscription [22], and may have a population comprising of participants not accustomed to intense periods of physical activity. Studies with lower reported incidences (9.7 – 349.1/1,000 person-years) were from countries without conscription, where high levels of physical fitness are a requirement of recruitment [21,125,190–192], and so may contain participants more accustomed to intense periods of physical activity. Within the general population, the 10-week incidence for novice runners was comparable to the incidence in conscripted military recruits, at 1080.5 cases per 1,000 person-years [126]. These data seem to agree with the model that attributes short periods of unaccustomed high levels of physical activity as a risk factor for the development of PFP. Contemporary thinking about training loads and injury risk challenges the idea that PFP could be an overuse injury, with evidence suggesting that under-training may be a risk factor for an increase in injury risk in athletes [195]. Exposure to appropriate training loads and periodisation, without "spikes" in training, is thought to be one method of risk management [195].

There was some consistency in the data relating to ratios of females to males, seemingly confirming the commonly cited claim that females are twice as likely to develop PFP than males [29]. One study demonstrated that females were approximately twice as likely to develop PFP as males during military training, however the same study also demonstrated no statistical difference in point prevalence between males (12.3%) and females (15.3%) (p = 0.09) prior to the start of the training programme; suggesting that the transition to elite military fitness from the general population is an important factor in PFP [21]. Another study reported annual prevalence within the general population as 29.2% in females and 15.5% males [1]. Prevalence comparison between sexes for adolescents also demonstrates this phenomenon, with one study showing that females made up 69% of participants with PFP, compared with 31% in males [130]. This phenomenon is affirmed by the pooled estimates of point prevalence, with mixed gender being calculated at 16.3% and female only at 22.7%.

These data may be used to identify possible populations who are at risk, which may help with clinical decision-making and the allocation of healthcare and research funding. For example, this review suggests that people attempting to increase physical activity levels may be at increased risk of developing of PFP, with subsequent development of pain and physical disability, and possible withdrawal from the programme, with loss of associated health benefits [196–198].

2.4.3 Strengths and limitations of included trials

A systematic and rigorous approach was taken to identify relevant studies, which included electronic database searching, hand searching, citation searching; with an endeavour to find unpublished studies.

The primary sources of heterogeneity within the included studies were likely to be from differences in populations and ages. Other potential sources of heterogeneity are different study design methodologies, for example, the nature of measures such as point or period, and differences in case definitions. There was no consistency within the included studies on the case definition used, with no two the same. Historically PFP was considered a separate pathology to intra-articular pathologies such as bursitis, plica syndromes and chondromalacia patellae [199]; however, only seven of the included 23 studies in this review had a contemporary case definition consistent with the 2015 IPRR [1,20,28,140,191,193,194].

2.4.4 Limitations of this review

The study presented with two key limitations. For pragmatic reasons, only one reviewer screened titles and abstracts. An extensive literature search was carried out, with two reviewers independently screening full-texts for inclusion, and two reviewers independently extracted the data. An attempt was made to retrieve unpublished trials; however, it may be that not all trials were retrieved, particularly considering the search terms included only papers published in English. It is likely that the inclusion of such data could influence the estimates of incidence and prevalence for PFP.

2.4.5 Implications for this thesis

This review found reported incidence rates across all populations of 9.7 – 1080.5 cases per 1,000 person-years; based on primary-care data in Spain the incidence rate for knee osteoarthritis is reported as 8.3 cases per 1,000 person-years for females and 4.6 cases per 1,000 person-years for males, far lower than that of PFP [200]. Furthermore, disability, function and pain scores are comparable; disability and function as measured with the KOOS [201], are similar with both conditions [28,40,41]; likewise, pain on activity, as measured on a 100mm VAS, is equivalent [202,203].

Additionally, PFP often affects younger populations, with a significant degree of persistence, potentially making it a much more significant problem, with work absenteeism, and long-term health implications through loss of physical activity [196–198]. There appears to be a large discrepancy with research funding and priorities for PFP compared with knee osteoarthritis. For example, there have been over 14,000 papers indexed in MEDLINE for knee osteoarthritis in the last 20 years, with only 1,500 papers indexed on PFP. This, despite the fact that incidence rates for PFP far exceed those reported for knee osteoarthritis.

One of the barriers research and healthcare funding faces for PFP is that historically it has been labelled a "benign, self-limiting condition" [204]. An influential 1985 cohort study by Sandow and Goodfellow [204] that followed 54 adolescents for two to eight years with a new diagnosis of PFP concluded that a policy of non-intervention was justified in the management of this condition and that the condition improved over time with few reporting disability. This interpretation contrasts with the APA2011 cohort from Denmark [205]. The authors demonstrated that at two-year follow-up, adolescents with PFP are more likely to be still reporting pain than people with other knee conditions [205]. Indeed, a recent re-analysis of Sandow and Goodfellow's data does not seem to support their conclusions, with Luhmann et al. [57] highlighting that of the original 54 adolescents, 94% still had pain at final follow-up, with 54% reporting same or worse severity of symptoms. This pattern of poor long-term prognosis continues in the adult populations, with a large proportion (> 50%) of people still reporting pain and dysfunction five to eight years after a six-weeks multi-model physiotherapy treatment programme [206]; yet the impression that PFP is a benign and self-limiting condition, with non-intervention advised, has continued to guide funders and stakeholders decision making for decades [207]. In the context of the high incidence and prevalence numbers, poor long-term prognosis and high disability levels, PFP should be an urgent research priority.

2.5 Conclusion

PFP is a common condition, with approximately one in ten military recruits and one in 14 adolescents suffering at any one time; and one in five of the general population experiencing pain within the last year. Due to a paucity of evidence uncertainty remains with regards to these estimates of incidence and prevalence, and further published, or unpublished work is likely to revise the estimates. There is some consistency with data showing females are twice as likely to experience PFP as males. GPs need to be aware of high-risk groups, such as adolescents and adults increasing physical activity levels, and the persistent nature of the problem, and ensure timely referrals to physiotherapy to maintain physical activity levels.

Part two: should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis

Summary

This chapter section presents a systematic review investigating pain in relation to exercise prescription in the management of chronic MSK pain, with the view of generating evidenced based recommendations to inform future exercise programmes and research design.

2.6 Background

Previous systematic reviews have assessed the effectiveness of various interventions for MSK disorders, including pharmaceutical therapies [208–211]; psychological-based therapies [212–215]; and physical-based therapies, including manual therapy [216–218], and exercise [215,219–223]. These have all presented conflicting results regarding effectiveness at improving pain and function and have identified limitations in the quality of included trials when concluding.

No previous systematic reviews have evaluated the effectiveness of exercises that were prescribed with instructions for patients to experience pain, or where patients were told it was acceptable and safe to experience pain. In this thesis, these exercises are referred to as "painful exercises". Therefore, the object of this review was to compare the effect of painful exercises, compared with non-painful exercises, on pain, function or disability, in patients with any chronic MSK pain within RCTs. Specifically, studies must include exercises that were prescribed with instructions for patients to experience pain, or where patients were told it was acceptable and safe to experience pain; and to compare any difference in contextual factors (any specific conditions surrounding the exercise) and prescription parameters of the prescribed exercise intervention.

2.7 Method

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [135], and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero/, reference CRD42016038882).

2.7.1 Search Strategy

An electronic database search was conducted on titles and abstract from inception to October 2016 on the following databases: The Allied and Complimentary Medicine Database (AMED), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library, Embase, Medline, SPORTDiscus and Web of Science. For the keywords and keywords search strategy used, see Table 6. The database searches were accompanied by hand searches of the reference list of included articles and the grey literature, and ongoing trials were searched using the following databases OpenGrey, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov and the NIHR portfolio.

For inclusion, the studies had to meet the following criteria — adults recruited from the general population with any MSK pain or disorder greater than three-months. Participants with pain suggestive of non-MSK pain, e.g. headache, migraine, bowel/stomach pain, cancer, fibromyalgia, chest pain, and breathing difficulties were excluded. Studies had to have a primary treatment arm of therapeutic exercises that was advised to be purposively painful, or where pain was allowed or tolerated. The comparison group had to utilise therapeutic exercises that were pain-free. Included studies were required to report pain, disability or function. Studies had to be full RCTs published in English. Studies that were not randomised or quasi-random were excluded.

2.7.2 Study Selection

One reviewer (BES) undertook the searches. Titles and abstracts were screened by one reviewer (BES), with potential eligible papers retrieved and independently screened by two reviewers (BES & PH). Initial inclusion agreement was 81%, and using Cohen's statistic method kappa agreement was k = 0.47, which is considered "fair to moderate" agreement [224–226]. All initial disagreements were due to intervention criteria, specifically the levels of pain during the therapeutic exercises in each intervention arm [120,227–233], and were resolved through consensus. Three trials needed further information with regards to their control exercise to ascertain if they met the inclusion criteria, and all three were contacted [113,118,121]. All three responded with further information, and after discussion, there was consensus to include two of the three trials [113,118].

2.7.3 Data Extraction

The following data were extracted from the included articles: trial design, participant information, intervention and control exercise, setting, follow-up periods and outcome data [234]. The data were independently extracted and transcribed to a standard table by one reviewer (BES), and then 25% of the data were independently checked by a second reviewer (PH). Effectiveness was judged at short-term (≤3 months from randomisation), medium-term (>3 and <12 months) and long-term (≥12

months) as recommended by the 2009 Updated Method Guidelines for Systematic Reviews in the Cochrane Back Review Group [235].

Table 6 - Search strategy (systematic review 2).

	Search Term
1	Randomized Controlled Trials as Topic/
2	randomized controlled trial.pt
3	controlled clinical trial.pt
4	or/1-3
5	Exp Pain
6	Exp Musculoskeletal Disease
7	Exp Musculoskeletal Pain
8	Or/5-7
9	Rehabilitation
10	Bone
11	Joint
12	Muscle
13	Exp Exercise therapy
14	Physiotherapy
15	Physical therapy
16	Physical-therapy
17	Exp Exercise
18	Or/9-17
19	(exercise adj7 pain$).af
20	High load
21	Loaded$
22	Resistance$
23	Eccentric$
24	Concentric$
25	Weight loaded
26	Weight-loaded
27	Weight resistance
28	Weight-resistance
29	High-load
30	Heavy load
31	Heavy-load
32	Direction$ preference
33	Directional-preference
34	Or/19-33
35	4 and 8 and 18 and 34 (Limited to English)

2.7.4 Quality Assessment

Each included study was appraised independently by two reviewers (BES & PH) for methodological quality using the Cochrane Risk of Bias Tool for randomised clinical trials [236]. The tool was initially developed in 2008, and updated in 2011, and was based on seven key bias domains [50]; sequence generation and allocation concealment (both within the domain of selection bias or allocation bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) [236]. For each domain, reviewers judged the risk of bias as "high", "low" or "unclear". Percentage agreement between the two reviewers for the individual risk of bias domains for the Cochrane Risk of Bias Tool was 86%, with a kappa of κ=0.76, which is considered "substantial or good" [224–226], and disagreements were resolved through consensus.

The GRADE system was used to rate the overall quality of the body of evidence in each pooled analysis [82]. The GRADE classification reduced confidence in the estimate of the effect from high by one level for each factor evaluated:

I. Design limitation (>25% of included studies in an analysis with low methodological quality and high risk of bias, as assessed by the Cochrane Risk of Bias Tool);

II. Inconsistency of results (if there was a wide un-expected variance in treatment effect estimates across studies, as estimated by a large statistical heterogeneity; $I^2 > 50\%$);

III. Indirectness of evidence (if there is a direct comparison of appropriate interventions, with similar and applicable population and outcome measures);

IV. Imprecision (< 400 participants for each outcome).

The publication bias domain was not evaluated in this review as it is not recommended to assess funnel plot asymmetry with a meta-analysis of fewer than ten trials [237]. A GRADE profile was completed for each pooled estimate. Where only single trials were available, evidence from studies with <400 participants were downgraded for inconsistency and imprecision and rated as low-quality evidence. Three reviewers assessed these factors for each outcome and agreed by consensus (BES, PH & TS).

The quality of evidence was defined as:

I. High quality - further research is unlikely to change the confidence in the estimate of effect. The Cochrane Risk of Bias Tool identified no risks of bias, and all domains in the GRADE classification were fulfilled;

II. Moderate quality - further research is likely to have an important impact on the confidence in the estimate of effect; one of the domains in the GRADE classification was not fulfilled;

III. Low quality - further research is likely to have an important impact on confidence and is likely to change the estimate; two of the domains were not fulfilled in the GRADE classification;

IV. Very low quality - there are uncertainties about the estimate; three of the domains in the GRADE classification were not fulfilled [238,239].

2.7.5 Statistical Analysis

Clinical heterogeneity was assessed through visual examination of the data extraction table on details related to participant characteristics, intervention, study design and process in the included studies. Based on this assessment, the reviewers judged there to be low clinical heterogeneity and accordingly, it was appropriate to perform a meta-analysis where feasible. The primary outcome was a measure of pain, disability or function. As pain scores were reported on different scales, the standardised mean difference (SMD) was used [240]. Effect size interpretation was defined *a priori* as 0.2 for a "small" effect size, 0.5 a "medium" effect size and 0.8 a "large" effect size as suggested by Cohen (1988) [241]. If data were not available, the associated corresponding author was contacted; failing this, the mean and standard deviation were estimated, assuming a normal distribution, from medians and inter-quartile ranges [242]. Statistical between-study heterogeneity was assessed with the I^2 statistic. With 0% - 25% considered as low, 26% - 74% moderate and 75% and over as high statistical heterogeneity [149]. When outcomes presented with low statistical heterogeneity data were pooled using a fixed-effects model [243]. When analyses presented with moderate or high statistical heterogeneity, a DerSimonian and Laird random-effects model was adopted [244].

All data analyses were performed using the OpenMetaAnalyst software [245].

2.7.6 Sensitivity Analysis

A sensitivity analysis was performed for the primary and secondary analysis using only trials which presented with a low risk of bias [236]. In addition, a sensitivity analysis was carried out to assess the impact of studies where: mean and standard deviation were estimated from medians and inter-

quartile ranges; outcome measures of pain were pooled scores set within pain domains from patient-reported outcome measures, e.g. the Shoulder Pain & Disability Index (SPADI) [246].

2.8 Results

2.8.1 Study Identification

The search results are presented in Figure 6. The database search produced 9,081 results, with no additional findings from reference list searches or unpublished searches. After duplicates were removed, 37 papers were appropriate for full-text review.

After full-text review, 28 articles were excluded; five due to participants not meeting criteria [120,121,247–249]; 26 because the intervention did not meet the criteria [116,120,121,228–230,232,233,247–264]; three because of study design not meeting criteria [114,248,265], and one due to inappropriate outcome measures [260]. Some articles were excluded for multiple reasons. Therefore nine trials were included in the final review [113,115,118,227,231,266–269].

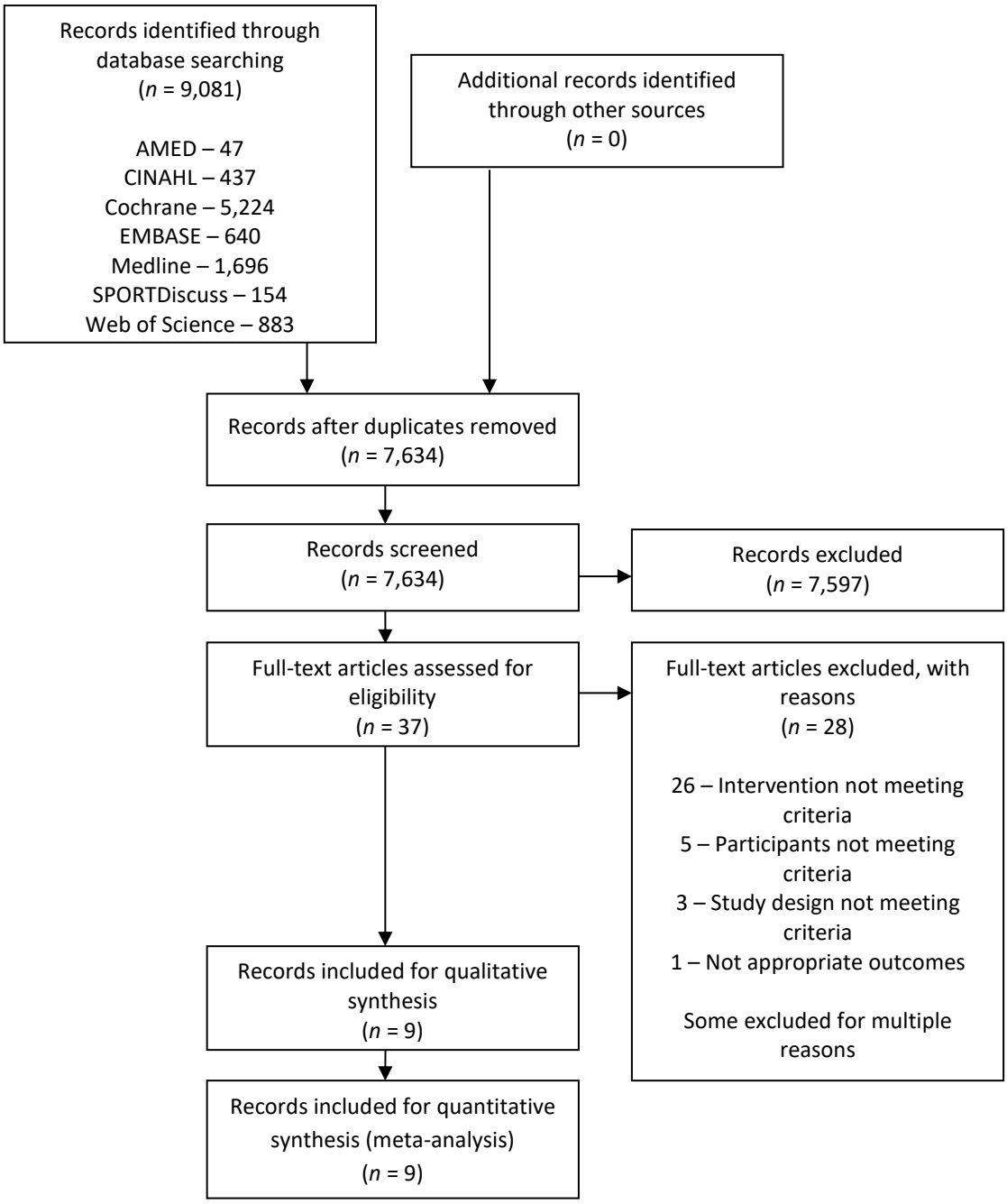

Figure 6 – PRISMA 2009 flow diagram (systematic review 2).

2.8.2 Characteristics of included trials

A summary of the characteristics and main findings of the included trials can be found in Table 7.

Table 7 - Characteristics of included trials (systematic review 2).

Study characteristics	Participant characteristics	Intervention & Setting	Outcome data/results
Aasa 2015 [227] Michaelson 2016 [269] 2 groups: 1. High-load lifting (HLL) exercise 2. Low-load motor control (LMC) exercises	70 patients recruited from occupational health care services in Sweden (mean age 42, 56% female). Inclusion criteria included: a. Adults with LBP > 3 months' duration b. With or without leg pain	Physiotherapy clinic, sports centre and home setting. 1. *N*=35. Group exercises based at a sports centre (5 participants in each group), with **pain up to 50mm visual analogue scale acceptable, such that the pain subsided after each set of exercises**. 12 treatment sessions over an 8-week period (weeks 1-4, 2 sessions per week; weeks 5-8, 1 session per week). 60 minutes in duration. No home exercises. 2. *N*=35. **Pain-free** individual exercises at a physiotherapy centre. 12 treatment sessions over an 8-week period (weeks 1-4, 2 sessions per week; weeks 5-8, 1 session per week). 20 – 30 minutes in duration. Exercises involved improving control around joint neutral positions. In supine, four-point kneeling, sitting, and/ or standing positions. Plus home exercises, 10 repetitions 2 – 3 x a day.	Main outcome assessed at baseline, 2 months and 12-month follow-up was: 7-day average pain on a visual analogue scale (0-100mm) and Roland-Morris Disability Questionnaire (RMDQ) (0–24). Group 1 mean pain at baseline 43 (SD 24); 2 months 22 (SD 21); 12 months 24 (SD 27) and 24 months 27 (SD 27). Group 2 mean pain at baseline 47 (SD 28); 2 months 30 (SD 26); 12 months 25 (SD 22) and 24 months 30 (SD 29). Group 1 mean disability at baseline 7.2 (SD 4.3); 2 months 3.8 (SD 4.0); 12 months 3.6 (SD 4.2) and 24 months 3.8 (SD 3.9). Group 2 mean disability at baseline 7.1 (SD 3.9); 2 months 3.6 (SD 4.2); 12 months 3.3 (SD 3.6) and 24 months 3.6 (SD 3.7). Both groups had significant improvements in their pain and disability levels. No significant between-group difference for pain at any follow-up, (2 months p=0.71; 12 months p=0.94; 24 months p=0.89). No significant between-group difference for disability at any follow-up, (2 months p=0.77; 12 months p=0.74; 24 months p=0.99).
Holmgren 2012 [115] Hallgren 2014 [266] 2 groups: 1. Specific exercises group 2. Control exercise group Patients given the option at 3 months of continuing to have an arthroscopic subacromial decompression.	97 patients recruited from the waiting list for an arthroscopic subacromial decompression from a University Hospital in Sweden (mean age 52, 37% female). Inclusion criteria included: a. Adults with lateral shoulder pain > 6 months b. Failed 3 months of previous primary care c. Signs of impingement symptoms d. Positive Neer's impingement test of a subacromial anaesthetic injection	Physiotherapy and home setting. 1. *N*=51. Eccentric rotator cuff exercises and concentric/eccentric scapula exercises. **Recommendation of 5/10 numerical rating scale for pain during exercises, such that the pain subsided by the next exercise session.** 7 physiotherapy appointment, weekly first 2 weeks, alternative weeks thereafter. Exercises to be performed at home once or twice a day for 12 weeks 2. *N*=46**. Pain-free** upper limb and neck exercises. 7 physiotherapy appointment, weekly first 2 weeks, alternative weeks thereafter. Exercises to be performed at home once or twice a day for 12 weeks	Main outcome of Constant-Murley score (C-M) (0 – 100), along with shoulder assessment scores and pain scores were taken at baseline, 3 months and 12 months, including pain at rest measured on a visual analogue scale (0-100mm). Group 1 mean C-M at baseline 48 (SD 15); 3 months 72 (SD 19) and 12 months 83 (SD 14). Group 2 mean C-M at baseline 43 (SD 15); 3 months 52 (SD 23) and 12 months 76 (SD 18). Group 1 mean pain at rest at baseline 15 (SD 19); 3 months 10 (SD 14) and 12 months 2 (SD 6). Group 2 mean pain at rest at baseline 20 (SD 21); 3 months 20 (SD 25) and 12 months 4 (SD 13). Both groups had significant improvements in all outcomes at 3 months and 1-year follow-up. Significantly more patients in the control group decided to have surgery (63%) than those in the specific exercise group (24%; p<0.0001).

Littlewood 2015 [113] 2 groups: 1. Self-managed exercises 2. Usual physiotherapy	86 patients recruited from UK, NHS Physiotherapy waiting list (mean age 55, 50% female). Inclusion criteria included: a. Adults with shoulder pain > 3 months b. Maintained shoulder ROM c. Pain with resisted movements	Physiotherapy and home setting. 1. *N*=42. Single shoulder exercise guided by the symptomatic response**, requiring pain to be produced during exercise, such that the pain subsided after the exercises.** Typically involving a weighted shoulder abduction exercise of 3 sets of 10 – 15 repetitions. Pragmatic approach to number of follow-ups, timings of appointments and point of discharge; i.e. the treating physiotherapist and patient will determine these factors. 2. *N*=44. **Usual physiotherapy***; including advice, stretching, exercise, manual therapy, massage, strapping, acupuncture, electrotherapy, corticosteroid injection at the discretion of the treating physiotherapist. Pragmatic approach to number of follow-ups, timings of appointments and point of discharge; i.e. the treating physiotherapist and patient will determine these factors.	Main outcome of the Shoulder Pain & Disability Index (SPADI) (0-100) at baseline, 3, 6 and 12 months. Group 1 mean at baseline 49.1 (SD 18.3), 3 months 32.4 (SD 20.2), 6 months 16.6 (SD 19.7) and 12 months 14.2 (SD 20.0). Group 2 mean at baseline 49.0 (SD 18.0), 3 months 30.7 (SD 19.7), 6 months 24.0 (SD 19.7) and 12 months 21.4 (SD 25.4). Statistically significant and clinically important within-group changes for SPADI from baseline to all three follow-up points. There were no statistically significant differences between the groups across all the outcomes at three, six or twelve months, (p=0.75, 0.19 and 0.32 respectively).
Maenhout 2013 [231] 2 groups: 1. Traditional rotator cuff training with heavy load eccentric training 2. Traditional rotator cuff training	61 patients recruited from a shoulder surgeon's clinic in Belgium (mean age 39.8, 41% females). Inclusion criteria included: a. Adults with > 3 months of shoulder pain b. Painful arc c. 2 out of 3 impingement tests d. Pain on palpation of rotator cuff tendons	Physiotherapy and home setting. 1. *N*=31. The same exercises as group 2, plus a heavy loaded eccentric exercise of abduction within the scapular plane. 3 sets of 15 repetitions, such that the **patient experiences pain on the last set, up to 5/10 visual analogue scale, such that the pain subsided by the following morning**. 2. *N*=30. **Pain-free,** traditional rotator cuff exercises of internal and external rotation with a resisted rubber band. Performed once a day, with 3 sets of 10 repetitions. Both groups had exercise prescription and monitoring through 9 physiotherapy appointments over 12 weeks.	Main outcome of the Shoulder Pain & Disability Index (SPADI) (0-100) at baseline, 6 weeks and 12 weeks. Group 1 mean at baseline 44.3 (SD 11.5), 6 weeks 17.7 (SD 12.0) and 12 weeks 14.5 (SD 11.7). Group 2 mean at baseline 42.0 (SD 11.0), 6 weeks 25.4 (SD 11.9) and 12 weeks 17.0 (SD 11.4). In both group pain and function, measured with the SPADI score, improved significantly over time (p>0.001). When comparing between groups, improvement of the SPADI score was not significantly different.

Norregaard 2007 [267] 2 groups: 1. Eccentric exercises 2. Stretching exercises	45 patients recruited from a Clinic of Sports Medicine in Denmark (mean age 42, 49% female) Inclusion criteria included: a. Adults with Achilles pain > 3 months b. Local thickening > 2mm on ultrasound c. Diffuse posterior ankle pain	Sports Medicine Clinic and home setting. 1. *N*=21. Information leaflet with home exercise programme on. To be performed twice a day, for 12 weeks. 1 follow-up appointment at 3 months. 3 sets of 15 repetitions of eccentric calf exercises, with knee straight and semi-flexed. **Patients told to expect pain during the exercises but to avoid increasing daily pain or morning stiffness** 2. *N*=24. Information leaflet with home exercise programme on. To be performed twice a day, for 12 weeks. 1 follow-up appointment at 3 months. **Pain-free** standing stretches for gastrocnemius and soleus; 5 repetitions of 30 seconds each.	Outcome measures were tenderness on palpation, ultrasound, pain, as measured by the knee injury and osteoarthritis outcome score (KOOS) (0-4) and patient's global assessment. Follow up was at baseline, 3, 6, 9, 12 weeks and 1 year. Group 1 mean pain domain from KOOS at baseline 1.6 (SD 0.6), 3 weeks 0.1 (SD 0.1), 6 weeks 0.3 (SD 0.1), 9 weeks 0.4 (SD 0.2), 12 weeks 0.4 (SD 0.2) and 1-year score was 1.0 (SD 0.2). Group 2 mean pain domain from KOOS at baseline 1.6 (SD 0.6), 3 weeks 0.2 (SD 0.1), 6 weeks 0.3 (SD 0.1), 9 weeks 0.3 (SD 0.2), 12 weeks 0.4 (SD 0.2) and 1-year score was 0.7 (SD 0.2). There were significant improvements in all dimensions of the KOOS compared to baseline, with no differences between-group differences.
Rathleff 2015 [118] 2 groups: 1. High-load strengthening exercises 2. Stretching exercises	48 patients recruited from a University hospital, regional hospital and private clinic in Denmark (mean age 46, 66% female) Inclusion criteria included: a. Adults with plantar fasciitis > 3 month b. Pain on palpation c. Local thickening > 4mm on ultrasound	Home-based exercises. 1. *N*=24. Information leaflet, heel inserts and a prescription of a high-load strength programme. Consisting of single calf raises with a towel rolled up under the toes for maximum toe extension, activating the windlass mechanism. Each calf raise was 3 seconds up, 2 seconds pause, 3 seconds down. Weight was added in rucksacks, starting at 12 repetition maximum for three sets, and slowly progressed over 3 months. Patients were advised to perform the exercise every other day. **Exercises were allowed to be painful, with no post increase in pain.** 2. *N*=24. Information leaflet, heel inserts and a prescription of **pain-free*** plantar-specific stretches. Patients were asked to stretch the plantar fascia in a cross-legged position by extending their toes. Hold for 10 seconds, 10 times, 3 x a day for 3 months.	Primary outcome was foot function index (FFI) at 1, 3, 6 and 12 months; including pain at worse and pain on first step on a numerical rating scale (0 – 10). Mean scores for group 1 pain at worse at baseline was 7.9 (SD 1.7), 1 month 6.1 (95% CI 5.1 - 7.2), 3 months 3.5 (95% CI 2.3 - 4.7), 6 months 2.5 (95% CI 1.4 - 3.6) and 12 months 2.9 (95% CI 1.7 - 4.0). Mean scores for group 2 pain at worse at baseline was 7.5 (SD 1.6), 1 month 6.1 (95% CI 5.2 - 7.1), 3 months 6.1 (95% CI 4.4 - 7.7), 6 months 3.4 (95% CI 2.0 - 4.7) and 12 months 1.8 (95% CI 0.7 - 3.0). At 3 months group 1 had significantly lower pain scores than group 2 ($P < 0.05$). At months 1, 6 and 12 there was no significant difference between groups.

Silbernagel 2001 [268] 2 groups: 1. Eccentric exercises 2. Regular concentric/eccentric exercises	40 patients recruited from mailings to hospitals, clinics and sports clubs in Sweden (mean age 45, 23% female) Inclusion criteria included: a. Adults with Achilles pain > 3 months	Clinic and home setting **1.** *N*=22. Progressive eccentric exercise programme to be performed 2 x a day. Plus, three sets of six different stretching exercises, 20 seconds each. As well as balance, toe/heel walking exercises. Weekly physiotherapy contact for 12 weeks. **Pain was allowed during the exercises up to 5/10 visual analogue scale, such that the pain subsided by the following morning with no morning stiffness.** 2. *N*=18. 3 x a day of regular concentric and eccentric calf strengthening, plus two sets of the stretching exercises from group 1. Physiotherapy contacts 3 – 5 x during the 12 weeks. **Exercises must be pain-free.**	Outcomes of pain on palpation (visual analogue scale) (0-100mm) taken at baseline, 6 weeks, 3 and 6 months. Other outcomes included pain on walking and pain on stairs (yes/no), various objective measures, plus a non-validated functional questionnaire. Median ± IQR scores for pain on palpation for group 1 at baseline was 49 ±26.2, 6 weeks 40 ±27.5, 3 months 35 ±24.8 and 6 months 21 ±20. Median ± IQR scores for group 2 at baseline was 27 ±21.5, 6 weeks 20 ±20, 3 months 31 ±26 and 6 months 9 ±17.5. There was a significant decrease in pain on palpation in both treatment groups. No significant differences between groups were seen.
Bold text highlights the contextual factors of each exercise programme; *, information not within the publication, authors contacted for clarification			

The two occurrences of the same trial reporting different time points over two articles were analysed as single trials to prevent multiplicity in analyses [115,227,266,269]. All trials investigated home-based exercises, had a roughly even composition of females and males (46% females), with similar mean ages of participants (mean age 47, range 19 - 83). One trial included low back pain [227,269], three included shoulder pain [113,115,231,266], two included Achilles pain [267,268], and one included plantar heel pain [118].

Three trials used a VAS to measure pain [115,227,266,268,269], two trials used the SPADI [113,231], one used the Knee Injury and Osteoarthritis Outcome Score (KOOS) [267], and one used the Foot Function Index (FFI) including pain at worse and pain on "first step" on a numerical rating scale (0 – 10) [118].

Where pain outcomes were included within patient-reported outcome measures, these data were extracted [113,231,267]. Two trials that used the SPADI had insufficient data in the publication to complete a meta-analysis for pain [113,231], and both were contacted and asked to supply pain domain data. Littlewood et al. [113] replied and provided all the available data, however, Maenhout et al. [231] did not respond. One trial reported outcomes in medians and inter-quartile ranges [268] and was contacted and asked for further data. They were unable to supply this, so the mean and standard deviation were estimated assuming normal distribution [242].

All seven trials recorded short-term follow-up of pain, four trials recorded medium-term follow-up of pain [113,118,231,268], and five trials recorded long-term follow-up for pain [113,115,118,227,266,267,269].

2.8.3 Trial quality and bias

The two papers reporting long-term outcomes for the trials that reported different time points referred to the short-term outcome papers about design parameters. Therefore trial quality and bias were assessed accordingly [115,227,266,269].

No trial had greater than three "high risk" of bias scores for a domain (Figure 7).

The greatest risk of bias was with the blinding of participants and personnel (100%) (Figure 8). The greatest amount of uncertainty was regards to selective reporting bias since many of the trials failed to include trials register details, or protocol details (44%) [118,231,267,268]. Other common areas of bias with the included trials were with attrition bias, one trial failed to describe attrition adequately [227], and two trials had large drop-out rates [113,267], however Littlewood et al. [113] received a "low risk" score since their participant attrition was balanced across the intervention and control

groups [270], and an intention-to-treat analysis was performed. The risk of bias assessment tool highlights common trial write up errors, with a number of papers failing to give an appropriate level of detail to adequately assess selection bias risk (33%) [227,231,268].

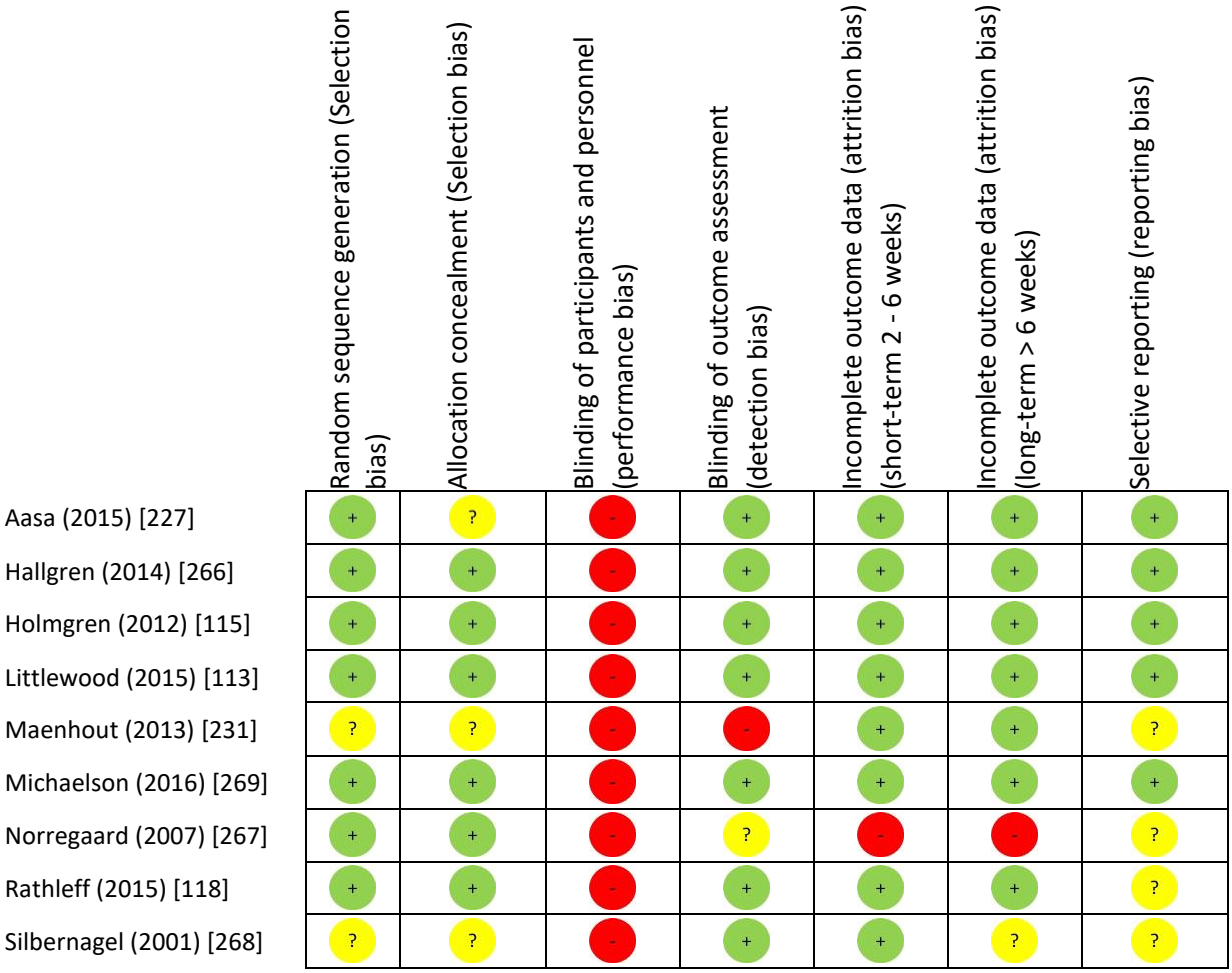

Figure 7 – Risk of bias summary (systematic review 2).

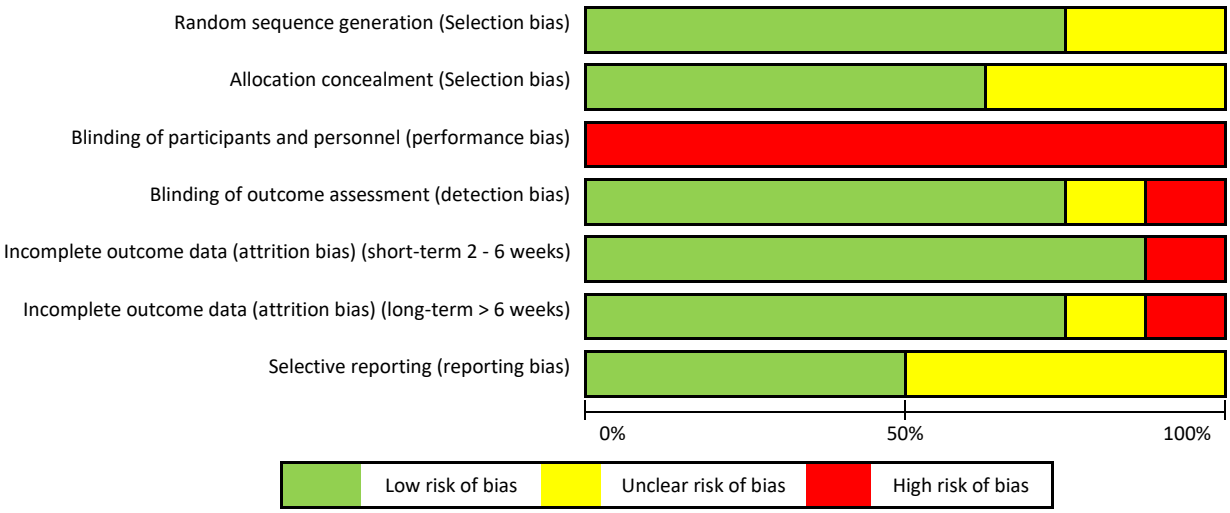

Figure 8 – Risk of bias graph (systematic review 2).

2.8.4 Narrative Synthesis of Disability and Function Outcomes

Of the seven trials, six reported some form of patient-reported outcome measure of disability or function. One reported Roland-Morris Disability Questionnaire (RMDQ) [227,269], one reported Constant-Murley and the Disabilities of the Arm Shoulder and Hand score (DASH) [115,266], two reported SPADI [113,231], one reported the KOOS [267], and one reported the FFI [118]. With the exception of Rathleff et al. [118], there were clinically significant improvements in all outcomes at all time points, with no clear superiority (long-term SMD range: -0.25 – 0.09). At three-months follow-up for Rathleff et al. [118] the intervention group had a statistically significant lower FFI than the control group ($p = 0.016$). At one, six and 12 months, there were no differences between groups ($p > 0.34$).

2.8.5 Contextual Factors

With regards to the parameters of pain in the exercise intervention the participants were advised to adhere to, each trial gave different instructions, the key differences being if pain was allowed [118,227,268,269], or recommended [113,115,231,266,267]. In addition other differences were if an acceptable level of pain measured on a pain scale was advised [115,231,266,268]; and a time frame for the pain to subside by, for instance, if the pain had to subside immediately [113,118,227,269], by the next session [115,266], or by the next day [231,267,268]. Clinically significant improvements in patient-reported outcome measures were reported across all interventions and control exercises, and all time points. It is not clear from the data if one approach was superior to the others.

2.8.6 Meta-Analysis of Pain

2.3.5.1 Short-Term Results

Six trials, with 385 participants reported post-treatment effect on pain. Combining the results of these trials demonstrated a significant benefit (SMD) of painful exercises compared with pain-free exercises for MSK pain at short-term follow-up, with a small effect size of -0.28 (95% CI -0.49 to -0.08) (Figure 9). Statistical heterogeneity was negligible, I^2=0%. The quality of evidence (GRADE) was rated as "low quality", due to trial design and low participant numbers (Table 8).

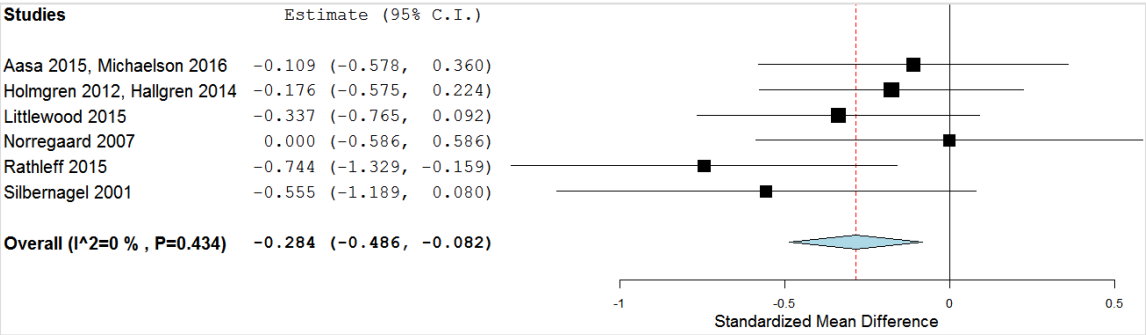

Figure 9 – Forest plot of painful exercises versus pain-free exercises – short term. *Negative values favour painful intervention, positive favour pain-free.

For sensitivity analysis at short-term follow-up, the meta-analysis was repeated, removing two trials that used a patient-reported outcome measures index and had high drop-out rates [113,267] and the Silbernagel et al. [268] trial where mean and standard deviation were estimated from medians and inter-quartile ranges. The results of the data synthesis produced very similar results, with a small effect size of -0.27 (95% CI -0.54 to -0.05), with low statistical heterogeneity of I^2=22%. The quality of evidence (GRADE) was rated as "moderate quality", due to low participant numbers (Table 8).

2.8.5.2 Medium Term Results

At medium-term follow-up, meta-analysis demonstrated a significant benefit (SMD) for painful exercises compared with pain-free exercises for MSK pain, with a medium effect size of -0.59 (95% CI -1.03 to -0.15), see Figure 10. The statistical heterogeneity was moderate, I^2=50%. The quality of evidence (GRADE) was rated as "low quality", due to trial design and low participant numbers (Table 8).

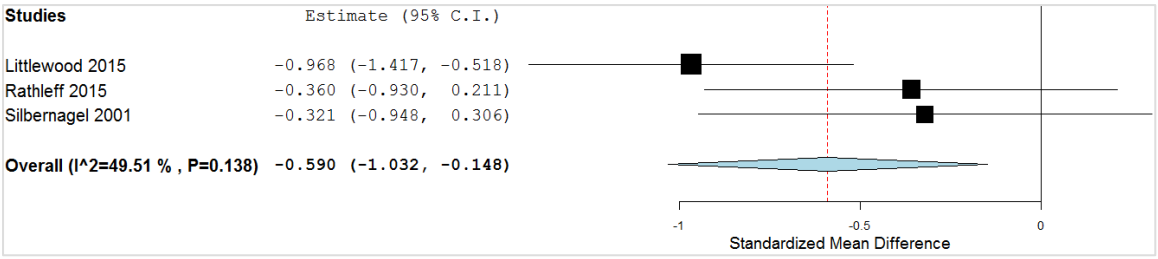

Figure 10 – Forest plot of painful exercises versus pain-free exercises – medium term. *Negative values favour painful intervention, positive favour pain-free.

Sensitivity analysis was not possible for medium-term results, as two trials were excluded, one for using a patient-reported outcome measures index [118], and one due to means and standard deviations being estimated from medians and inter-quartile ranges [268]. The one remaining trial showed no significant difference at medium term [118]. The quality of evidence (GRADE) was rated as "low quality", due to it being only from a single trial (Table 8).

2.8.5.3 Long-Term Results

At long-term follow-up, meta-analysis demonstrated no statistical difference between painful exercises and pain-free exercises, with an effect size of 0.01 (95% CI -0.39 to 0.41) (Figure 11). The statistical heterogeneity was high, I^2=70%. The quality of evidence (GRADE) was rated as "very low quality", due to trial design, heterogeneity and low participant numbers (Table 8).

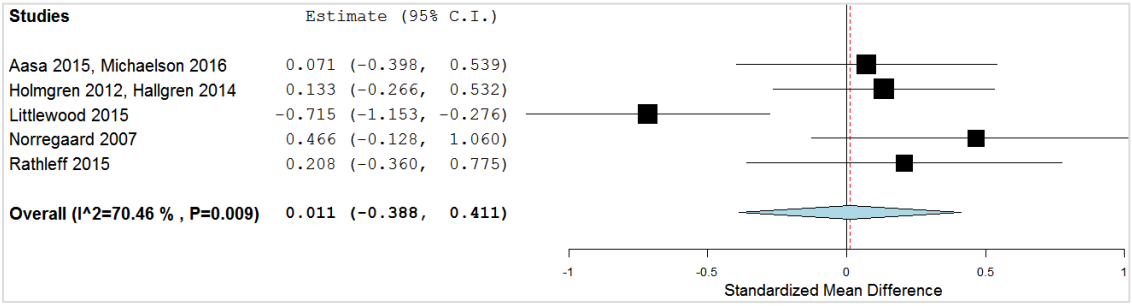

Figure 11 – Forest plot of painful exercises versus pain-free exercises – long term. *Negative values favour painful intervention, positive favour pain-free.

For sensitivity analysis at long-term follow-up, the meta-analysis was repeated, removing the two trials that used a patient-reported outcome measures index [113,267]. The results of the data synthesis found no statistical difference between painful exercises and pain-free exercises, with an effect size of 0.13 (95% CI -0.14 to 0.40). The statistical heterogeneity was negligible, I^2=0%. The quality of evidence (GRADE) was rated as "moderate quality", due to low participant numbers (Table 8).

Table 8 - GRADE summary of findings table (systematic review 2).

Summary of results				Quality of the evidence (GRADE)			
Outcome	**No of Participants (trials) Follow-up**	**SMD (95% CI)**	**Design**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Pain	385 (6 trials) Short term	-0.28 (-0.49 to -0.08)	Limitations[1]	No inconsistency	No indirectness	Imprecision[3]	**Low** ⊕⊕◯◯
Pain	173 (3 trials) Medium term	-0.59 (-1.03 to -0.15)	Limitations[1]	No inconsistency	No indirectness	Imprecision[3]	**Low** ⊕⊕◯◯
Pain	345 (5 trials) Long term	0.01 (-0.39 to 0.41)	Limitations[1]	Inconsistency[2]	No indirectness	Imprecission[3]	**Very Low** ⊕◯◯◯
Sensitivity Analysis				**Quality of the evidence (GRADE)**			
Pain	215 (3 trials) Short term	-0.27 (-0.54 to -0.05)	No Limitations	No inconsistency	No indirectness	Imprecision[3]	**Moderate** ⊕⊕⊕◯
Pain	40 (1 trials) Medium term	-0.32 (-0.95 to 0.31)	No Limitations	Inconsistency[4]	No indirectness	Imprecision[3]	**Low** ⊕⊕◯◯
Pain	215 (3 trials) Long term	0.13 (-0.14 to 0.40)	No Limitations	No inconsistency	No indirectness	Imprecision[3]	**Moderate** ⊕⊕⊕◯

SMD: standardised mean difference; CI: confidence interval; short term: ≤3 months; medium term: >3 and <12 months; long term: ≥12 months

High quality: further research is unlikely to change the confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on the confidence in the estimate of effect
Low quality: further research is very likely to have an important impact on the confidence in the estimate of effect
Very low quality: uncertainties remain about the estimate

[1] Lack of blinding of participants and personnel, attrition bias, unable to adequately assess selection bias risk
[2] Large statistical heterogeneity; I^2 = 70%
[3] < 400 participants for each outcome
[4] Only single trial available, <400 participants, therefore, downgraded for inconsistency and imprecision

2.9 Discussion

2.9.1 Summary of main findings

This is the first systematic review to evaluate the current evidence-base of painful exercises for the management of MSK pain. The overall results of the meta-analysis indicate that there was a significant short-term benefit for painful exercises over pain-free exercises for patient-reported outcomes of pain, with a small effect size and moderate quality of evidence. There appears to be no difference at medium or long-term follow-up, with the quality of the evidence rated as moderate to low.

2.9.2 Strengths and limitations of included trials

Subgroup analyses by anatomical region or tissue structures were not conducted; the diagnostic labelling of MSK structures as sources of pain has been debated for many years, with polarising opinions [271,272]; however, the diagnostic labelling of patients into tissue-specific pathology characteristically suffers from poor reliability and validity [273–278]. A strength of this review is that despite the trials including subjects suffering from MSK pain at different body locations, there exists low statistical heterogeneity at short-term follow-up, and for the sensitivity analyses carried out.

The overall quality of the included papers can be considered relativity high, with only three domains in the Cochrane Risk of Bias Tool (disregarding blinding of participants) demonstrating a clear risk of bias across all domains for all trials. However, taking into account other factors assessed with the GRADE analysis, the quality of the evidence was rated as moderate to low. Therefore, the results can be considered to have moderate to low internal validity, with future research likely to alter further conclusions.

The primary source of bias within the included trials was blinding; no trial blinded the participants to treatment allocation. Knowledge of group assignment may affect participants' behaviour, for example with patient-reported outcome measures such as pain scales, or compliance with therapy interventions [279]. However, it is accepted that blinding in physiotherapy, and physical intervention trials are difficult to achieve [223].

Another limitation of the included trials is the high level of attrition suffered by some of the trials in both treatment groups. For example, Littlewood et al. suffered from 51% dropout at 12-months follow-up [113]. A high level of attrition can overestimate the treatment effect size and could bias the results of the meta-analysis. However, the risk of bias was minimised by conducting a sensitivity analysis on trials with a large dropout, identified using the Cochrane Risk of Bias Tool, and assessed level of evidence using the GRADE classification.

2.9.3 Limitations of this review

An extensive literature search was carried out, with two reviewers independently screening full-texts for inclusion, and a sample of the data extraction independently verified. Additionally, an attempt was made to retrieve unpublished trials. However, it may be that not all trials were retrieved, particularly considering the search was conducted for papers published only in English.

2.9.4 Implications for this thesis

Traditionally, healthcare practitioners have been reluctant to encourage patients to continue with painful exercises when they are treating MSK pain, with qualitative research demonstrating patients being advised to avoid pain [280,281]; with some research suggesting clinicians' fear of exacerbation or tissue damage being the primary barrier [282]. The results of this systematic review show that there does not appear to be a scientific basis for this fear in relation to outcome measures of pain, function and disability. This is an important point when considering what advice is given on any short-term exacerbations of MSK pain during physical activity or exercise by healthcare practitioners; particularly when considering the impact of poor physical activity levels [283].

A theoretical rationale for a positive response to painful exercises is the positive impact upon the central nervous system [89,119] and is discussed more fully in this thesis in Chapter 5, development of the intervention.

Significant improvements in patient-reported pain can be achieved with varying degrees of pain experiences (the level of pain the patient experiences during the exercise) and post-recovery time (how long the pain takes to settles after performing the exercise) for therapeutic exercise. In addition to the aspect of pain, an important difference between the intervention arm and the control arm is the higher loads, or levels of resistance, employed with the painful exercises; and it is unknown if the difference in responses can be attributable to these two elements of the different exercise programmes. Research has shown a "dose-response" to exercise for MSK pain, the more incremental exercise (with an appropriate recovery period) a person does, the greater their improvements in pain [28,120,284]; the short-term benefits of painful exercises over pain free exercises could be explained by this dose-effect or response to load/resistance. However, the optimal "dose" of therapeutic exercise for any MSK pain is yet to be established.

This review investigated patient-reported outcome measures of pain, function/disability. As been hypothesised, exercise therapy, where it has been advised that the experience of pain is safe and allowed, may address other patient-reported outcome measures: fear avoidance, self-efficacy and catastrophising beliefs [66,119], and therefore may lead to improvements in function, quality of life and disability, despite pain levels. Unfortunately, none of the trials included in this review recorded the level of pain patients actually experienced during their exercise programme, therefore preventing any detailed attempt to explain any mechanisms of effect fully. This aspect of exercise prescription warrants further investigation in relation to chronic MSK pain outcomes. Any future trials should consider the role of pain with exercises, and clearly define the parameters employed to ensure translation of findings into practice and further evaluation of optimal "dosage".

The data presented in this review offers some initial insights into the development and application of painful exercise programmes for chronic MSK pain. Significant improvements in patient-reported pain can be attained with varying degrees of pain and recovery period whilst performing an exercise protocol, giving a pragmatic approach to exercise prescription in people with chronic MSK pain.

2.10 Conclusion

The results of this systematic review indicate that protocols using painful exercises offer a small, but significant benefit over pain-free exercises at short-term follow-up, with a moderate quality of evidence. There appears to be no difference at medium or long-term follow-up, with a moderate to low quality of evidence. Pain during therapeutic exercise for chronic MSK pain need not be a barrier to successful outcomes. Further research is warranted to evaluate the effectiveness of painful exercises fully; psychological outcome measures, such as fear avoidance, self-efficacy and catastrophising beliefs, and the "dose-response" to MSK pain.

2.11 Summary of the literature reviews

Although data are limited, these systematic reviews have been able to offer some preliminary guidance with contextual factors of loaded exercise protocols. Furthermore, the data presented demonstrate a high incidence and prevalence for PFP; within the context of this, and poor long-term prognosis and high disability levels, PFP should be an urgent research priority. These guiding principles will be used to refine and develop the intervention used in this thesis, which will be presented in Chapter 5.

The next chapter builds on this understanding, and in preparation to inform research design, describes the procedures, methods and results used in this thesis to define usual care, for people with PFP being

treated by a physiotherapist in the UK. This will be combined with the development of the intervention (Chapter 5) to inform the development of the protocol (Appendix C), including training of the physiotherapists in both the intervention arm and usual care arm.

Chapter 3 - Current Management Strategies for Patellofemoral Pain

Summary

This chapter presents the methods and results from a cross-sectional online questionnaire survey to ascertain the current UK physiotherapy management strategies for PFP. Current management strategies were considered, particularly in relation to exercise prescription and therapists' response to pain. This was used to inform research design and identify physiotherapists' treatment preference.

3.1 Introduction

Previous chapters have demonstrated high prevalence, incidence data, coupled with poor long-term prognosis and a lack of evidence-base on which to determine conservative management of people with PFP, particularly in relation to exercise prescription. It did, however, highlight some preliminary guidance with contextual factors of loaded exercise protocols that might be extrapolated to fill the gaps in understanding the role of exercise prescription for PFP.

Building on this understanding, and in preparation to inform research design, a clear understanding is needed on the current management approach physiotherapists undertake in the NHS. The MRC framework identifies that it may be difficult to identify the "active ingredient" of complex interventions [4], and perhaps no more so than with exercise prescription [119]; however, it must be clear how the intervention differs from usual care.

There has been one previous survey of UK physiotherapy practice for PFP undertaken in 2011 [285], this demonstrated considerable heterogeneity in the prescription of physiotherapy interventions. This survey drew participants from a small demographic area (North Wales) with a small sample of 30 participants. Therefore, the generalisability of the results is limited. Subsequently, a wealth of information has been published, and understanding of the concepts of chronic pain states has grown considerably [75]. More is also now understood on the impact of patients' and therapists' attitudes and beliefs on pain and function [89]. For example there is a growing body of evidence that physiotherapists with a biomedical orientation to pain are more likely to advise patients to limit their physical activity due to pain [76–78]; and consequently may induce fear-avoidant behaviours onto

their patients [78,89]. The previous survey did not include questions relating to exercise parameters, e.g. dosage, frequency and intensity; nor self-management strategies about pain response and physical activity. In respect to these factors, and the still insufficient evidence-base on this poorly managed condition, there remains a continuing need to clearly define the range of current practice within the UK to underpin future research.

This study, therefore, aimed to ascertain the current UK physiotherapy management strategies for PFP, particularly with exercise prescription and therapists' response to pain. This used to identify future research needs and in relation to the main aims of the thesis as a whole, to identify treatment preference and any future potential barriers to implementation.

With reference to previous physiotherapy surveys of current practice, it is thought that physiotherapists with a special interest (defined as, someone who self-declares as having a special interest) in PFP might have different insights into the management strategies of this condition [280,286]; this may lead to substantially different approaches to exercise prescription and therapists' response to pain during exercise and leisure activities. Therefore, a secondary aim of this survey was to establish whether the level of interest in PFP influences the management strategies used.

3.2 Methods

3.2.1 Design

The survey was designed by the research team (Appendix A), with reference to the previous PFP survey of UK practice [285]; recent surveys of UK physiotherapy practice for shoulder pain, plantar fasciitis and hip and knee replacements [280,286–288]; and recent systematic reviews on conservative management strategies of PFP [51].

The study was a cross-sectional online questionnaire survey. The project was approved by the Faculty of Medicine and Health Sciences Research Ethics Committee, University of Nottingham (H10052016 SoM RHA) (Appendix B) and reported following the STROBE statement [289].

3.2.2 Participants

Practising physiotherapists within the UK (including private, NHS and researchers) who reported treating patients with PFP were invited to take part and provide informed consent. Physiotherapists were recruited via an invitation email sent through professional networks, the "interactive CSP" (iCSP) message board, and social media (Twitter) [290]. The invitation included a summary, a link to the final survey and author contact details.

3.2.3 Procedures

As a pilot exercise, the survey was written in draft form and distributed to four physiotherapy outpatient departments in the East Midlands in England, with 27 responses. Feedback was sought with regards to content, format, usability and general suitability from the physiotherapists. Based on this, slight adjustments were made with regards to the range of possible answers and the rewording of two questions.

The final survey addressed the following main areas: participant characteristics; management strategies; exercise prescription (types, dosage, frequency, intensity); self-management strategies, approaches to painful exercises and estimated standard treatment period. The survey was uploaded to Bristol Online Survey (https://nottingham.onlinesurveys.ac.uk) in July 2016 and was open until 100 respondents had completed the survey. For pragmatic reasons the number of responders was limited to 100; this reflects surveys of physiotherapy practice previously undertaken [280] and was thought to give a robust and useful amount of data [291,292].

3.2.4 Data Analysis

Data were imported into Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and analysed using descriptive statistics of counts and proportions for categorical variables for all completed responders. Responses from physiotherapists with a special interest were compared to those without a special interest using the chi-square test, using SPSS, version 22 (IBM Corp. Armonk, NY: IBM Corp), with the level of significance set at $p < 0.05$. Text responses were summarised narratively.

3.3 Results

One hundred physiotherapists responded, with 100 completed responses.

3.3.1 Respondent Characteristics

- *Are you a UK based physiotherapist that regularly sees patients with patellofemoral pain?*

For unknown reasons, one respondent indicated they were not a UK physiotherapist but nonetheless went on to complete the survey. This participant's answers were removed from the dataset, leaving 99 completed responses from UK physiotherapists. Please see Table 9 for descriptive statistics.

- *Do you have a special interest in treating patellofemoral pain?*

Thirty-three (33%) physiotherapists responded they had a special interest in PFP, and 66 (66%) responded they did not.

- *What is your primary role?*

All 99 responders answered this question. In general, there was a wide variety of roles, across different levels and settings. The most common three settings were NHS Band 6 (28%), Private Practice (27%) and NHS Band 7 (15%). There was no significant difference in primary role between those with a special interest and those without ($\chi 2=1.121$ $p=0.98$).

- *How many times do you typically see patients with PFP?*

There was a considerable variation in the number of treatment sessions provided by the UK physiotherapists, ranging from one to 10+ appointments (Figure 12). There was no statistically significant difference between physiotherapists with and without a special interest ($\chi 2=7.496$ $p=0.28$).

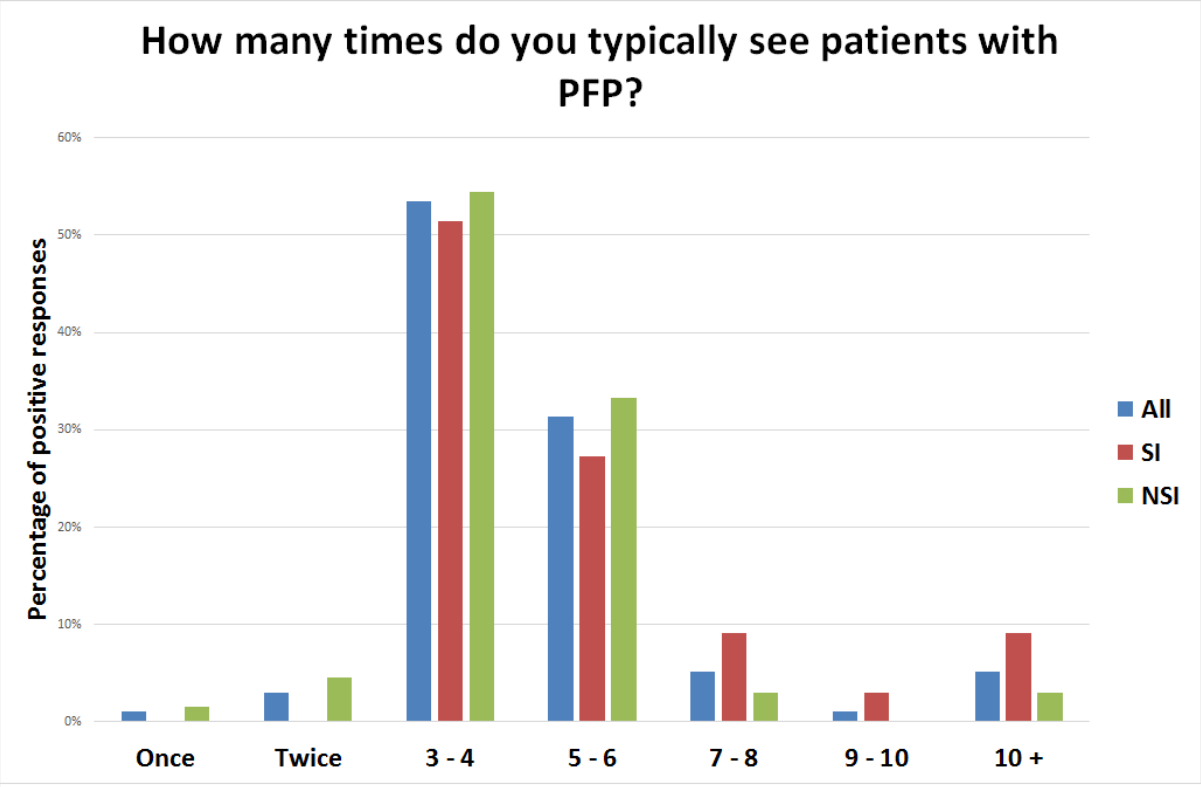

Figure 12 - Number of appointments. All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest.

- *How long would you typically expect to see patients with PFP?*

The vast majority of UK physiotherapists (95%) within this study would expect to see patients for no more than six-months (Figure 13). There was no statistically significant difference between

physiotherapists with and without a special interest (χ2=1.624 *p*=0.80).

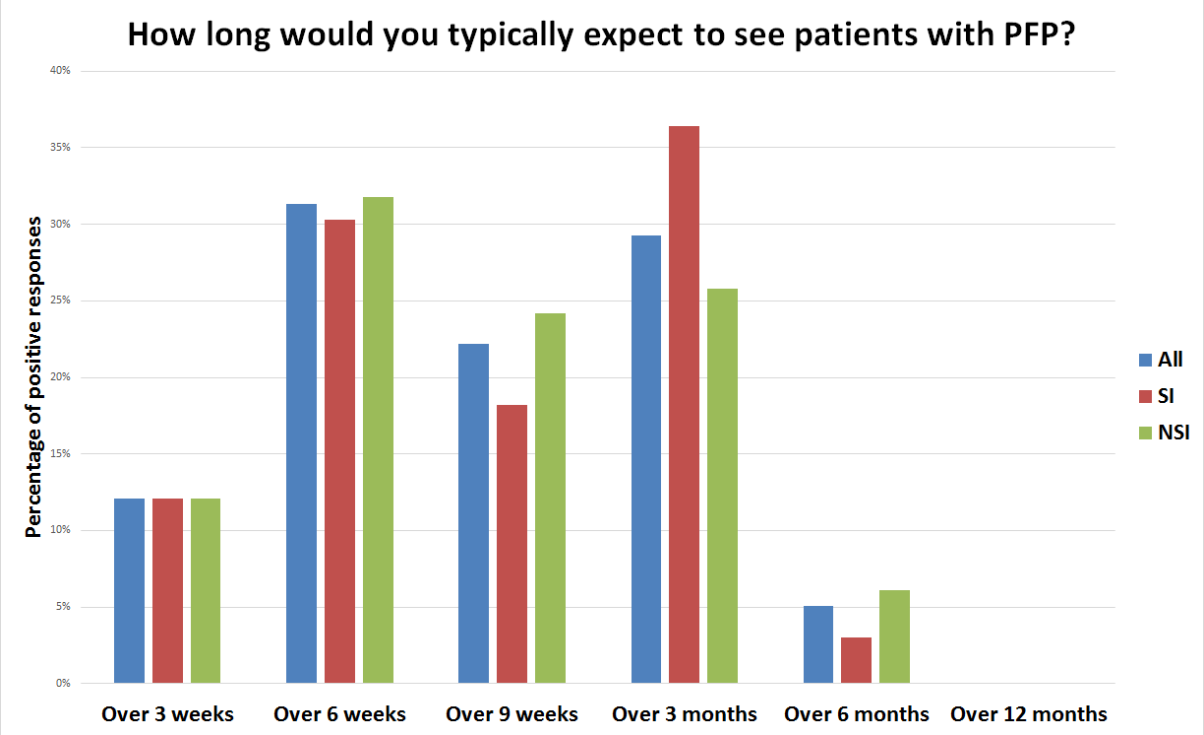

Figure 13 - How long would you typically expect to see patients with PFP? All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest.

3.3.2 Management Strategies

- *What management strategies do you use for PFP? Tick all that applies?*

UK physiotherapists currently offer their patients a wide variety of treatment options (Figure 14). The five most common options chosen were: closed chain strengthening exercises (98%); education and advice (96%); open chain strengthening exercises (76%); taping (70%) and stretches (65%). Responders with a declared special interest in PFP were more likely to prescribe open chain exercises (88% versus 69%); orthotics (70% versus 46%) and bracing (21% versus 3%); these differences were statistically significant (χ2=3.960 *p*=0.04; χ2=5.198 *p*=0.02; χ2=8.800 *p*=0.01 respectively). The pattern of responses was closely matched between those with a special interest and those without for the remainder of management options (*p*>0.05) — ten responders specified "other". Responses included: deep transverse friction, soft tissue massage, foam rolling and myofascial release.

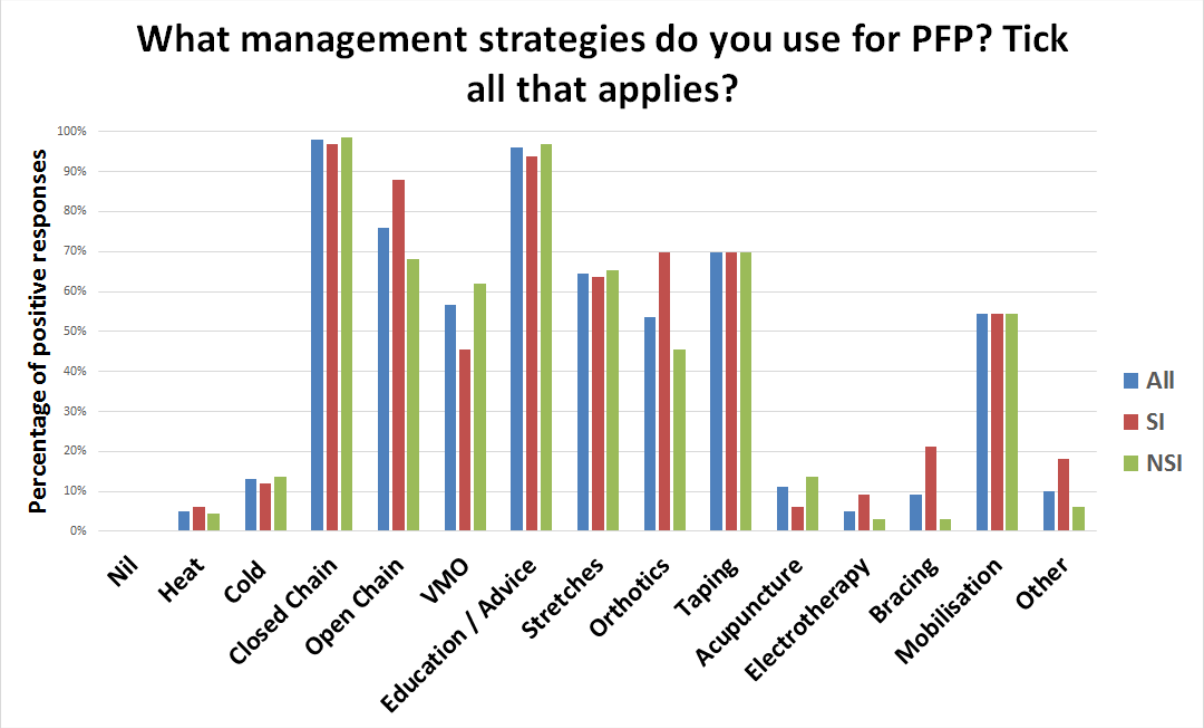

Figure 14 –What management strategies do you use for PFP? All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest.

3.3.3 Exercise Prescription

- *If you prescribe exercises, how many different exercises do you prescribe at any one time?*
- *If you prescribe exercises, how often do you ask them to be performed?*
- *If you prescribe exercises; how many total repetitions do you usually prescribe for an exercise?*

There was a wide variety in the total number of exercises prescribed, with physiotherapists offering between one and five exercises; with differing number of total repetitions. There was also a wide variety in how often the exercises were to be completed, from every other day up to more than twice a day. There was no significant difference between those with a special interest and those without (p>0.05).

- *If you prescribe exercises, do you encourage patients to continue if they were painful?*

A higher number of physiotherapists with a declared special interest in PFP responders reported that they would not encourage patients to continue if the exercises were painful (61% versus 52%) (Figure 15). This difference between physiotherapists with and without a special interest was not statistically significant ($\chi 2$=2.234 p=0.33). Thirty-two physiotherapists indicated “other”, and all 32 qualified their answers by completing the comment box. The criteria for continuing with the exercise differed among therapists, with some suggesting they would continue if the exercises were: less than a certain level

of pain measured, with answers ranging from 2/10 to 4/10; only moderately painful; acceptable to the patient; dependent on severity and irritability or that it would vary from patient to patient. No pain scale was offered, but all comments used the VAS 0 – 10.

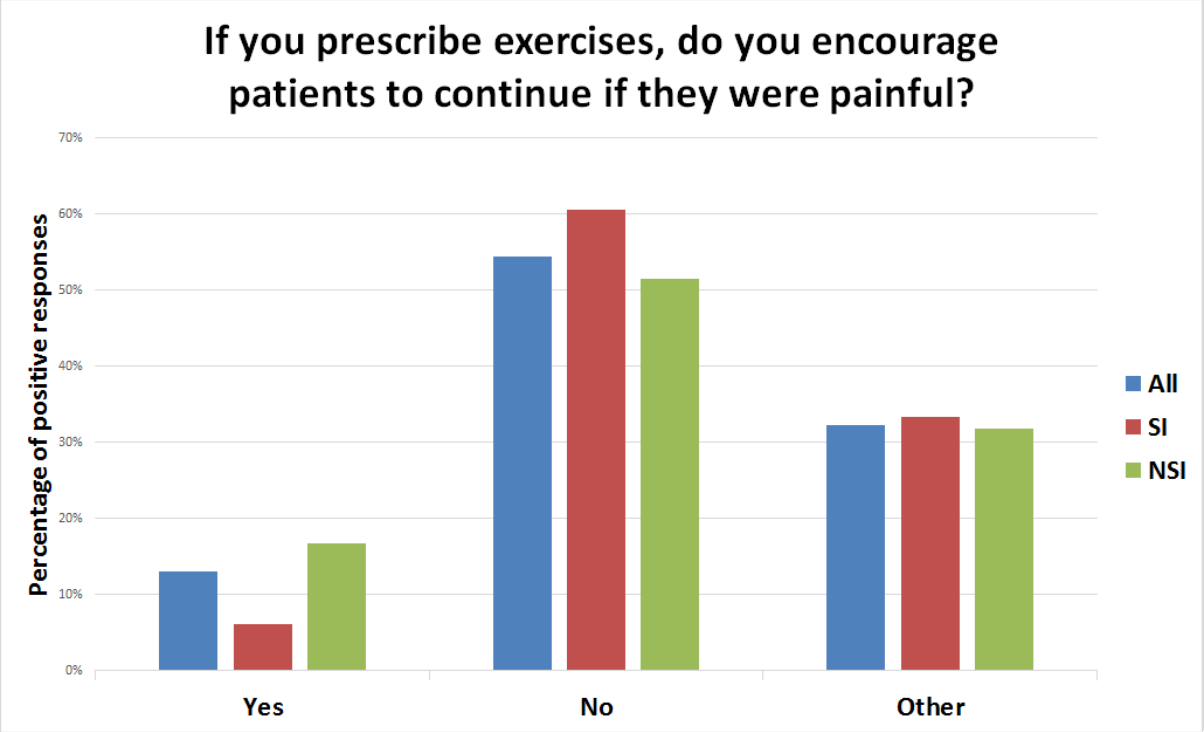

Figure 15 - If you prescribe exercises, do you encourage patients to continue if they were painful? All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest.

3.3.4 Advice on Sport and Leisure Activity

- *Do you encourage patients to continue with their recreational/sporting activities?*

The majority of UK physiotherapists (93.7%; 97% with a special interest; 93% without a special interest) in this study would only encourage patients to continue with leisure and sporting activity if it was pain-free, or if the pain was below a certain level (Figure 16). There was no significant difference between those with a special interest and those without ($\chi 2=2.153$ $p=0.71$). Forty-seven respondents qualified their answers in a variety of ways, suggesting they would encourage the patient to continue if: the pain was less than a certain level of pain measured on the VAS, with answers ranging from 2/10 to 6/10; whether the pain settled immediately; the pain settled within a few hours; the pain settled the same day; the pain settled within 24 hours; dependent on severity and irritability or that it would vary from patient to patient. No pain scale was offered, but all comments that used one used the VAS 0 – 10.

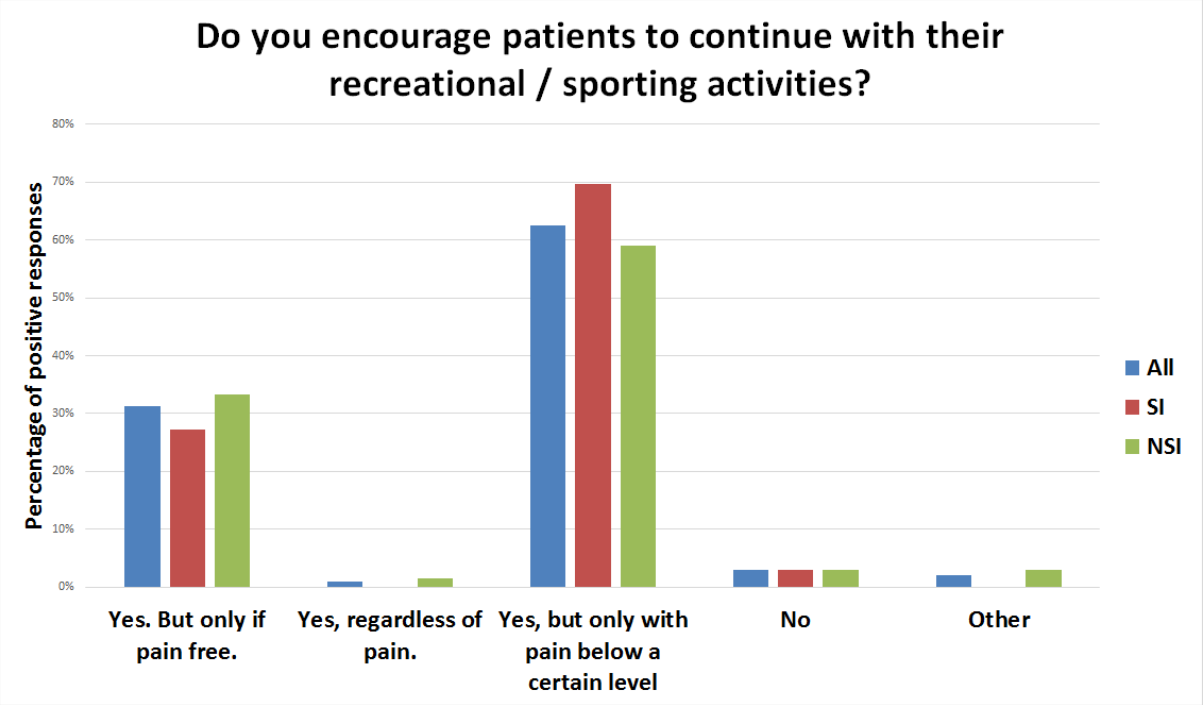

Figure 16 - Do you encourage patients to continue with their recreational/sporting activities? All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest.

3.3.5 Self-Management

- *Do you expect patients to self-manage?*

All 99 responders answered this question (Figure 17). There was no significant difference between physiotherapists with and without a special interest ($\chi 2=3.347$ $p=0.34$).

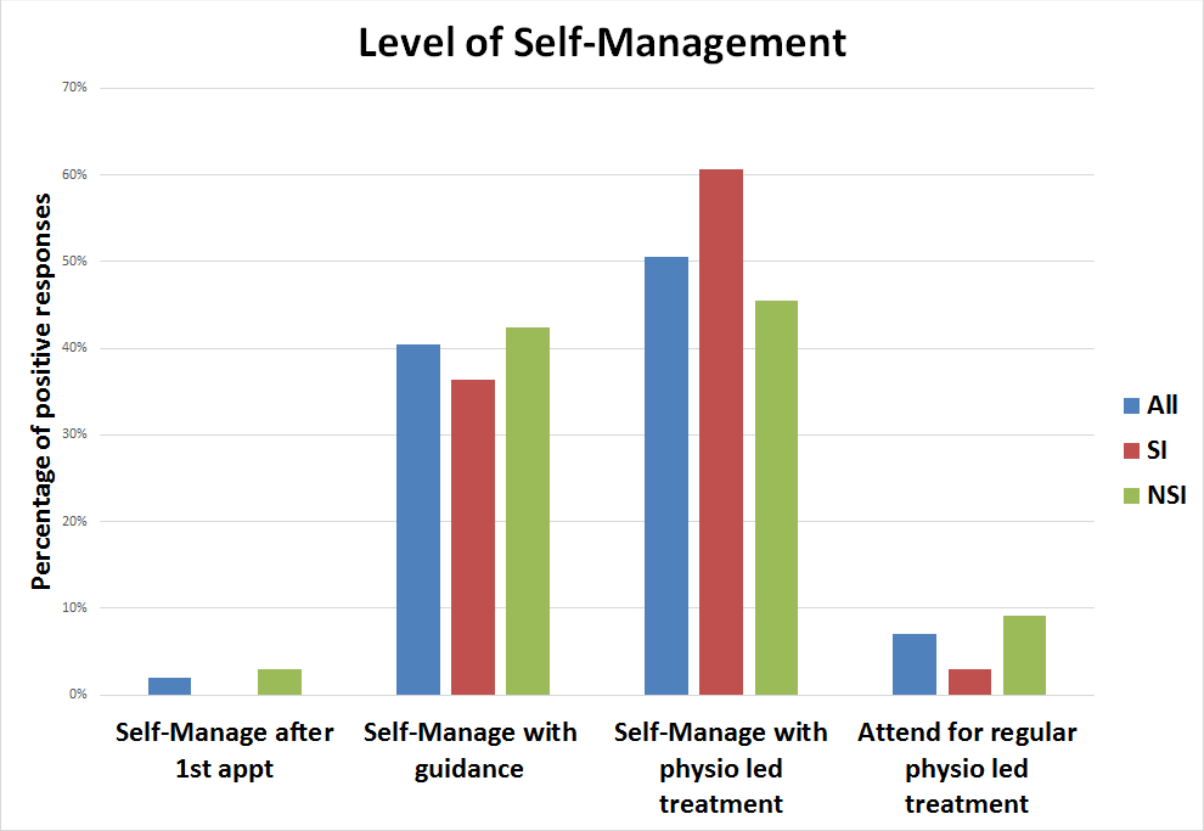

Figure 17 - Level of self-management. All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest.

Table 9 - Descriptive survey data (survey).

Respondent Characteristics								
		What is your primary role?						
n (%)		NHS Band 5	NHS Band 6	NHS Band 7	NHS Band 8a or above	Private	Sports	Educational / Researcher
All (*n = 99)*		8 (8.1)	28 (28.3)	15 (15.1)	9 (9.1)	27 (27.3)	6 (6.1)	6 (6.1)
SI (*n = 33)*		2 (6.1)	10 (30.3)	6 (18.3)	2 (6.1)	9 (27.3)	2 (6.1)	2 (6.1)
NSI (*n* = 66)		6 (9.1)	18 (27.3)	9 (13.6)	7 (10.6)	18 (27.3)	4 (6.1)	4 (6.1)
		How many times do you typically see patients with PFP?						
n (%)	Once	Twice	3 - 4	5 - 6	7 - 8	9 - 10	10 +	
All (*n = 99)*	1 (1.0)	3 (3.0)	53 (53.5)	31 (31.3)	5 (5.1)	1 (1.0)	5 (5.1)	
SI (*n = 33)*	0 (0)	0 (0)	17 (51.5)	9 (27.3)	3 (9.1)	1 (3.0)	3 (9.1)	
NSI (*n* = 66)	1 (1.5)	3 (4.5)	36 (54.5)	22 (33.3)	2 (3.0)	0 (0)	2 (3.0)	
		How long would you typically expect to see patients with PFP?						
n (%)		Over 3 weeks	Over 6 weeks	Over 9 weeks	Over 3 months	Over 6 months	Over 12 months	
All (*n = 99)*		12 (12.1)	31 (31.3)	22 (22.2)	29 (29.3)	5 (5.1)	0 (0)	
SI (*n = 33)*		4 (12.1)	10 (30.3)	6 (18.2)	12 (36.4)	1 (3.0)	0 (0)	
NSI (*n* = 66)		8 (12.1)	21 (31.8)	16 (24.2)	17 (25.8)	4 (6.1)	0 (0)	

Management Strategies

			What management strategies do you use for PFP? Tick all that applies?												
n (%)	Nil	Heat	Cold	Closed Chain	Open Chain	VMO	Education Advice	Stretches	Orthotics	Taping	Acupuncture	Electrotherapy	Bracing	Mobilisation	Other
All (*n = 99)*	0 (0)	5 (5.1)	13 (13.1)	97 (98.0)	75 (75.8)	56 (56.6)	95 (96.0)	64 (64.6)	53 (53.5)	69 (69.7)	11 (11.1)	5 (5.1)	9 (9.1)	54 (54.5)	10 (10.1)
SI (*n = 33)*	0 (0)	2 (6.1)	4 (12.1)	32 (97.0)	29 (87.9)*	15 (45.5)	31 (93.9)	21 (63.6)	23 (69.7)*	23 (69.7)	2 (6.1)	3 (9.1)	7 (21.2)*	18 (54.5)	6 (18.2)
NSI (*n* = 66)	0 (0)	3 (4.5)	9 (13.6)	65 (98.5)	45 (68.2)*	41 (62.1)	64 (97.0)	43 (65.2)	30 (45.5)*	46 (69.7)	9 (13.6)	2 (3.0)	2 (3.0)*	36 (54.5)	4 (6.1)

Exercise Prescription

	If you prescribe exercises, how many different exercises do you prescribe at any one time?			
n (%)	1	2 - 3	4 - 5	6 +
All (*n = 99)*	2 (2.0)	76 (76.8)	21 (21.2)	0 (0)
SI (*n = 33)*	0 (0)	29 (87.9)	4 (12.1)	0 (0)
NSI (*n* = 66)	2 (3.0)	47 (71.2)	17 (25.8)	0 (0)

	If you prescribe exercises, how often do you ask them to be performed?			
n (%)	Every other day, or less	Once a day	Twice a day	More than twice a day
All (*n = 99)*	15 (15.2)	34 (34.3)	34 (34.3)	16 (16.2)
SI (*n = 33)*	7 (21.2)	11 (33.3)	11 (33.3)	4 (12.1)
NSI (*n* = 66)	8 (12.1)	23 (34.8)	23 (34.8)	12 (18.2)

	If you prescribe exercises; how many total repetitions do you usually prescribe for an exercise?			
n (%)	Less than 30	30 – 50	50 +	Patient self-directed
All (*n = 99)*	52 (52.5)	19 (19.2)	3 (3.0)	25 (25.3)
SI (*n = 33)*	17 (51.5)	5 (15.2)	1 (3.0)	10 (30.3)
NSI (*n* = 66)	35 (53.0)	14 (21.2)	2 (3.0)	15 (22.7)

	If you prescribe exercises, do you encourage patients to continue if they were painful?		
n (%)	Yes	No	Other
All (*n = 99)*	13 (13.1)	54 (54.5)	32 (32.3)
SI (*n = 33)*	2 (6.1)	20 (60.6)	11 (33.3)
NSI (*n* = 66)	11 (16.7)	34 (51.5)	21 (31.8)

Advice on Sport and Leisure Activity

	Do you encourage patients to continue with their recreational / sporting activities?				
n (%)	Yes. But only if pain free.	Yes, regardless of pain.	Yes, but only with pain below a certain level	No	Other
All (*n = 99)*	31 (31.3)	1 (1.0)	62 (62.6)	3 (3.0)	2 (2.0)
SI (*n = 33)*	9 (27.3)	0 (0)	23 (69.7)	1 (3.0)	0 (0)
NSI (*n* = 66)	22 (33.3)	1 (1.5)	39 (59.1)	2 (3.0)	2 (3.0)

Self-Management				
	Do you expect patients to:			
n (%)	Self-Manage after 1st Appt'	Self-Manage with guidance	Self-Manage with physio led treatment	Attend for regular physio led treatment
All (*n = 99)*	2 (2.0)	40 (40.4)	50 (50.5)	7 (7.1)
SI (*n = 33)*	0 (0)	12 (36.4)	20 (60.6)	1 (3.0)
NSI (*n* = 66)	2 (3.0)	28 (42.4)	30 (45.5)	6 (9.1)

All values are reported as actual number of responders. Values in parenthesis indicate percentages.

All, all responders to the survey; SI, physiotherapists with a special interest; NSI, physiotherapists without a special interest; NHS, National Health Service;

*, statistically significant difference between physiotherapists with a special interest and physiotherapists without a special interest ($p < 0.05$)

3.3 Discussion

3.3.1 Summary of main findings

This chapter describes a sample of UK physiotherapists who treat PFP regarding their level of self-declared interest and setting. It identifies and quantifies the management strategies used, exercise prescription parameters and perceived likely treatment length. A total of 99 responses were gained from a broad sphere of UK physiotherapists, with variable experience and practice settings. There was no difference in the proportion of physiotherapists with or without a special interest in PFP across the different practice settings. The physiotherapists in this sample currently offer a wide variety of interventions; and provide a wide variety of education and advice in response to pain. The amount of variability in how physiotherapists treat PFP might in part reflect the lack of sufficient clinical guidelines, or the uncertainty and lack of sufficient Level 1 evidence on which to base practice.

In terms of management strategies and treatment options, the results indicate that advice/education and exercise seem to be the mainstay of treatment, with 100% of physiotherapists prescribing an exercise of some description, although the actual prescription parameters vary considerably; there was no consistency with regards to the number of different exercises prescribed, the total number of repetitions and how frequently they should be performed. A possible dissonance between research and practice are demonstrated concerning the passive interventions: taping, orthotics, bracing, and mobilisation, with a recent systematic review of systematic reviews highlighting no Level 1 evidence to support their use in the long-term [51]. However, respondents were not given the opportunity to specify if treatments were employed short-term or long-term. An observation from the results is that physiotherapists with a special interest in treating PFP are statistically more likely to manage patients with orthotics (70% versus 46%) and bracing (21% versus 3%) than physiotherapists without a special interest. The reason for this difference is unclear.

The named treatment options available for responders to select appear to cover most physiotherapists' usual practice, as only ten responders specified "other". Responses typically included variations of passive mobilisation treatment, such as; deep transverse friction, soft tissue massage, foam rolling and myofascial release. These can all be considered different variations of soft tissue massage [293], and as such lacks the Level 1 evidence to support their use [51].

Approximately 55% of physiotherapists within this sample would not prescribe an exercise if it was painful. This proportion is higher in physiotherapists with a special interest in PFP (61% versus 52%). Following a similar theme, 31% of the physiotherapists would advise patients not to continue with leisure or sporting activity if the patient experienced any pain. Many of the physiotherapists within this sample qualified their answers by completing an open text box and stating an upper level of pain they would remain comfortable with whilst encouraging the patient to continue with their exercise, leisure or sporting activity. A wide range of pain scores and phrases were offered, ranging from 2/10 to 4/10 VAS; only moderately painful; acceptable to the patient; dependent on severity and irritability or that it would "vary from patient to patient". This demonstrating a highly heterogeneous approach to exercise prescription. This belief on pain and exercise may predominate from the historical clinical reasoning model that labels one major cause of PFP as patella mal-tracking / malalignment [53]. As discussed in Chapters 1 and 2, the current thinking in relation to understanding chronic and persistent pain states, and the importance of patients' and therapists' attitudes and beliefs, challenges the view that patients should avoid painful activity [66,75,89,294]. This is an important element when considering: 23% of patients with PFP will stop participating in all physical activity because of their knee pain [42]. Physical inactivity accounts for one in six deaths in the UK [295] and costs an estimated 7.4 billion a year in England through direct costs of treating lifestyle-related disease and indirect costs of sickness absence [296].

The range of responses provided by the physiotherapists within this survey about the number of predicted appointments and length of treatment was diverse. Comparing these results to prognostic data within the literature, a systematic review and meta-analysis indicate that exercise interventions will improve pain on activity by 5.4mm to 23.9mm on a zero to 100mm VAS in the short term (≤ 12 weeks) when compared to no treatment. With a minimal clinically important difference of 13mm, this includes the possibility of a clinically important effect on pain in the short term [52]. At long-term (> 12 weeks) exercise interventions will improve pain on activity by 2.1mm to 19.3mm on a zero to 100mm VAS. Strikingly, pooled data indicate that exercise interventions over no treatment will result in only 88 more patients (95% CI two fewer to 210 more) per 1000 reporting a clinically important improvement in their pain in the long term (> 12 weeks) [52]. Contrast this with the two largest RCTs on adults, Van Linschoten et al. [26] and Collins et al. [202], it can be seen that between 51 to 81% of patients reported successful outcomes at 12-months follow-up (defined as "completely recovered or strongly improved" and "moderate or marked improvement" on a seven and five-point Likert scale respectively). The large variability in the answers provided to the survey seems to reflect the level of uncertainty of prognosis prediction within the literature [26,52,202].

The Best Practice Guidelines published in 2015 [51], and the recommended physical interventions from the 4th IPRR in 2015 [30], both recommend a multimodal individualised approach, and broadly, current UK practice is in line with these guidelines. Exercise therapy is endorsed as the main treatment, with the addition of taping and bracing in the short term, for pain relief [30,51]. However, the impact of these short-term treatments on long-term outcomes and psychological outcomes such as fear avoidance, self-efficacy and catastrophising are not yet understood.

3.3.2 Strengths and Limitations

In designing the survey and characterising the sample, it was decided not to collect demographic data such as age, sex and level of experience; with reference to past UK surveys, it was considered more meaningful to establish if participants had a self-declared special interest in treating patients with PFP [280,286].

The main aim of this chapter was to understand the management strategies used by UK physiotherapists for PFP. Other methods for gaining this knowledge could have included the use of focus groups, notes audits, paper surveys, or online survey with the addition of a case study vignette [280]. It is possible that the use of a vignette may have resulted in a different data set, as it is thought that they may clarify and explore attitudes and beliefs more fully [297].

For pragmatic reasons recruitment for this survey was open for six-months with the number of responders limited to 100; this is consistent with previous surveys of physiotherapy practice [280]. However, a larger sample size better representing the UK physiotherapy population may improve the generalisability of the results. It is worth noting though that a wide range of practice settings, including different levels of NHS banding were represented in the sample of 99 UK physiotherapists.

A strength of this study is that despite the survey being open for six-months, it reached its target of 100 responders within one day. It is unknown the number of physiotherapists recruited from each electronic mailshot; iCSP, twitter or email. Social media is a relatively new form of communication for professional networking and professional development [298], and it may be that the form of communication this survey used unfavourably biased recruitment towards typical “early adopters” of technology, biasing the results in favour of “early adopters” of health research. However, it is worth noting the wide range of management strategies and exercise prescription used by the sample of physiotherapists within this survey.

3.4 Conclusion and implications for this thesis

This chapter has described the current approach UK physiotherapists undertake in the management

of PFP. There appears no standardised method for treatment and management of PFP in the UK with respect to exercise prescription and therapists' response to pain during exercise and leisure activities. Responders in this survey stated they would undertake: a wide range of management strategies, including exercises prescriptions and dosage; differing degrees of education and advice with regards to continuing with leisure and sporting activity; and offer a broad prediction in physiotherapy appointment frequency and duration. This indicates that current UK practice in the management of PFP is widely variable. This variability might reflect the individualised treatment approach traditional physiotherapy assessments, and treatments used [53,54], or could also reflect the level of uncertainty and lack of sufficient Level 1 evidence on which to base practice.

Having now understood the prevalence of PFP, the evidence-base of pain and exercise, and the heterogeneous approach to management in the UK, this thesis now moves on consider how these elements are viewed by patients suffering from PFP, in a qualitative research methodology. It is thought qualitative research may enhance understanding of such a burdensome condition. For example, understanding detailed qualitative work exploring the rationale behind beliefs and attitudes to pain and exercise prescription may help advance future research into exercise interventions. Additionally, advocates of qualitative research methods suggest that qualitative inquiry can disclose the lived experience of people with pain and therefore be used to understand patients' motivation, social engagement and provide a wealth of information about the sociocultural context to pain [299,300]. To date, no qualitative body of work has been published on PFP. Qualitative inquiry can provide an insight that may lead to the development of ideas and hypothesis generation within the context of the contemporary biopsychosocial model of pain. This hypothesis could then be used to develop new conservative management approaches that could then be tested with efficacy and effectiveness trials.

The next chapter presents a qualitative method of enquiry on the experience of people living with PFP that will be used for hypothesis generation and refinement of the development of the intervention used in this thesis (Chapter 5).

Chapter 4 - Phase One: Qualitative Interviews

Summary

This chapter presents a qualitative method of inquiry on the experience of people living with patellofemoral pain, with a view of generating new knowledge that might explain, explore and understand PFP. This new knowledge was used to refine the intervention and feasibility study. This study is referred to as Phase One in the protocol, (Appendix C).

4.1 Introduction

The biopsychosocial model of persistent pain has recognised that psychological factors, such as fear and catastrophising can, through changes to behaviour, modulate physiological responses to pain with the development and maintenance of persistent pain [95,301–304]. Psychological distress has been identified in low back pain and tendon pain populations through systematic reviews [305,306], and qualitative methods in low back and shoulder populations [307–309]. Advocates of qualitative research methods suggest that qualitative inquiry can disclose the experience of people with pain, and therefore be used to understand patients' motivation, social engagement and provide a wealth of information about the sociocultural context to pain [299,300]. Contemporary models of persistent pain have identified the importance of thinking beyond muscles and joints [89], and qualitative inquiry can provide an insight that may lead to the development of ideas and hypothesis generation within the context of the biopsychosocial model of pain. No study using qualitative methods has been published regarding PFP. Therefore, this chapter aimed to give a more detailed account of the experience of people living with PFP, seeking secondary care within the UK, and explore beliefs and attitudes to pain and exercise, that will then be used to refine the new intervention (Chapter 5).

4.2 Method

To address gaps in the literature, this research focused on identifying themes within the participants' experience of living with PFP. A qualitative interpretive description design was chosen as an appropriate methodological approach [310]. Thematic analysis is the most appropriate method for this type of inquiry, as codes and themes can be created inductively to capture meaning and content without prior preconceptions allowing flexibility to generate a rich and detailed account of the data [311].

In this study, data were analysed thematically using the guidelines set out by Braun and Clarke [311] and was reported in line with the COnsolidated criteria for REporting Qualitative research (COREQ) checklist [312].

Braun and Clarke [311] describe a multi-stage approach to thematic data analysis; demonstrating clear distinction of the thematic approach, whilst allowing for the inherent flexibility in the process. They reasoned that a thematic analysis could be conducted from both realist and constructionist paradigms, although with differing outcomes. A realist approach allows theories about individual motivation and meaning to be developed since the epistemological position is that there is a unidirectional relationship between meaning, experience and language [311]. A constructionist perspective differs, as meaning and experience are socially produced and knowledge a human and social construct; therefore theories about individual motivation and meaning are inappropriate, and theories focus instead on sociocultural contexts [311]. This chapter did not set out to prove or disprove a hypothesis; it set out to generate new data from which an understanding of living with PFP might be developed. An epistemological position was taken that recognises the experience at an individual level, and any meanings attached, whilst considering the broader context within a sociocultural perspective. Sitting central on the spectrum of realism and constructivism, this position is described as "contextualist" by Braun and Clarke [311].

4.2.1 Recruitment

A convenience sample of ten participants with a diagnosis of PFP were recruited from an NHS physiotherapy waiting list. Based on similar studies of other MSK conditions, it was anticipated this sample size would be sufficient to reach data saturation and was agreed *a priori* [309,313]. Participants were initially contacted by mail and followed up by a telephone call (BES). Thirty-four information sheets were sent out, and 24 potential participants were contacted by telephone; two could not make the interview before physiotherapy was due to start; for five people physiotherapy had already commenced; one person reported resolution of symptoms, and six people declined to participate. Inclusion criteria were participants aged 18 to 40 with signs and symptoms of PFP, defined as anterior or retro-patella pain reported on at least two of the following activities; prolonged sitting, ascending or descending stairs, squatting, jumping and running [2]. These were pre-screened during an initial telephone conversation. Exclusion criteria included: previous knee surgery; awaiting lower limb surgery; knee ligamentous instability; history of patella dislocation; true knee locking or giving way; reasons to suspect systemic pathology or acute illness; pregnancy or breastfeeding; patellar or iliotibial tract tendinopathy, and those not able to speak or understand English. The exclusion criteria were screened before consent being taken (BES).

4.2.2 Data Collection

Participants were offered interviews at their home, or in a hospital-based physiotherapy department; all opted to be interviewed at the hospital. On arrival, the researcher (BES) introduced himself as a physiotherapist working in that department, and also a researcher conducting a PhD. The researcher explained the aims of the study. Written consent and verbal consent were taken to start recording.

With reference to previous literature on low back pain, shoulder pain and tendon pain [307–309], semi-structured interviews were designed by the researchers using a topic guideline with prompts to explore participants' experience of: living with PFP; past healthcare management; their interpretation of causation of their pain; beliefs, attitudes and behaviour in relation to their pain and expectations for the future. The semi-structured interviews allowed for a flexible interview, in a two-way conversation, allowing new ideas to be developed as they were brought up [314].

The researcher also maintained a reflective journal, noting down initial thoughts and ideas after each interview [309]. This identified that early interviews raised issues about other (past and present) MSK pain, and specific coping strategies employed by participants for their PFP. These were therefore incorporated into subsequent interview schedules.

4.2.3 Data Analysis

All audio files were collected and transcribed verbatim (BES). During transcription, initial thoughts and ideas were noted in the reflective journal. Audio files were listened to several times to check for accuracy, and transcriptions were read and re-read a number of times; this initial process of data familiarisation allowed for "data immersion" by the researchers, and generation of preliminary ideas [311]. Data coding then identified and coded relevant features of the data giving equal priority over the whole dataset. These steps were independently conducted by two researchers (BES & FM) who met to compare codes and develop agreement on the grouping of codes into themes. The generated themes were reviewed and refined, ensuring that they explained the data in relation to the coded data, and the whole dataset. The researchers then consulted on the final two stages; themes and sub-themes were named and defined to demonstrate a clear narrative, using compelling extracts as illustrations. Consideration was given to each theme individually, but also to how they related to the dataset as a whole and other themes [311].

Data were organised and analysed using QSR International's NVivo 11. After ten interviews, it was determined by the researchers that data saturation had occurred as no new thoughts or concepts were generated in the later interviews.

4.3 Results

Participants ranged from 26 to 37 years of age (mean age 30.6), with a diagnosis of PFP for a mean duration of 78 months (range: 3 months to 16 years). For participants' characteristics see Table 10. The interviews ranged from 13 to 43 minutes (mean time: 27 minutes).

Table 10 - Characteristics of participants (qualitative interviews phase 1).

Participant Number	Gender	Age	Duration of symptoms (m)	Type of Employment
1	F	26	60	Healthcare Worker
2	M	33	60	Builder
3	M	37	8	Office worker
4	F	26	192	Healthcare Worker
5	F	34	36	Office worker
6	F	27	84	Waitress
7	F	28	120	Technician
8	M	29	36	Office worker
9	F	36	3	Office worker
10	F	30	180	Office worker

F, female; M, male; m, months

The first theme that emerged from the data, impact on self, describes the participants' sense of loss, with respect to their self and self-identity. The further themes that emerged describe how the participants deal with this loss in a climate of uncertainty, how they understand or make decisions regarding exercise/activity and pain management, and how they prognosticate for the future. Data are presented to demonstrate the range and meaning to each theme.

4.3.1 Theme 1: impact on self

Participants offered rich and detailed accounts of the impact and lived experience of PFP. Loss of self and loss of self-identity was evident in the stories told by many of the participants in this study. Self and self-identity are different concepts about ways in which individuals evaluate and interpret themselves; they are nested elements that are shaped by the contexts of individual's lives, with direct influence on decisions and behaviours [315]. Self, in its broader sense, can be defined as one's individuality and process of making sense of the world around them; it is a cognitive structure that defines one's sense of worth [316]. Self-identity, however, is the cognitive structure of internalised meanings and expectations associated with one's position and role within a social network [317].

Loss emerged as a continuous sub-theme, and descriptions of the negative effect on their lives were broad and far-reaching. Symptoms affected all participants' daily life, with pain being a pervasive and

disruptive feature of their day, with resulting loss of physical ability:

> *"I struggle at work, bending down to get bottom shelf and getting back up, I literally have to hold onto the table to pull myself up. I can't do it off just my knees." [P7].*

> *"Yeah, well, it's a pain really because I'm walking around. I'm very stiff with that leg. Going up the stairs, down the stairs at work, getting out of a chair, getting into the car." [P6].*

Several participants described the negative impact of PFP on their mental well-being, with subsequent loss of self-identity:

> *"I would say the reason I got my horse was because I have mental health problems and so having a horse is my routine, structure, thing that I look forward to doing — the positive in my life. And having the knee problem makes that, makes that, not so effective. You can't do, what I imagined I would be able to do." [P4].*

Physical activity has been identified as a key quality of life domain, and the one most affected among patients with persistent pain [318]. Loss of activities for these participants included: walking; exercise; driving; holidays; time with family and friends; playing with children; duties at work and kneeling. This loss of activities directly affected participants' role and position within their social network, triggering feelings of loss of self-identity. For example, some participants explained how PFP affected their work and made them question their career aspirations:

> *"I would say, it makes me like wonder, if I can do the job, not at this point but maybe when I get older and older, maybe I won't be able to do it". [P4].*

Judgemental attitudes from colleagues, friends or family, were described by a number of participants, with subsequent feelings of loss of self-identity, acting as moderators to low moods and feelings of premature ageing:

> *"They're saying that I'm a grandma. They say, 'Yeah. If you were a horse, they'd put you down (laughter). Just joking me, but obviously, it has affected me in the way that I've had to go out of work to go over to get physio. And I have had this time off, so I don't know if they're a bit, 'Well, it's not that bad.' Because day-to-day I try to be as normal as I can." [P9].*

> *"The guys at work kind of joke about it, 'you're breaking down'" [P8].*

Loss of significant relationships has emerged as a key aspect of loss in previous studies of patients with persistent pain [319–321]; and disruption to important and meaningful relationships was a strong and

common theme found in patients with PFP. For example:

> *"I've missed out of things over the years, spending time with friends, spending time with family and that kind of thing, because I've not been able to do it." [P6].*

As identified by the above extracts, PFP had a compelling and far-reaching impact on the participants and their lives. The pain and its disruption to life; loss of self-identify; and loss of relationships were themes that emerged from the data.

4.3.2 Theme 2: uncertainty, confusion and sense-making

Confusion and sense-making formed a central part in the lives of the participants, with a strong desire from all to elucidate the cause of their pain.

> *"If I could find out what it was that was causing the pain, then you hope it would be gone within a year. But because we don't really know what's caused it, it's kinda trial and error. So I don't really know." [P1].*

The predominant focus of the participants' beliefs and attempts at making sense of their pain was that biomechanical factors were causative, with individuals trying to link these factors to the development and maintenance of their pain.

> *"My running technique or, I'm not sure. I'm not sure about that. I'm not sure. I think that's one thing, maybe something to do with the running technique, or something, or something to do with that." [P8].*

Furthermore, confusion was also related to the episodic nature of the symptoms, with participants attempting to relate "flare-ups" to the same biomedical factors.

A number of participants told stories of structural and biomedical beliefs becoming deep-rooted and established when reinforced. For example, one participant recounted multiple encounters with healthcare practitioners that influenced and reinforced her structural belief.

> *"The work physio guy said to me that he thinks that my heels have maybe gone in which has then pulled my kneecap out of alignment. So instead of going smoothly over the joint where it's supposed to, that it's probably moving over the bone and that's the sharp pain that I'm feeling. Which did make sense because it, like I said, felt like I'd got a rock underneath my kneecap at some stage." [P9].*

Some participants remembered biomechanical focused diagnoses they had been given by a healthcare practitioner they had seen many years in the past; highlighting the power and lasting influence healthcare practitioners have on their patients. For example, one participant remembered the diagnosis she had received from a healthcare practitioner over ten years ago:

> *"I had to go to the hospital once to have x-rays… I don't know if he [doctor] was trying to scare me into doing some exercise or something, but he basically said the only thing they could do is break both of my thighs and twist them a bit and then heal them back together. And it would take me years to get back to walking properly." [P4].*

Joint noises are a common feature of normal joint movement [309]; however, participants commonly reported distress and confusion at joint noises, often finding healthcare practitioners' explanations inadequate.

> *"It was the noise that was concerning me more than the pain. I'm used to hurting. I'm too small to play rugby for a start, and I'd been fighting for 20 years, so, erm, it's one of those, you get used to the pain, but it's just the noise. When you start, you sort of [say] no, that's not right." [P3].*

This was in agreement with previous research, which identified negative emotions and inaccurate etiological beliefs with joint noises in patients with PFP [322].

Expressly linked to participants' confusion and need to find the cause of their pain was also a strong desire to pursue radiological imaging and feelings of not being taken fully seriously by the healthcare profession when this was not forthcoming.

> *"I want to know exactly what the problem is. Obviously, the doctor said, previously going back, they said tendonitis, and now they're saying it's runner's knee or whatever. But you know, it's still like, is that 100%, are you sure that's what it is? Because I was going to ask the doctor to send me for an MRI..." [P8].*

> *I thought I was going to have to get sent for a scan or something. Because I thought something was underneath my knee. So I thought that I've got a tumour... I still think that now." [P9].*

Previous research has linked poor outcomes with radiological imaging in populations with low back pain, suggesting overuse of imaging has a detrimental effect on outcomes [323]. There was one example of the resulting radiological findings compounding the confusion and distrust, for example,

Participant Six explained her feelings on a normal MRI finding as:

> *"I mean I was a bit concerned because they didn't turn around and say, you have hurt it, but it's not major but this is what you've done, but they didn't actually, they said nothing's wrong, take the knee brace off, and carry on. [I was] almost deflated because I was like wanting to know why it was hurting, but they weren't explaining any of that to me. So it's a bit like, difficult." [P6].*

Another participant's story demonstrates the negative impact of discordance between healthcare practitioners' diagnosis and advice, further compounding confusion and mistrust:

> *"Well, it makes you wonder then which one to believe, because I'm like, 'Well okay, he's told me not to do anything until I'm pain-free, because he doesn't want me to aggravate it,' but when, when I came here, and obviously they said that it would probably be best to start putting an impact on it again … " [P9].*

The sense-making processes that participants described were established from past experience of healthcare treatment, past experience of pain and cultural beliefs around structure and pain.

4.3.3 Theme 3: exercise and activity beliefs

All participants identified specific beliefs regarding barriers to exercise and activity. These were informed by factors relating to diagnosis uncertainty; cultural beliefs around pain; fear-avoidant behaviours and the iatrogenic effect of healthcare.

Diagnosis uncertainty contributed to participants' beliefs regarding exercise and activity. In particular, it underpinned a dilemma regarding the relationship between activity and potential harm:

> *"It's 'are you making it worse?' And that's the crux of it really. As I'm doing it and thinking, 'if this is hurting, should I really be doing this, or shall I pack this in and do something else?' But it's the not knowing …" [P5].*

Cultural beliefs around pain being a direct sign of tissue damage was evident in a large proportion of the participants' narratives, resulting in negative behaviour towards exercise and activity.

> *"…with me it's always been if something hurt it because your body's telling you if you do that you're going to cause more injury. You'll make things worse." [P6].*

Associated with the cultural beliefs on pain and damage was the resultant fear-avoidant behaviour.

Participants frequently contradicted themselves, however; many participants would express the sentiment that they would not let the pain stop them from doing what they wanted to do, yet demonstrated clear activity withdrawal.

> *"So for example, we went to [holiday resort] last year; on your feet all day, walking miles and miles, I would be, like, in tears by the end of the day. I wouldn't let it stop me the next day because I would be, like, I'm doing this" [P4].*

> *"When I was in [holiday resort]; a couple of days I didn't go out, and I stayed back at the hotel. Because I couldn't do it, I needed to rest." [P4].*

A predominant sub-theme was the association of sport and exercise, even in the absence of pain, as a potential precursor to future joint pain and "damage". Some participants attributed their current PFP to past sporting activities, despite no apparent mechanisms of injury.

> *"Yeah. Obviously, it stems from doing long distance running." [P7].*

> "Another reason why I probably think this happens is because I've been very active from a very young age. Talking from the age of like eight or nine I've been involved in sports: football and cricket and badminton and whatever. I've just been all my life. And I didn't always see that as catching up with me, where that excessive amount of playing sports is having an effect on my body. [It's] going to start affecting [me] and I'm feeling it these days as I get older." [P8].

Some participants discussed the direct impact of healthcare practitioner's advice and diagnosis labelling on their exercise and activity levels, suggesting an iatrogenic effect of healthcare for PFP patients.

> *"I have been told by doctors before I shouldn't run because it would jar my knee and shouldn't run or walk on an uneven surface because it will wonk my knee from side to side." [P4].*

> *"But then when I started the physio at work and he told me that I shouldn't walk or that I shouldn't swim because he just wanted to obviously manipulate it and get me pain-free before I did anything that could possibly aggravate it. So I stopped." [P9].*

This theme identified a number of beliefs associated as a barrier to activity and exercise engagement. These included diagnosis uncertainty, cultural beliefs around pain, fear-avoidant behaviours, and the iatrogenic effect of healthcare.

4.3.4 Theme 4: behavioural coping strategies

A central coping strategy for participants of this study was the concept of rest. Many of them associated rest, and avoidance of activity, with the idea that time was necessary for the healing process, and that aggravating activities should be avoided.

> *"I don't do running. I try not to do the bike." [P2].*

> *"I try, obviously, sit down as much as I can." [P4].*

One participant expressed an expectation that healthcare professionals would advise him not to continue with activity and exercise:

> ***Researcher:*** *So you think physios would say no [to keep physically active]?*

> ***P8:*** *Physios would probably say no. Yeah, you shouldn't do it.*

Another common coping strategy was postural adjustments; participants often talked of preferred sitting positions in relation to knee flexion.

In keeping with previous research on the high levels of analgesic use in patients with PFP [47], a familiar narrative shared with participants was the use of analgesics, with some acknowledging they were not effective.

> *"I have had some strong painkillers from the doctors. They gave me some naproxen and some codeine to manage it when it was at its worst, but I try not to take them." [P9].*

The use of knee supports was also common in the self-management strategies employed by the participants.

> *"If it hurts, it hurts. I'll try and strap my knee up. Because if I know, I'm going harder in like gym classes, I'll strap my knees up before I go. And then when I get too much pain, I'll stop the exercise." [P10].*

4.3.5 Theme 5: expectations of the future

A number of participants expressed views, which could be contextualised as an external locus of control, with expectations of passive physiotherapeutic treatment options.

> *"I would presume manipulation of muscles groups, joints and tendons." [P3].*

Even though the majority of participants expressed negative views about the future, they all expressed

a desire to be pain-free, over and above any functional improvements.

R: *With the physio, what would you class as a success?*

P8: *Getting rid of the pain.*

Nine of the ten participants held negative beliefs about the future; particularly about prognostic prediction following their referral to physiotherapy.

"But then when I'm going up the stairs, and it hurts it does concern me that it's going to be every day for the rest of my life I'm going to be struggling to walk upstairs. And then I think about getting old, and I think I'm going to end up with a stair lift and living downstairs and that sort of thing." [P1].

" [the pain is] definitely preying on my mind. Is it gonna stop me from going into the police, is that gonna stop me doing the things I want to do later on in life? So yeah, it does prey on my mind a little bit." [P6].

Central to their negative beliefs about the future and their prognosis was low self-efficacy. Participants felt they had very little control over their symptoms.

"[In] my head, my thought process is I just hate it. Do an operation. Get rid of it. In my head, and obviously not being from the medical profession, but I'm just like, "Just get rid of the pain however it can be done." [P8].

"Yes, I'm 37 now, and they feel older than that. You just get that feeling, don't you, I've bounced back from lots of injuries before, but this is the one that is making me think. You know, when this gets cold I can feel it and thinking there's already arthritis there, I'm in trouble, it sets the brain going." [P3].

Low expectation of physiotherapy and past physiotherapy failed treatments were also a core theme within future expectations.

R: *Have you got any expectations of what might happen when you walk in to see the physio?*

P10: *I expect them to turn around and say physio can't help.*

"When I did get the physiotherapy it kinda didn't really do anything anyway. So it just made me think, it's pointless, 'cause they was trying to remove the fluid from out my knee, that like I say, made it worse, to begin with. She did say your knees will feel sore, but it went back to

how it was anyway, so, it just seemed like a pointless process." [P7].

There was one exception, with one participant having a positive outlook to the future and their physiotherapy referral.

"*Oh yeah, I think it will get better. Yeah, I'd go for the better option." [P9].*

The main sub-themes that emerged under the future were: beliefs that their pain will get worse; external locus of control with regards to treatment; low self-efficacy; poor opinion of physiotherapy and previous failed physiotherapy treatments and an overwhelming desire to be pain-free, over and above any practical goals for rehabilitation.

4.4 Discussion

4.4.1 Main Findings

Quantitative research methodologies dominate the literature for PFP. This chapter is the first study to use a qualitative method of inquiry to gain data on the experiences of people living with PFP. The five major themes that emerged from the data were: (1) impact on self; (2) uncertainty, confusion and sense-making; (3) exercise and activity beliefs; (4) behavioural coping strategies and (5) expectations of the future.

A key finding of this study is that loss of physical ability is profound and considerable, and plays a significant role in participants' lives; despite previous research suggesting that PFP is a benign and self-limiting condition [204]. An inability to continue with significant and meaningful activities has been identified as a cause of anxiety in people with persistent pain [324]. Persistent pain interrupts behaviour and a person's self-identity by affecting a sense of who they are, and what they might become [325]. As a result, lives are socially and environmentally restricted by persistent interruptions, or an inability to complete, or even attempt important tasks and activities [325]. With changes and loss of participants' position and role, for example with employment or family duties, the internalised meanings and expectations associated with one's self-identity is further threatened [317].

Participants expressed intense confusion around their pain and symptoms. For instance, the causative reasons were elusive and troubling, as too was the ability to predict and control the pain intensity; and any attempts that participants made at understanding were firmly within the biomechanical sphere of reasoning. An inability to make sense of pain and the process associated with sense-making and pain-related fear has been proposed in low back pain populations [326]. Previous research has identified that an inability to make sense of pain places "lives on hold" [327], and may lead to more

"catastrophising" [328].

As discussed in previous chapters, there remains scientific debate and uncertainty around the underlying aetiology of PFP [49], and there is a considerable variation in the way PFP is managed by physiotherapists in the UK (Chapter 3) [281]. The majority of participants in this study had previous experience of healthcare management for PFP suggesting that variation in healthcare treatment may have a negative impact on the patients' lived experience. Participants characteristically attributed their pain to structure or anatomical problems, in a similar way historically biomedical models of pain do [63]. Three participants had no previous healthcare management for PFP, but nevertheless gave a biomechanical/structural cause for their pain; all three had previous physiotherapy for other pain conditions, including back, hips and ankles. This may suggest that exposure to biomechanical approaches to the management of MSK pain, in general, could, potentially, have a carryover to other locations of pain, with a negative effect.

The iatrogenic effect of healthcare is an emerging field of research in the low back pain population [323,329]. This study is the first to find such a theme in patients with PFP. These findings are consistent with the research findings from Chapter 3 that showed that the majority of UK physiotherapists would not encourage their patient to continue with exercises if they experienced any pain [281]. The fear-avoidance model of pain is a well-established with patients with persistent pain, particularly persistent low back pain [304]; additionally, research has shown that fear-avoidance behaviour may also exist with clinicians [89,280,281]. The central concept of the model is cognitions and emotions that underpin fear of the pain; with fears about potential physical activities exacerbating the pain and further "damaging" bodies. The fear leads to safety seeking behaviours and hypervigilance that paradoxically maintains or exacerbates the pain and disability [309].

In contrast, if pain is perceived in a non-threatening way patients are likely to sustain physical activity levels, through which recovery can be achieved [330,331]. All of the ten participants in this study described fear-avoidant behaviour at some stage of their interview. This chapter is the first known study that identifies this behaviour in patients with a diagnosis of PFP.

PFP is often described as an "overuse" injury [62], and these data seem to be consistent with the patients' belief and behaviour with a definition more aligned with the English language meaning of "overuse". Research in relation to epidemiology and population groups that may be at risk of PFP (Chapter 2, part one) challenges the idea that PFP is simply an "overuse" injury, with evidence suggesting that persistent and long-term under-use may be a risk factor, with consistent exposure to tissue load being considered one method of management [195]. The fear-avoidant behaviours

revealed within this study would, therefore, be seen as negative pain behaviour, with long-term detrimental consequences.

A key finding of this research is the low expectation for the future and low self-efficacy demonstrated by the majority of the participants that could be conceptualised as "catastrophising". Catastrophising is conceptually within the same model of pain behaviour as fear-avoidance, with largescale overlap [306]. Low self-efficacy, fear of the future and catastrophising is a common finding in patients with persistent pain [300,332]. The National Institute of Health and Care Excellence describes pain as a complex biopsychosocial issue, associated with expectations, self-efficacy, mood and coping abilities [86]. In addition, it has been shown that self-efficacy is a strong predictor of successful outcome, irrespective of the intervention delivered, for patients with persistent pain; suggesting that rehabilitation programmes for persistent MSK pain should be designed with the aim of improving self-efficacy [87].

4.4.2 Study limitations and strengths

Two authors independently coded all transcripts, and this study employed a clear, transparent and reproducible methodological approach to data analysis. The authors make it clear that their clinical and research experience lie within the biopsychosocial framework of MSK pain and this study forms part of a larger body of research investigating pain education, self-management strategies and exercise interventions for individuals with PFP [333]. It is worth noting that the interviewer made it explicit to the participants that he was a physiotherapist working in the department conducting the research; a number of them did proceed to ask clinical questions about their condition, highlighting a power dynamic between the interviewer and participant. Furthermore, it is important to note that recruitment took place in the same department that the researcher was working as a physiotherapist. This may, in part, have influenced participants' inclination to take part, and also their responses.

The main limitation of this study is that for pragmatic reasons a convenience sampling technique was used. It is possible that this sample may differ from other samples within the UK, and how representative these findings are to the greater population of individuals with PFP is unknown. A purposive sampling technique may have better represented sociodemographic groups or targeted identifiable subgroups. However, it is worth noting that the sample in this study had a good representation of male and females, and included a variety of ethnic groups; additionally, population age, gender and duration of symptoms were similar to larger NHS based studies on PFP [74]; it is, therefore, questionable how different the data would be.

4.4.3 Implications for this thesis

This study established that a sample of patients with PFP demonstrated: pain-related fear, such as fear-avoidance; damage beliefs; difficulty with making sense of their pain; low self-efficacy and fear of the future.

The current consensus that best evidence treatments consisting of hip and knee strengthening may not be adequate to address the fears and beliefs identified in the current study. Future studies are needed to explore biopsychosocial targeted interventions for this population, particularly with regards to pain experienced by patients during exercise, followed by efficacy and effectiveness trials. Interventions may be patient education packages and self-management strategies targeting self-efficacy and physical activity. Furthermore, future qualitative work will be beneficial to understand the role of medical terminology commonly used with this patient group, for example, “weakness” and “patella mal-tracking” [281], and its impact and interpretation by patients.

4.5 Conclusion

These findings offer an insight into the experience of individuals living with PFP. Previous literature has focused on pain and biomechanics, rather than the individual experience, attached meanings and any wider context within a sociocultural perspective. The participants provided rich and detailed narratives of loss of physical and functional ability; loss of self-identity; pain related confusion and difficulty making sense of their pain; pain-related fear, including fear-avoidance and “damage” beliefs; inappropriate coping strategies and fear of the future. The findings suggest future research is warranted into biopsychosocial targeted interventions, such as exercise programmes designed to load and temporarily aggravate patients’ symptoms, pain education programmes and self-management strategies around exercise and physical activity.

Thus far, the thesis has argued that traditional pain models that describe tissue pathology as a source of nociceptive input directly linked with pain expression, have been insufficient for assessing and treating MSK pain. The next chapter will build towards the development of the intervention and further describes the understanding on potential mechanisms behind usual care exercise (pain-free) and builds on this by discussing the additional theoretical mechanisms of painful exercises. This includes three systems that appear to respond differently to painful stimulus: central and peripheral pain mechanisms, the immune system and affective aspects of pain.

Chapter 5 - Development of the Intervention
Part one: musculoskeletal pain and exercise - challenging existing paradigms and introducing new

Summary

Traditional pain models that describe tissue pathology as a source of nociceptive input directly linked with pain expression have been insufficient for assessing and treating musculoskeletal pain. The aim of this chapter section is to provide an understanding on the potential mechanisms behind therapeutic exercise, and to build on this into discussing the additional theoretical mechanisms of painful exercises, that informed the design of the exercise intervention.

5.1 Introduction

Exercise interventions are the cornerstone of management for MSK pain conditions [334], with demonstrated effectiveness in low back pain [215,221,223]; whiplash associated disorder [217,335]; osteoarthritis [86]; knee pain [52]; and shoulder pain [284]. The benefits of exercise are well-established [334,336], with positive effects on pain and physical function. Despite this strong evidence, the exact mechanisms underpinning this effect on MSK pain are currently unclear [337]. The question is not if people with chronic pain should exercise, but how should they exercise. Little is known on the optimal dose and type of exercise, with therapists' and patients' behaviour and beliefs around pain during exercise often overlooked in exercise prescription. Treatments may be promising, but effect sizes remain small to modest, with large variability of results [215,221–223]. New perspectives are needed; there is little or no consensus on how physical interventions should be delivered.

The need for pain to be avoided or alleviated as much as possible has been challenged, with a paradigm shift from traditional biomedical models of pain towards a biopsychosocial model of pain, which is particularly relevant in the context of performing therapeutic exercise (Chapter 1). For example, the systematic review and meta-analysis of painful exercises versus pain free exercises for chronic MSK pain in Chapter 2, part two found that protocols using painful exercises offered a small, but statistically significant, benefit over pain-free exercises in the short-term with moderate quality of

evidence (SMD −0.27; 95% CI −0.54 to −0.05) [338]. Exercise interventions for chronic MSK pain have demonstrated a "dose-response" to exercise, in the limited research that has been undertaken to date; characteristically, the more exercise the patient does, the better their pain and function in the long term [28,120,284,338,339]. A key aspect of the painful exercise protocols compared to pain-free was the difference in load and resistance in the exercise protocols; typically they were higher intensity exercises, and thus were higher dosages [338].

Understanding the potential mechanisms behind the effects of therapeutic exercise, in the context of factors associated with chronic MSK pain, is key to optimising current exercise prescriptions for managing MSK pain. This chapter provides an overview of the current understanding of MSK pain in relation to central and peripheral pain mechanisms, the immune system and affective aspects of pain. These systems appear to respond differently to a painful stimulus, compared with a non-painful stimulus [340–343]; and are discussed in relation to the biological effect of exercise for people with chronic pain, with a broader overview of possible central and peripheral mechanisms behind the potentially additional beneficial effect of painful exercises over pain free exercises for individuals with chronic MSK pain.

5.2 Brief background into the current understanding of chronic pain

This chapter section will begin with a critique of the historical biomedical model of pain, followed by a discussion on the contemporary understanding of pain. This current understanding is based on factors relating to pain mechanisms, the immune system and affective aspects of pain.

5.2.1 The biopsychosocial model of pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [344]. The traditional biomedical view of pain further summarises that: 1) pain is viewed as a symptom and warning sign, the function of which is to avert the person from harm; 2) it provides a pivotal role in identifying underlying pathology; 3) ethically, medical and rehabilitation practice should aim to avoid or alleviate pain as much as possible [344,345].

This model typically attributes the sensing of harmful stimuli to nociception and fails to distinguish between the sensation and perception of pain. Pain was thought to be conveyed to the brain directly from the nociceptors [346], which, as previously defined in Chapter 1, are specialised primary sensory neurons situated in various body tissues, such as skin, muscles and tendons, which are involved in the transduction and transmission of information from the periphery to the central nervous system

[91,92].

The biomedical model is frequently attributed to the dualistic philosophy of René Descartes (1596 – 1650) [345]. Referred to as "mind-body dualism", it was a philosophical viewpoint that the mind and body were two separate distinctions. The body was thought to work like a machine, whereas the brain was considered the soul, not conforming to the laws of natural science. It initiated a paradigm of medical practice by which the body was considered a machine that had "broken down"; Descartes describes pain as functioning "to indicate to the soul the bodily damage suffered" [345]. However, this orientation of medical practice neglects to consider important psychosocial factors in health and illness [345].

More recently, knowledge surrounding pain and pain mechanisms has expanded beyond this. For example, Melzack and Wall's (1965) gate-control model proposed that pain signals could be modulated in the spinal cord and brain creating a feedback system [347]. The biopsychosocial model of pain developed further in the 1980s, partly in response to Melzack and Wall's seminal paper, but also in response to inconsistent treatment outcomes in chronic MSK conditions [345], and due to innovative non-harmful noxious stimuli in vivo experiments, that cast doubt about the validity of the biomedical model of pain [75]. These experiments recorded activity in nociceptors, whilst simultaneously monitoring pain levels during experimentally induced pain. The authors demonstrated that pain did not correlate with tissue damage and that relationships between pain and nociception were variable. It is now understood that while nociceptors provide a physiological sensory input, pain emerges in the person as a result of a scrutiny process and is felt it in an area of the body deemed under threat [348], and that the severity of the pain response is not always associated with the intensity of the stimulus [75].

There are several modern models of pain perception, and nociception, including the mature organism model [349], the pain and movement reasoning model [350], and predictive processing [351]; however, the most widely accepted is the neuromatrix model, proposed by Melzack in 2001 [346,352]. The neuromatrix model of pain proposes that pain is a multidimensional experience produced by characteristic patterns of nerve impulses generated by a widely distributed neural network. Conceptually, pain is perceived and experienced when tissue is considered to be under threat. Many inputs into the central nervous system will affect the perception of threat, with each one further influencing other inputs. This includes nociception from the MSK system; psychosocial factors like memories, anxiety, and beliefs; and affective factors such as pain behaviour. The output, or "neurosignatures", may be triggered by sensory input from nociceptors alone, or independently from them from other inputs [352]. For example, it is not uncommon for people to experience the pain of

an injection when observing somebody else receive one. This is, in part, thought due to the activation of the pain "neurosignature".

5.2.2 Mechanisms of central and peripheral sensitisation

The central nervous system is thought to play a role in many chronic MSK conditions, including osteoarthritis [353]; whiplash associated disorders [354–356]; low back pain [357]; pelvic pain [357]; lateral elbow pain [357]; shoulder pain [119]; and knee pain [97,101,358]. It has recently been suggested that central sensitisation presides on a pain continuum that is present in all pain conditions [359], and so understanding the associated mechanisms, how to assess them, and the clinical manifestations could be important.

Central sensitisation is a common phrase in the pain literature, typically describing increased responsiveness of nociceptive neurons in the central nervous system to normal input [360]. With central sensitisation, there are changes in the properties and function of neurons in the central nervous system, with pain no longer linearly related to the presence and intensity of noxious peripheral stimuli [348,361].

In humans and clinical studies, surrogates or proxies are measured which are thought to be reflective of central sensitisation and covers many different underpinning mechanisms [348]. Central sensitisation can be seen as an umbrella term [348], the main mechanisms of which are: hyperalgesia; allodynia; temporal summation of pain (TSP) and diffuse noxious inhibitory control (DNIC) [348,360–362].

Hyperalgesia is an increased pain sensitivity, meaning an increased pain response to normally painful stimuli [363]. This process can occur locally, e.g. at a localised painful region, or over time can become more widespread [364]. It thought to be primarily driven by the interaction between neurotransmitters and receptors on the postsynaptic membrane, most notably glutamate, growth factors, cytokines and chemokines [348]. This interaction produces an increase in intracellular metabolism resulting in a heightened sensitivity to inputs [348]. If someone were to experience a pinprick to their ankle, they might score the pain one out of 10, for example. However, if they currently had an inflamed and swollen ankle from an acute ankle sprain, they would likely be experiencing hyperalgesia. In this scenario, the same pinprick would result in a more painful response and a higher pain score being recorded.

Allodynia, by contrast, is a pain response to a stimulus that is not normally painful [361,363]. The exact mechanisms are widely contested; however, it is thought that structural alterations occur, known as

structural plasticity, in the dorsal horn of the spinal cord. “Sprouting” from myelinated fibres to nearby nociceptive neurones occurs, so that non-noxious thermal, mechanical or joint movement inputs can contribute to the pain experience [348,361,365]. An example of allodynia is the person who is suffering from persistent low back pain who complains of low back pain when they are hugged.

TSP is a progressive increase in pain perception in response to repeated stimuli of the same intensity. This psychophysical response in humans mimics the initial phase of the wind-up process measured in animal dorsal horn neurons, representing increased excitability of spinal cord neurons to successive stimuli [360]. A variety of stimuli can be used to assess TSP in humans, including, heat, cold, pressure and electrical. In clinical studies, TSP has been shown to be present in patients with osteoarthritis [362]. For example, a patient with chronic knee pain performing knee exercises may complain of increasing levels of pain the more repetitions of the same exercise they perform, which could be attributed to TSP.

Another commonly assessed pain mechanism in MSK pain research is the DNIC paradigm [362]. It describes a descending endogenous pain modulation system encompassing an array of overlapping mechanisms from the central nervous system that can modulate and reduce pain perception [366]. The two primary mechanisms are the activation of descending nociceptive inhibitory mechanisms [367]; and the release of endogenous opioids [368]. The descending inhibitory system originates in the cingulate cortex and ventromedial prefrontal cortex projecting to the periaqueductal gray (PAG) [369,370]. The PAG interacts with subcortical regions, including the amygdala and hypothalamus, which in turn have bidirectional connections to the dorsal horn of the spinal cord. Here it synapses onto neurons that activate the opposite effects of nociceptive signalling [371]. DNIC is assessed in humans through the conditioned pain modulation (CPM) response (also known as “pain inhibits pain”) [314].

During CPM, the descending pain inhibitory responses are challenged during a painful conditioning stimulus. This is used proxy of the overall effectiveness of the endogenous analgesic system, likely occurring through both the opioid and non-opioid pathways. The results are a decrease in the excitability of neurons, a decrease in neurone firing rates, and inhibition of neurotransmitters, contributing to anti-nociception [372]. An example of CPM in action is when one might report lower pain scores for a primary complaint, say low back pain, in the presence of a painful secondary stimulus, for instance placing the hand in ice cold water. Impairments in CPM are evident in long-standing pain conditions such as osteoarthritis, (and it may be associated with the development of postoperative pain), and in other non-arthritic chronic pain conditions [373]. An example of an impaired CPM response in these patient groups would be continuing to report the same pain scores, despite the

presence of a painful secondary stimulus.

In summary, studies have demonstrated that increased pain sensitivity may be present in patients with osteoarthritis [353]; whiplash associated disorders [354–356]; low back pain [357]; pelvic pain [357]; lateral elbow pain [357]; shoulder pain [119]; and knee pain [97,101,358]. For example, a study of 91 patients with unilateral PFP, with 23 pain-free controls, examined quantitative sensory testing by combining tactile and vibration sensation, warmth and cold thresholds [101]. The authors observed that patients with unilateral PFP pain had significantly increased tactile thresholds and altered thermal threshold on bilateral knees; indicating altered central pain processing [102]. These findings are supported by other studies demonstrating altered sensory function on the painful knee and non-painful knee [358]; lowered pressure pain thresholds on the painful knee and distal to the knee [97]; and thermal alterations in patients with PFP [103,104].

5.2.3 The role of the immune system

It is now becoming recognised that the immune system plays an important role in chronic pain states, including the development of long-term hyperalgesia and allodynia [374–376].

It is well-understood that strong noxious stimuli to body tissues result in the activation of inflammatory cells with traditional signs and symptoms of inflammation, such as heat, oedema, erythema, pain and hyperalgesia [377,378]. The innate immune response of inflammation is activated by various processes, including exposure to microbial cell wall fragments, toxins, irritant chemicals and autoimmune reactions [378]. Typically these are detected by a family of pattern-recognition receptors (PRRs) called toll-like receptors (TLRs) that regulate the central nervous system's innate immune response [375]. TLRs are predominantly made up of glial cells and sense the presence of damage or danger originating both endogenously and exogenously, translating this into central immune signals that can be interpreted by the central nervous system [374,376].

This process by which the immune system is thought to influence hyperalgesia and allodynia is through alterations of glial cells from a normal immune function to be capable of acting on dorsal horn neurons as a nociceptor [348]. It is thought that the chain of events of the innate immune response leads to the secretion of cytotoxic factors from glia cells, such as nitric oxide, superoxide radicals, and agents that potentiate synaptic plasticity; which leads to the production of pain mediators that can sensitise and lower transduction thresholds. This, in turn, maintains long-term pain states by further releasing pain mediators, working on a positive feedback loop [374]. Some studies report increased glial activity with individuals with chronic pain [374]. The mechanisms by which glia cell activation leads to synaptic plasticity is not fully understood, but this pathological pain state is thought to correlate with central

sensitisation, with a considerable overlap of contributing mechanisms [374].

5.2.4 Affective aspects of pain

Identification of pain-related fear and negative emotional states, such as kinesiophobia, catastrophising, low self-efficacy, anxiety and depression are becoming increasingly recognised in some MSK disorders [379,380]; indeed Chapter 4 of this thesis has identified these factors in PFP populations. Research has shown that these psychological factors not only affect the function and quality of life in patients with pain, but can modulate the individuals' pain experience, and therefore may play a role in the development and maintenance of chronic pain states [75,95,301–304,369]. As previously discussed in Chapter 1, a systematic review of self-management interventions for chronic MSK pain found self-efficacy and depression were the strongest prognostic factors (irrespective of the intervention) [87], and pain catastrophising and increasing physical activity were the strongest mediating factors [87].

Pain can interrupt physical activity and thought processes, and requires cognitive resources [381,382]. It has been proposed that pain-related fear amplifies the experience of pain; indeed there is strong evidence that pain is experienced more strongly when there is a greater focus of attention on it [383–387]. A person with pain-related fear will have a greater amount of attention bias, by which it means they pay the pain greater attention, with greater emotional meaning attached to it [95]. The mechanisms by which pain-related fear is thought to influence central sensitisation are: 1) increasing nociceptive transmission via spinal gate mechanism [388]; 2) via modulation of the descending pathways [388]; and 3) temporal summation, where increasing magnitude of spinal dorsal horn neurons activation increases glutamine sensitivity, thus producing a pain response disproportionate to the stimulus experienced [95,348]. Evidence from neuroimaging has demonstrated the role of the amygdala and pain-related fear, and its potential overactivity, as a facilitator of chronic pain and central sensitisation [389–391].

5.2.5 Summary

This section demonstrates that traditional pain models that describe tissue pathology as a source of nociceptive input directly linked with pain expression are insufficient for assessing and treating MSK pain [345]. Other models reconceptualise pain and put forward concepts that are based upon the premise that pain does not always provide a measure of the state of tissue, that many factors modulate it, and the relationship between pain and tissue becomes less predictable the longer pain persists [75]. Altered central processing of pain has been shown to be present in many pain conditions [97,101,119,354–358]; with the immune system playing a role in the development and maintenance

of pain sensitisation [374–376]. Furthermore, unhelpful thoughts of patients and clinicians towards pain, including the belief that pain will not get better and that movement will cause further tissue damage and worsening of the pain, are also important issues to remain mindful of [379,380].

5.3 How exercise effects pain

The following section will discuss the mechanisms associated with central pain processes, the immune system and affective aspects of pain, by which therapeutic exercise might improve pain and function for patients with MSK pain. It begins with a critique of historically identified mechanisms associated with the biomedical model of pain; with further discussion on what is known about exercise and MSK pain; including a theoretical rationale for the additional benefit of painful therapeutic exercise, over and above pain-free exercises alone.

5.3.1 Changes in biomechanics

It has been suggested that one mechanism by which exercise improves pain and disability in chronic MSK pain is its effect on biomechanics and corresponding changes in loading of the MSK system [336]. Joint range of movement, strength, muscular endurance and postural control improve after exercise programmes and may contribute to changes in loading at the painful site, thus reducing pain / painful stimuli [392].

However, current empirical evidence challenges this belief [336,338]. For example improvements in pain and function have been demonstrated after exercise programmes, in the absence of any changes to joint position and movement in knees, shoulders and backs [35,392,393]. For example, Rathleff et al.'s (2014) systematic review examining risk factors associated with PFP highlighted the discrepancy between prospective and cross-sectional research findings [35]. It concluded that whilst improving pain and symptoms, hip strengthening exercises do not appear to change any kinematics or alignment dysfunction at the knee or patella [35]. Similarly, a 2012 systematic review with 16 studies investigating changes in pain and, joint position and movement with exercise interventions for low back pain, demonstrated that pain reduction was not attributable to changes in joint position or movement [392].

Equally, a 12-week strengthening programme for patients with knee osteoarthritis improved pain and symptoms, without any changes in joint load [394]. Bennell et al. (2010) conducted an RCT (n = 89) comparing therapist-supervised exercise program to no intervention in people with medial tibiofemoral osteoarthritis and varus malalignment [394]. With cross-sectional research showing varus malalignment and higher peak knee adduction moment, when compared to healthy age-

matched controls in patients with knee osteoarthritis [395,396], it was thought strength improvements would reduce joint load (as measured by the knee adduction moment) and improve pain and function. The results also demonstrated a discrepancy between prospective and cross-sectional research findings, with patients improving in symptoms and function, with no effect on medial knee load [394].

Furthermore, Drew et al. (2014) conducted a systematic review examining the relationship between tendon structural change and clinical outcomes following exercise protocols [397]. It included 20 studies that looked at loading programmes on tendon pain and concluded that there was moderate evidence to support the use of high-load exercises for clinical outcomes [397]. However, it also demonstrated that there was strong evidence to refute any observable structural changes in tendons following improvements in pain and function after exercise interventions [397].

This model of clinical reasoning, whereby pain improves as a result of biomechanics, or tissue structure, fails to take into account the full biopsychosocial spectrum of factors. This may be the reason why there is a lack of evidence supporting any specific exercise intervention. It may be that factors common to all exercises have the greatest mediating effect on pain and disability, which is factors which may explain how different treatments may work. The role of these additional factors will be discussed in the following sections.

5.3.2 Reconceptualisation of pain-related fear

Some patients report fear of doing further tissue damage if an activity or exercise is painful [307–309]. A major consideration of the beneficial effects of painful exercise is the potential associated learning involved. Painful exercises have the potential to help reconceptualise pain-related fear, that is, patients may be challenged to think differently about pain and tissue damage, with painful exercises offering an opportunity for patients to re-introduce movement that was previously perceived as a threat. The amygdala is often referred to as the fear centre of the brain [340] and plays a key role in the shaping of the response to fear, particularly the response to pain-related memories and fear [340]. The cingulate cortex also plays a role in the response [391], with both areas of the brain communicating directly via the descending nociceptive inhibitory system [369–371]. In chronic pain states the brain acquires long-term mal-adaptive pain memories that associate tissue stress and load with danger and threat [90]; for example bending forwards in individuals with low back pain, raising the arm or lifting objects with shoulder pain, or squatting type movements with individuals with knee pain.

Contemporary thinking about movement adaptation and pain argue that activity avoidance proceeds

the development of pain, with pain causing the behavioural changes [398]. However, research has demonstrated that even mental preparation for such movements and activities can trigger the fear-memory centre of the brain; thought to be an overactive threat protective mechanism, triggering pain, in the apparent absence of nociception [399]. This is an important finding, as it links with other work that has demonstrated that an individuals' beliefs and attitudes to pain, and what constitutes "threatening" pain or not, leads to altered movement behaviour in those that perceive the same stimulus as threatening [400].

It is thought that by thinking differently about pain-related fear, a person is not eliminating or unlearning a conditioned fearful response, but instead learning a new inhibitory response [401]. During painful exercises, with appropriate "safety-cues", new inhibitory associations are made; these new inhibitory associations compete with the original conditioned response so that it becomes suppressed [401]. Research supporting this concept has come from animal studies [402,403], that have reported the involvement of the medial prefrontal cortex (mPFC) in the learning of new inhibitory associations, which has direct projections onto the amygdala [401]. For instance, the mPFC might have a role in the storing of long-term extinction memories that block and suppress the amygdala. Human studies on military personnel with and without a clinical diagnosis of posttraumatic stress disorder (PTSD) have confirmed this inverse relationship between activity in the mPFC and amygdala [404]. Patients with PTSD had decreased activation of the mPFC, with correlated increased activation of the amygdala [404]. Clinically this is an important point since it highlights that despite a positive response to therapy, pain-related fear has never truly been eliminated. It may, given certain conditions, for example during an acute flare-up, resurface.

It is hypothesised that pain-related fear, triggered by an activity itself, or mental preparation of an activity can trigger "neurotags" or "neurosignatures" (a pattern of nerve impulses), with an output of altered movements and behaviours, and the experience of pain. Therefore, it is suggested that painful therapeutic exercises should be prescribed with the "safety-cues" to facilitate the reconceptualisation of pain, with an emphasis on descriptions of pain neuroscience rather than psychology [405,406], that will then reduce the threat perception, and thus the activity of the amygdala and somatosensory cortex [407], with positive modulation of the nociceptive inhibitory systems. An example of this in practice would be provoking thought and providing safety-cues to a patient who is fearful of moving a painful knee they have been resting for long periods. Such safety-cues might be; "Your knee is painful because it has become de-conditioned and not used to movement. We need to exercise your knee, so it will become strong and conditioned to enable you to do what you need to do".

Self-efficacy, one's ability to cope, another psychosocial factor associated with pain-related fear, may

also be used to explain fear reduction. As previously discussed, self-efficacy is a key prognostic factor for the success of self-management interventions for MSK pain [87]. The potential mechanisms behind the effect of painful exercises are thought to be that painful exercises may alter both the response-outcome and efficacy expectation, both components of self-efficacy [408]. Within the context of the theory presented, the hierarchy construction of painful exercises, from easier to more difficult/higher load, could improve one's response-outcome expectation, where the patient begins to expect that they can tolerate harder exercises, without triggering the previous experience of pain-related fear, and pain flare-ups [409]. Furthermore, it is suggested that a progressive hierarchy of exercises begins to show and provide evidence to the patient that they are systematically approaching their clinical and personal goals [409].

5.3.3 Central pain processes

It has been recognised that an acute bout of exercise can result in analgesia, and this phenomenon is termed exercise-induced hypoalgesia (EIH) and is one form of endogenous pain modulatory processes [410]. It is thought that EIH is dependent on multiple analgesic mechanisms that contribute to changes in pain sensitivity [411]. Evidence for the analgesic effect of exercise comes from experimental studies that attenuate pain sensitivity, as measured by pressure pain thresholds, and TSP [360,373,411]. A number of different exercise interventions have been investigated, including cardiovascular exercise (running and cycling) and resistance exercise, including isometric and dynamic resistance [410]. It is thought the endogenous opioid system is triggered by exercise-induced activation of arterial baroreceptors following increases in heart rate and blood pressure, with an associated dose-response [337,412,413]. Exercise can trigger the release of β-endorphins from the pituitary and hypothalamus, in turn activating μ-opioid receptors peripherally and centrally, triggering the endogenous opioid system [414]. The hypothalamus projects onto the PAG resulting in further endogenous analgesic effects via the descending nociceptive inhibitory mechanisms [337].

Another possible reason painful exercises may work to reduce pain is through the CPM response. As previously explained, during CPM the descending pain inhibitory responses are challenged during a painful conditioning stimulus [372]. Studies have demonstrated that pain-related fear negatively disrupts the endogenous pain inhibitory systems via the process of CPM, for example, higher levels of catastrophising during experimental studies, was strongly associated with lower activation of the DNIC and higher pain ratings [341]. The network of subcortical and cortical structures associated with DNIC and CPM include the amygdala [415]. Painful exercises could provide the painful conditioning stimulus needed to trigger the CPM response, within the context of reducing pain-related fear (as discussed in the previous section) and activity of the amygdala, which may provide a mechanistic rationale for

improvements in pain and function.

5.3.4 Pain-related fear and the immune function

As mentioned in the previous section, the immune system has an important role in chronic pain states, and the development of long-term hyperalgesia and allodynia [374–376]. This section now returns to this topic, in relation to exercise and, specifically, painful exercises.

It is well recognised that regular exercise reduces the risk of developing age-related illnesses, such as heart disease and diabetes [43,416,417]. But regular physical exercise also reduces susceptibility to viral and bacterial infections, suggesting that there are mechanisms at play that improves the overall immune function [418,419]. The mechanisms by which these positive effects occur are not fully understood [377], but they are thought to involve a decrease in age-associated immunosenescence [420], improvements in the innate immune response [418], and a decrease in chronic inflammation [420].

Studies examining TLRs in physically active individuals compared with physically inactive individuals found that those active participants have significantly lower cell-surface TLR expression [421–424]. It is known that exercise results in the release of a range of factors associated with the immune function, such as epinephrine, cortisol, growth hormone, and prolactin [425]; this chain of events leading to the decreased expression of TLRs [426], and consequently the reduction in the aforementioned secretion of pain mediators that sensitise and lower transduction thresholds that contribute to the maintenance of long-term pain states.

Turning now to painful exercises specifically, it is known that the amygdala projects onto areas of the brain that play key roles in the sympathetic response to threat, such as the locus coeruleus and pons [427], with inflammation being directly activated by the sympathetic nervous system response [428,429]. For example, two functional MRI (fMRI) studies investigating brain and immune function during experimental periods of induced psychological stress reported increased activity of the amygdala, with subsequent increases of inflammatory markers [342,343]. Therefore, painful exercises, set within a framework of reducing fear-avoidance, with reconceptualisation of pain-related fear may provide a potential mechanism to reduce the threat perception and thus the activity of the amygdala and somatosensory cortex, with positive modulation of the sympathetic nervous system over and above the usual effect of physical activity. Resulting in a greater reduction in the cascade of the physiological immune response and the inflammatory system.

Evidence for this comes from studies examining the sympathetic nervous system's response to pain-

related fear and movement or exercise. For example, during painful movements patients with persistent pain showed more activation of the right insular cortex, thought to have direct interactions with the sympathetic nervous system, than pain-free controls [430,431]. Similarly, patients with chronic arm pain demonstrated increased swelling, in response to motor imagery, without any actual movements, which was related to fear of pain and catastrophising [431]; demonstrating that these psychosocial factors may modulate the relationship between the motor and sympathetic system [431].

Clinically, one might explain to a patient suffering with long-term knee pain, that avoiding physical activity, such as regular walking, will have a long-term detrimental effect on their physical activity levels with an associated negative effect on the immune function. That by gradually increasing their physical activity levels through, for example, regular walking, they will likely have a positive impact on their immune function with associated health benefits and improvements in pain levels. This should be combined with safety-cues to challenge beliefs around pain and tissue damage to set the rehabilitation programme in a framework of reducing pain-related fear.

5.3.5 Summary

Central pain processes, the immune system, and affective aspects of pain appear to respond to exercise positively. There might be some additional advantages when the exercise is painful, over and above pain-free. These overlapping mechanisms may mitigate and moderate MSK pain through the delivery of exercises that re-conceptualise pain as safe and non-threatening, facilitated by the appropriate clinical support and education (Figure 18). Allowing painful exercises may result in greater loads/volume of exercise but does challenge traditional prescription based solely on strength and conditioning principles with a tissue-focussed approach.

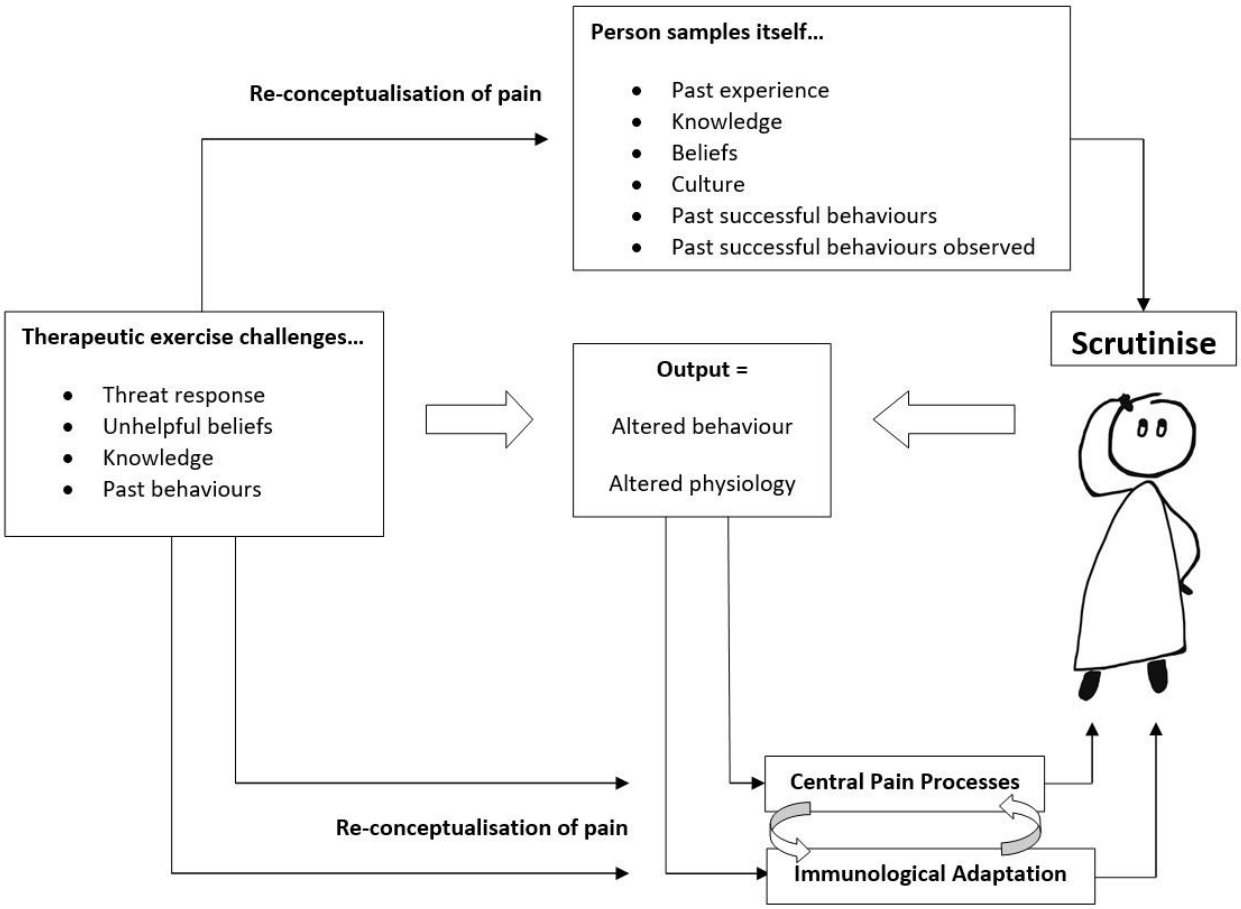

Figure 18 - The role of exercises in the management of chronic musculoskeletal pain. Therapeutic exercise challenges the threat response to pain. Central pain processes, the immune system, and affective aspects of pain may respond differently when pain is conceptualised as non-threatening. Adapted from Physiotherapy, 84(1), Gifford, Louis., 'Pain, the tissues and the nervous system: a conceptual model', 27–36, Copyright (1998), with permission from Elsevier.

Table 11 - How to reconceptualise pain-related fear through exercise – practical solutions.

Treatment goal	Example
Understand what the patient understands	Why do you think you have pain?
Challenge unhelpful beliefs	Is it safe for you to exercise? Why? Discuss with the patient. Prescribe exercises or movements that were previously avoided/or painful. New inhibitory associations may be made with painful exercises.
Enhance self-efficacy	Are you confident in completing this exercise? What do you think will happen? Discuss with the patient. The hierarchy construction of painful exercises, from easier to more difficult may improve self-efficacy.
Provide safety-cues	Your knee is painful because it has become de-conditioned and not used to movement. Pain is not a sign of tissue damage. We need to exercise your knee, so it will become strong and conditioned to enable you to do what you need to do.
Provide advice on suitable levels of pain	If you're coping with the level of pain, then continue with the exercise. If the pain is more than you find acceptable or flares up longer than 24 hours after the exercise, then decrease the amount of exercise until you're coping with it again.
Provide advice on exercise modification	Adjusting the exercises dependent on your symptoms is important. This may mean increasing the number of repetitions that you do or the amount of resistance that you use as it becomes easier, or decreasing if it gets too painful. Try not to avoid doing the exercises altogether as complete rest is unlikely to solve the problem. Instead, reduce the exercises to a level that is acceptable.

5.4 Conclusions and implications for this thesis

This chapter section has presented an understanding of MSK pain, particularly in relation to the central nervous system, the immune system and affective aspects of pain. This thesis has proposed that exercise interventions for chronic MSK pain could be designed around progressive loading and resistance programmes targeting movements and activities that can temporarily reproduce and aggravate patients' pain and symptoms [89,106,107]; and this chapter section has given a potential rationale for the mechanisms behind any additional benefit of painful exercises, over exercises alone, in the management of such a difficult condition. This additional mechanistic consideration (Table 11) will be used to support the development of the exercise intervention introduced in the next section of this chapter.

Part two: the exercise intervention

Summary

This section introduces the exercise intervention that has been developed with reference to the background evidence-base presented in Chapter 1, the findings of the systematic reviews in Chapter 2, the qualitative interviews in Chapter 4, and the proposed mechanisms of action considered in the previous section of this chapter.

5.5 Exercise Intervention

The “experimental” intervention is a loaded self-managed exercise programme for the knee and hip. It is aligned with the current best evidence of lower limb knee and hip strengthening exercises [51,52] and is set within a framework of reducing fear/avoidance and with an emphasis on self-management and reducing the need for direct physiotherapy intervention [432]. The intervention has been designed to be delivered by registered physiotherapists who have been trained by an expert in the technique and will have a manual to follow and regular supervision. The exercise will be completed by the participant, at home. The exercise involves weight-bearing movements of the knee, such as a double leg or single leg squatting type movement. The single leg squatting exercise will be performed sideways on a step.

5.2.1 Patient & Public Involvement

This research project, and particularly the exercise intervention, has been driven by the views of people suffering from PFP. Views and preference to current programmes of therapy and treatment were sought from patients, and their family members, who have received physiotherapy. These views have been incorporated into the planning, design and application of this study and exercise intervention.

Patients stressed the importance of ensuring a minimal number of exercises for improved adherence; the tailoring of the physiotherapy intervention around their usual sport/hobbies (where appropriate); and the capability of telephone support when required at short notice were stressed.

The main exercise of the intervention itself was adapted after consultation with patients. Initially, the intervention was an exercise based upon the “Step Down” function test [433]. The feedback from the patients was that performing the same manoeuvre sideways, rather than facing down the step, allowed them to use the guide of the wall or bannister with their hands. This has been incorporated into the intervention.

5.2.2 Evidence-base of the loaded self-managed exercise programme

The intervention was developed from the evidence-base currently available in the PFP population, with additional aspects warranting further investigation developed in the previous chapter sections. The current evidence-base on exercise prescription, previously synthesised in Chapter 1, principally derives from two systematic reviews on the conservative management of PFP; the “Best Practice Guide to Conservative Management of Patellofemoral Pain”, 2015 and the 2015 Cochrane review [51,52]. Overall, there seems to be some evidence to indicate that exercise is preferential over no exercise, for people with PFP. But overall, these studies highlight the lack of data about the nature and form of exercises. This appraisal, concerning the development of the intervention in this thesis, has been summarised in Table 12, with the intervention subsequently explained in detail.

Table 12 – Summary of exercise principles and evidence-base of intervention.

Current evidence-base			
Exercise prescription principle	***Indication***	***Source of evidence***	***Principle met?***
Exercise or no exercise	Exercise preferred	Level 1 evidence from systematic reviews [51,52]	✓
Open chain or closed chain	Unknown		?
Knee or knee plus hip exercises	Unknown		?
Supervised or unsupervised	Unknown		?
Duration and frequency	Unknown		?
Number of exercises	Unknown		?
Completed per week	Unknown		?
Principles warranting further investigation			
Exercise prescription principle	***Indication***	***Source of evidence***	***Principle met?***
Movement re-training	Not indicated	Chapter 1 and Chapter 5, part one	✓
Dose of exercise	Higher preferred over lower	Chapter 2, part two and Chapter 5, part one	✓
Exercise progression	Guided by the patient	Chapter 5, part one	✓
Pain with exercise	Pain provoked	Chapter 2, part two and Chapter 5, part one	✓
Level of pain with exercise	Unknown	Chapter 2, part two	?
Pain-related fear	Challenge unhelpful beliefs and enhance self-efficacy	Chapter 4 and Chapter 5, part one	✓
Physical activity levels	Maintain and promote levels	Chapter 5, part one	✓

5.5.3 Pain education

Before any prescription of exercise, the physiotherapist was taught to spend a period of time educating the participant about pain mechanisms. Descriptions of tissue-based pathology models of pain, e.g. patella mal-tracking, or limb mal-alignment were actively discouraged and challenged by the physiotherapist. The education of the patients regarding pain mechanisms took up a large portion of clinical time, such as to address any beliefs or fear within the participant that pain was a sign of tissue damage, and was delivered in a Socratic teaching style [75]; a cooperative dialogue based on asking questions to stimulate critical thinking and examine underlying beliefs [434]. A Socratic teaching style relies on a set of questions which was designed in a way to encourage the patient to think about and

question their basic understanding of pain and exercise (Table 11). By using questions, it was thought the physiotherapist was able to involve the patient more and create an atmosphere of learning, rather than trying to "parrot" information to the patient [434]. It was expected that the education period would be completed in the first session (30 – 40 minutes), but participants that required further re-assurance may have had this continue into their second session.

The participant will have gained an evidence based understanding of dysfunctional central nociceptive processing as an explanation of chronic and persistent pain [405], and the role and impact of fear [435]; as described in the previous section, with particular attention to Figure 18 and the pain-related fear identified in the qualitative study in Chapter 4. This period of intense learning was designed to facilitate the reconceptualisation of pain, with an emphasis on descriptions of pain neuroscience rather than psychology [406], and from the perspective and context of the participant and their pain [436].

5.5.4 Prescription of a loaded exercise

The exercise was prescribed by the physiotherapist. The skills required to deliver the intervention included complex MSK assessment; anatomy; tissue healing and remodelling; pain biology; peripheral and central sensitisation; psychological and social factors that might affect pain perception; self-management strategies; and education skills. Currently, in the UK, the degree training programme for physiotherapy provides a basic understanding of these skills.

The loaded exercise was tailored to each patient, such that it was designed to load and temporarily aggravate the patients' symptoms. Exercise selection and progression was guided by the symptomatic response, such that the participant was advised that on cessation of the exercise the pain should remain no worse than pre-exercise [291]. Physiotherapists carried out a baseline functional assessment. This was used to identify the participants' pain response to repeated functional movements of the knee, designed to load the joint progressively. The physiotherapist may, if required, started with squats, asking if it reproduced the participants' pain, settling to acceptable levels afterwards. If the pain was settling quickly, or the exercise didn't reproduce the patients' symptoms, the functional assessment moved on, for example to, step-ups or the modification of the "Step Down" test [433]. Participants with more severe pain could start on a lighter regime, and this was guided by the baseline functional assessment. The participant was advised to exercise to the point of fatigue, such that it reproduced their pain and discomfort, but ensuring the pain was manageable [291,437,438].

It was anticipated that the exercise would typically involve body weight resistance in the form of a modification of the "Step Down" function test for most participants [433]: a single leg squatting exercise sideways on a step. The exercise was chosen as it requires balance, knee extension strength, eccentric control and isometric hip strength; with cross-sectional studies demonstrating it increases PFJ load [314], and also causes short-term exacerbations of symptoms [109]. By performing sideways, the participant could use the guide of the wall or bannister more easily, as suggested by the patient representative on the steering group.

Participants were advised, with help from the physiotherapist, to exercise at a level they found acceptable and tolerable. Participants were able to start exercising, if they wished, at a very low level, with little or no short-term pain increases, and progressed when they felt comfortable and confident. Regression was in the form of reduced repetitions or lightening the exercise, for example, to double leg squats 0-30° knee flexion. Progression was in the form of increased repetitions or increasing the load by moving to plyometric exercises, such as jumping and hopping, for younger participants with higher sporting requirements. The exercise progression was based on the symptomatic response, rather than a traditional prescription based on strength and conditioning principles with a tissue-focussed approach. The physiotherapist planned the exercise, motivated and reviewed participant's physical performance and expectations [90]. The exercise was individualised to the participant, based up their baseline functional assessment, with clinical judgment around participants' sporting or physical activity background, occupation and overall health status.

A single exercise approach was used for this intervention. Poor levels of exercise adherence are well documented [439], and it has been suggested that a single exercise represents a pragmatic time-saving approach [440]. Additionally, as previously discussed, the optimal dosage of an exercise prescription is unknown, and a single exercise approach may allow better monitoring of dosage and adherence. Importantly, it enabled the participant to observe others (the physiotherapist) perform the task successfully and facilitate the development of mastery of the task. This combined with specific verbal and social persuasion from the physiotherapist to further promote reconceptualisation of the pain, specific to the participant and their context, all thought to be key modifiers of perceived self-efficacy [441].

A recent systematic review evaluated the completeness of exercise prescription in RCTs for PFP [442]. Out of 38 included studies, 35 described the number of times patients were asked to complete their exercises. The range was three – 21 per week, with three times being the most commonly prescribed (15 studies). However, only three studies monitored adherence, therefore preventing any detailed attempt to explain any effect on dosage and exercise frequency fully. The predominant principle of

exercise prescription of the included studies was based on strength and conditioning principles with a tissue-focussed approach. Therefore, building on principles guided by Chapter 2, part two, in relation to pain and exercise dose for all MSK disorders; and Chapter 5, part one, in relation to exercise and the central nervous system; participants were advised that the exercise should be performed twice a day [113].

The participant were encouraged to self-direct progressing/regressing of the repetitions, as guided by their pain response, as mentioned previously, such that on cessation of the exercise the pain should remain no worse than pre-exercise [291]. They were taught if the pain settles quickly, or the exercise didn't reproduce their symptoms, to self-adjust and increase the number of repetitions. Likewise, if the pain was above an acceptable level, or lasted for an extended period of time afterwards, they should self-adjust and decrease the number of repetitions. Thus further internalising the locus of control and moving towards self-management [441].

5.2.5 Self-management strategies

Goal setting was a central part of the intervention. A central concept of self-management is self-efficacy, as discussed in the previous chapter section, and is related to response-outcome and efficacy expectation [408], specifically the confidence to carry out behaviour to reach a desired goal [443]. The reconceptualisation of pain through the exercise intervention was thought to lead onto the reconceptualisation of pain in the participant's daily activities, including sport and leisure activity, and setting goals may help this transition [444].

Other self-management strategies employed was the discussion about managing "flare-ups" and potential or perceived barriers to successful outcomes [90,440]. This was through thorough questioning and discussion with the physiotherapist and participant. Questions such as: is this safe for your knee? Is exercise good for you? Are you confident in completing this exercise? What do you think will happen? Why do you think that? It was thought that a discussion based on this approach would reveal the participant's perception of exercise, and potential barriers and fears [90].

Keeping the treatment pragmatic, timing over follow-ups, the number of treatment sessions, frequency and discharge, physiotherapy concomitant treatments was at the discretion of the qualified physiotherapist, but with the aim of the programme being self-management, self-directed exercise and discouraging concomitant treatments. The mean number of sessions given by physiotherapist in the UK for routine treatment of PFP has been shown to be eight [445], and the prediction was that self-management strategies would lower the expected number of treatment sessions for the intervention group to three to five sessions. The timings of the follow-up appointments were also

pragmatic in nature, and at the discretion of the physiotherapist in discussion with the participant. Following the problem solving and barrier discussion the physiotherapist should have had an understanding of the participant's ongoing perception of their pain. Those that required further re-assurance may have returned sooner, one to three weeks; and those that were comfortable to self-manage sooner will have returned after a more extended period, four to six weeks, or not at all in some cases. All participants had the opportunity to telephone for support if required.

5.6 Conclusion

This chapter has described and appraised the development of the intervention, with reference to knowledge created in this thesis, and synthesised with the current evidence-base, for people suffering from PFP. The subsequent chapter will now describe the specific research methods and results of the feasibility RCT (Phase Two of the protocol), followed subsequently by the embedded qualitative interviews (Phase Three of the protocol).

Chapter 6 - Phase Two: Feasibility RCT

Summary

This chapter presents the third main component of the thesis: a feasibility randomised controlled trial (referred to as Phase Two in the protocol, Appendix C). It describes the methods used and presents and discusses the results. Feasibility indicators of process, resources, and management were collected, with follow-up of standardised questionnaires three and six months after recruitment.

6.1 Introduction

6.1.1 Why a randomised controlled trial?

RCTs are believed to hold the gold-standard in empirical evaluation of medical interventions [123]. The rationale is well established, with the randomisation process minimising the effect of confounding variables and selection bias, and blinding (where applicable) minimising further biases [123]. This view is well supported, with studies demonstrating that randomisation and concealment reduce bias [446,447]. Indeed, RCTs are positioned at the highest level under the GRADE system (used in the systematic review in Chapter 2, part two), and used for the evaluation of evidence for medical interventions and guidelines by the World Health Organisation and the UK National Institute of Clinical Excellence [238][446].

RCTs are not, however, without their limitations. For example, as briefly mentioned in the systematic review in Chapter 2, part two, it is accepted that blinding in physiotherapy, and physical intervention trials are difficult to achieve [223]; greatly impacting on the internal validity of the study. Furthermore, complexity in the intervention, setting and therapists, mean there is often difficulty standardising the treatments given (both the experimental intervention and control). Although physiotherapy interventions should be adapted and tailored to the individual need of the patient and nature of the pain disorder; Chapter 5 of this thesis highlighted the complexity in the presentations of MSK pain disorders that need to be accounted for in study design. Notwithstanding these limitations, if practically feasibility and acceptable, an RCT should be considered the most robust method for testing treatment effectiveness. Indeed, these limitations with RCTs underline the importance of the mixed-methods approach endorsed by the MRC Complex Interventions Framework [4], that has been used

for the development of this programme of work.

6.1.2 Aims

Definitive RCT trials are expensive to run, with many examples of trial "failure", resulting in a large waste of money and resources [446]. Trial "failure" is often down to not recruiting to target, and in order to reduce wastefulness, establishing program feasibility is an essential first step before testing efficacy [446]. Furthermore, as described in the MRC framework, understanding and determining the optimum components which inform the design of a larger, definitive study was required [4]. In plain English: can a large study be done? What are the operational aspects around recruitment (sample size and power calculations), engagement, retention and outcome assessment, which would not usually be presented in an intervention manual?

Another factor that needed to be considered was that feasibility studies may or may not be randomised [448]. However, considering the importance of randomisation in a definitive study at reducing bias, and the lack of prior knowledge on the acceptability of randomisation in this patient population, randomisation was a high-priority parameter to be established. For example, randomisation may not have been possible for any number of reasons, such as unfamiliarity of staff and participants with the randomisation processes; staff and participants treatment preference; or participants wanting healthcare professionals to decide on treatment management [449].

Therefore, considering the outstanding questions discussed above, a feasibility randomised controlled trial was justified with the primary aim of this chapter being to establish the feasibility and acceptability of conducting a definitive RCT. The RCT would evaluate the clinical and cost-effectiveness of an intervention based on pain science (where exercises are designed to load and temporarily aggravate patients' symptoms), self-management strategies and improvements in physical activity levels for people with PFP compared to usual physiotherapy. The intervention has been discussed in detail in Chapter 5 and is referred to as a loaded self-managed exercise programme.

6.2 Methods

This study was reported in accordance with the Consolidate Standard of Reporting Trials (CONSORT) statement [450] and Template for Intervention Description and Replication guidelines (TiDieR) [451].

The protocol was approved by the West Midlands - Black Country Research Ethics Committee (ref: 16/WM/0414) and sponsored by University Hospitals of Derby and Burton NHS Foundation Trust. A full description of the methods has been previously published [333]. A brief description is detailed below.

6.2.1 Study Design

A pragmatic, randomised controlled, single-centre, feasibility study, with an embedded qualitative component (presented in the subsequent chapter).

6.2.2 Participants

Participants were recruited between February 2017 and January 2018 from a physiotherapy waiting list at a large NHS teaching hospital. Patients were referred from general practitioners and orthopaedics and rheumatology hospital departments. An introductory letter accompanied by an information sheet and consent form were sent out to potential trial participants by a member of the clinical team. This was followed up by a telephone call from a member of the clinical team offering further information and inquiring about participation. Inclusion and exclusion criteria followed currently accepted definition [2] and were checked both verbally (by telephone initially, then face to face by the same physiotherapist with ten years' MSK experience) (Table 13). Historically, patellofemoral pain RCTs have focused on the adult population up to 40 years of age [26,27,127]. It is thought that people aged over 40 years of age are more likely to have degenerative changes [452]; radiographic signs of PFJ osteoarthritis have been demonstrated in 69% of people over the age of 40 complaining of PFP symptoms [453]. Therefore, this study has followed the precedent set within the literature [26,27,127].

The same physiotherapist took consent, before baseline data was taken and then randomisation.

Table 13 - Participant eligibility criteria (feasibility RCT).

Inclusion criteria
• Aged 18 to 40 years • Greater than three-months duration • Clinical diagnosis of unilateral or bilateral patellofemoral pain (if bilateral the worst knee was investigated) • Anterior or retropatella pain reported on at least two of the following activities: prolonged sitting, ascending or descending stairs, squatting, jumping and running
Exclusion criteria
• Previous knee surgery or awaiting lower limb surgery • Knee ligamentous instability • History of patella dislocation • True knee locking or giving way • Reasons to suspect systemic pathology or acute illness • Patellar or iliotibial tract tendinopathy • Pregnancy or breastfeeding • Not able to speak or understand English

6.2.3 Sample Size

Sixty participants were planned to be recruited; 30 participants per group.

A formal sample size calculation was not performed since the study was designed as a feasibility study. Sample sizes between 24 [454] and 50 [455] have been recommended as providing suitable data for performing a sample size calculation. Therefore accounting for an attrition rate of 20%, these sample sizes were chosen for the feasibility RCT to provide sufficiently robust, meaningful amounts of information [448].

6.2.4 Randomisation

Patients were randomised to either the intervention group (loaded self-managed exercises) or the control group (usual physiotherapy) (1:1) by a web-based randomisation service with secure password protected login using random variable block-size.

Due to the nature of therapeutic interventions, blinding of the participants and physiotherapists was not possible [223], and participants were aware of the purpose of the study. All participants were blinded to the criteria for feasibility.

6.2.5 Interventions

6.2.5.1 Training of the physiotherapists

The training package was delivered to the treating physiotherapists by the research team. The training package was designed to be easily deliverable and in a short space of time. It consisted of two, two-hour training sessions, scheduled to fit into the physiotherapy department's usual in-service training slots, and was based on successful training in previous trials for delivery of an exercise prescription [113].

The first session (Appendix D – training 1) delivered to all physiotherapists consisted of background information to PFP, the rationale for further study, an overview of research design, clinical equipoise, usual physiotherapy, discussion and, questions and answers.

To avoid cross-contamination between the two groups, the second training session (Appendix D – training 2), was delivered only to physiotherapists delivering the loaded self-managed intervention, consisting of revision of training session one, pain education, the loaded exercise, self-management strategies, discussion and, questions and answers.

All physiotherapists were supported to continue giving the interventions through weekly informal workshops.

6.2.5.2 Loaded self-managed exercise programme

The "experimental" intervention was a loaded self-managed exercise programme for the knee and hip, aimed at addressing lower limb knee and hip weakness, delivered by trained and supported NHS physiotherapists [52]. The intervention was set within a framework of reducing fear-avoidance, with an emphasis on participant self-management of the condition and exercise programme, and improvements in physical activity levels.

The intervention has been discussed in detail in Chapter 5, part two.

The intervention group was delivered by physiotherapists who were excluded from treating participants from the control group (and vice versa), to reduce the possibility of cross-contamination between the two groups.

6.2.5.3 The comparator

The comparator was usual physiotherapy as directed by the clinical judgement of the treating physiotherapist [281]. Usual physiotherapy often involves strengthening exercises, taping, stretches, foot orthoses, movement retraining and is typically aimed at reducing the load on the patella and avoidance of painful exercise and activity [51,281].

6.2.6 Outcomes

The following outcomes were measured.

6.2.6.1 Feasibility outcomes

6.2.6.1.1 Recruitment & eligibility

Recruitment rates were recorded and defined as the number of participants recruited each month, compared with expected and feasible recruitment rates. It was expected to be able to recruit 4.6 patients per month, based on estimates on the referral rate which was observed in the department between January 2013 and October 2013.

The consent rate was calculated by dividing the number of individuals who met inclusion criteria, by the number who consented to participate in the study.

6.2.6.1.2 Randomisation & blinding

Randomisation was assessed on the rate of participants randomised after consent, and on any challenges reported by the recruiting researcher. Baseline demographic data included; age, sex and duration of symptoms were collected.

6.2.6.1.3 Adherence & acceptability

Compliance levels with the intervention were monitored through a participant activity diary, in the form of a paper-based diary to be completed by hand (Appendix M). Participants were asked to complete an exercise diary daily for six-months to indicate how many exercise repetitions they had completed each day. Adherence to treatment was assessed by the adherence rate to treatment (%) from exercise diaries returned at six-months, calculated by the percentage of days they indicated they completed their exercise(s). Adherence to appointments (%) was based on the number of "did not attend" (DNAs), where a participant fails to attend their physiotherapy appointment.

6.2.6.1.4 Patient-reported outcome measures

The retention rate / loss at follow-up was assessed on the percentage of returned outcome forms at three and six months. The percentage of missing data was also recorded.

6.2.6.1.5 Resources & study management

Participant processing time was measured as the number of days from initial contact (information letter being sent) to consent and randomisation.

Fidelity was defined as adherent and competent delivery of the intervention and was evaluated by analysis of the physiotherapists' clinical notes against a three-point checklist outlining important details and components of intervention developed from Chapter 5. The three-point checklist included: specific pain education; delivery of a loaded exercise programme; and discussion on self-management strategies. This analysis was conducted for both the loaded self-managed, and usual physiotherapy groups.

6.2.6.2 Patient-reported outcome measures

Clinical outcome measures were collected at baseline, three and six months post-randomisation. The follow-up outcome measures were posted to the patients' home, with a pre-paid enveloped to return.

The primary outcome measure that was tested as feasible was the global rating of change (GROC) at follow-up, the proportion of participants who had recovered (defined as “completely recovered” or “strongly recovered”), measured on a seven-point Likert scale ranging from “completely recovered” to “worse than ever” [26,28,456].

Secondary outcome measures included: the visual analogue scale (VAS) for pain, average over the last week [457], the Tampa Scale for Kinesiophobia (TSK) [458,459], the “Pain Catastrophizing Scale” (PCS) [460], the General Self Efficacy Scale (GSES) [461], and the generic health outcome Euro-QOL using UK dataset (EQ-5D-5L) , which included a general health VAS [462]. Participation in leisure time sport or exercises within a week was also recorded. The occurrence of an adverse event as a result of participation within this study was not expected, and therefore no adverse event data were collected.

Participants who had not returned the questionnaires were telephoned after seven days to encourage them to complete and return these.

6.2.7 Data Analysis

Reflecting a feasibility study design [463], descriptive statistics along with point estimates, confidence intervals (95%), and effect sizes using independent t-tests, were presented for all appropriate clinical outcome measures. Participant characteristics were presented using means, standard deviations and ranges for quantitative variables and counts and proportions for categorical variables. Feasibility outcomes were described using descriptive statistics. Sensitivity analysis of the primary outcome measure, GROC, was carried out, examining the proportion of participants who had recovered defined as “completely recovered”, “strongly recovered” or “slightly recovered”.

Statistical analysis was undertaken using SPSS version 24.0 (Armonk, NY: IBM Corp). No data imputation was performed to account for missing data; intention-to-treat with complete-case analysis was conducted. As recommended by the CONSORT statement, statistical comparison of baseline data was not performed [464].

Feasibility thresholds, as agreed *a priori* [333], were set at 75% to assess reliability and completeness of outcome measures and used to indicate either success or if strategies are required to improve the viability of any future definitive trial, these are presented in Table 14, with feasibility results summarised in Table 18. Where it was not possible to use quantitative data to demonstrate success, outcomes were reported narratively.

Table 14 - Thresholds for feasibility outcomes.

Outcome	Indicator	Successful
Recruitment & eligibility	Recruitment rate (participants per month)	> 3.75
	Consent rate (%)	> 75
Adherence & acceptability	Adherence to appointments (%)	> 75
Outcome measures	Retention rate (%)	> 75
	Completeness of data (%)	> 75
Resources & study management	Adherence to intervention delivery (%)	> 75

6.3 Results

6.3.1 Feasibility outcomes

6.3.1.1 Recruitment & eligibility

Recruitment rate was 5.0 participants per month over a 12-month period, exceeding the recruitment rates for feasibility. See Figure 19 for recruitment rate comparisons, and Figure 20 for the flow of participants through the study. Over 12-months, 185 referrals were reviewed as potentially eligible, 185 recruitment packs were posted and five (3%) "opt out" slips were returned.

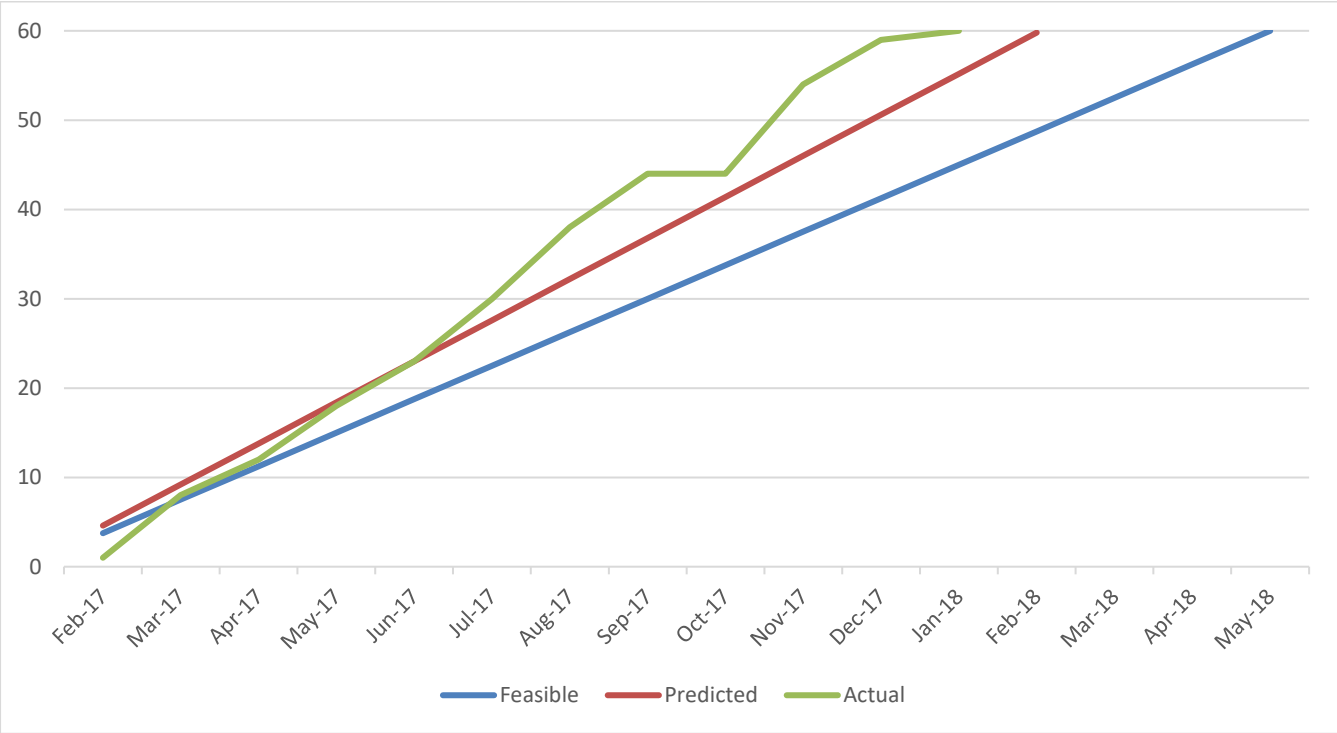

Figure 19 – Actual recruitment rate, compared to feasible and predicted (feasibility RCT).

6.3.1.2 Randomisation & blinding

The recruiting researcher reported no randomisation issues. All participants consented to be randomised. There were no baseline imbalances for demographics, baseline symptoms and clinical outcome measures (Table 15). Two noteworthy discrepancies were the longer duration of symptoms in the loaded self-managed group compared with the usual physiotherapy group; and the lower health VAS in the loaded self-managed group.

Table 15 - Baseline characteristics. Values are means (SD) unless stated otherwise (feasibility RCT).

Characteristics	LSM Group (n = 30)	UP (n = 30)
Age (years)	31.4 (7.1)	27.4 (6.6)
No of females (%)	15 (50%)	19 (63%)
Duration of knee pain (months)*	18 (6.5 - 48)	12 (5 - 27)
Average pain VAS	4.9 (1.9)	4.9 (2.1)
TSK	40.8 (6.5)	37.8 (7.1)
PCS	22.7 (14.1)	19.6 (9.3)
GSES	30.6 (3.2)	31.5 (3.4)
EQ-5D-5L*	0.65 (0.46 - 0.72)	0.72 (0.62 - 0.77)
Health VAS	60.2 (18.4)	72.7 (18.8)
Sport Participation*	2.5 (1 - 5)	2 (0.0 - 4)

* Median (interquartile range).
LSM, loaded self-managed; UP, usual physiotherapy; TSK, Tampa Scale for Kinesiophobia; PCS, Pain Catastrophizing Scale; GSES, General Self Efficacy Scale; EQ-5D-5L, EuroQol 5-dimensions; VAS, visual analogue scale.

6.3.1.3 Adherence & acceptability

Only one exercise diary (3%) was returned from participants in the loaded self-managed group. This indicated exercise adherence of 40% of the time. Two exercise diaries from participants in the usual physiotherapy group (7%) were returned, with a mean adherence rate of 43%.

Adherence to appointments was 87%; with 79% in the loaded self-managed exercise group and 92% in the usual physiotherapy group. The treatments provided by the treating physiotherapists can be seen in Table 16.

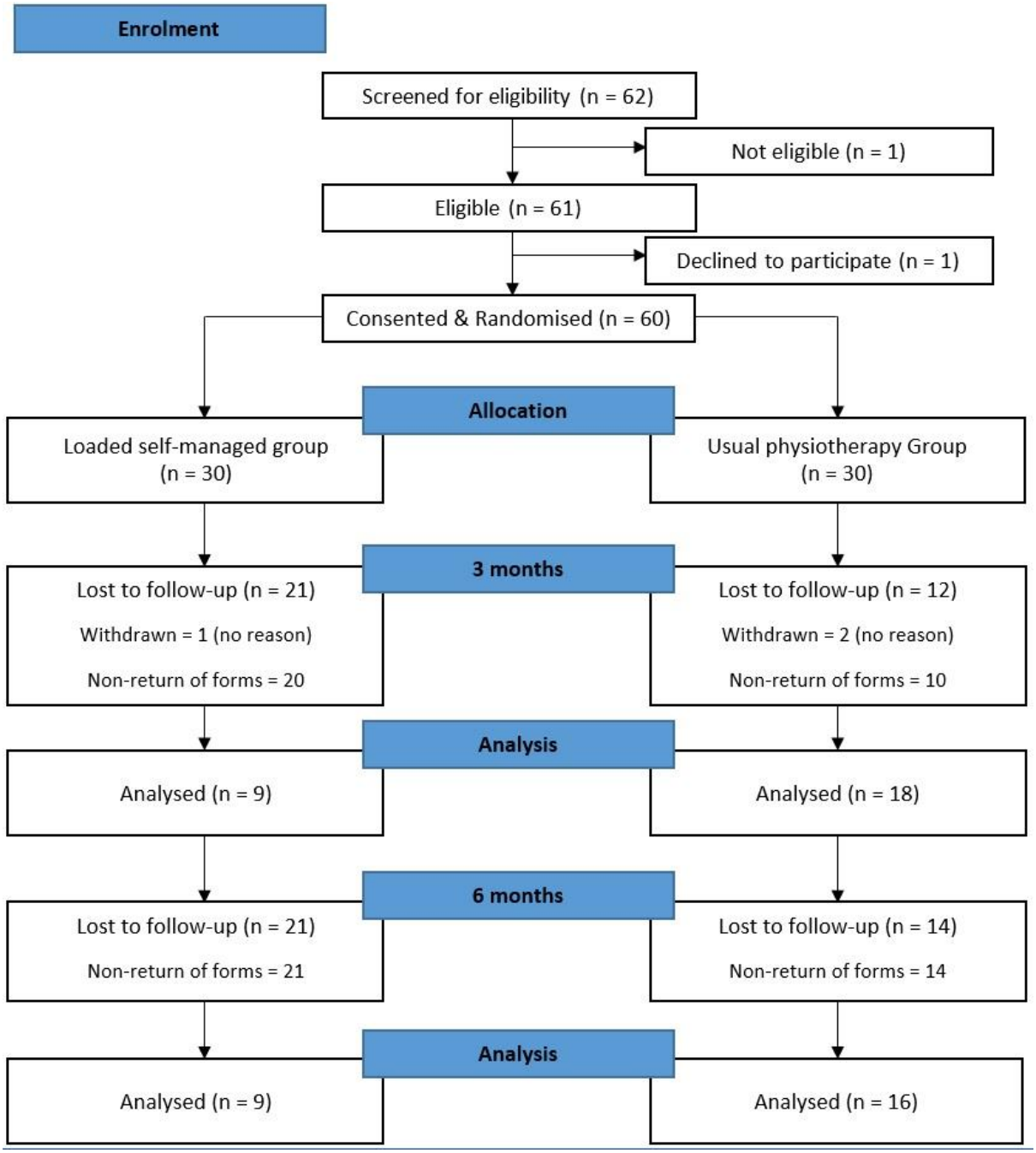

Figure 20 - Flow of participants through the study (feasibility RCT).

Table 16 - Treatments offered by physiotherapists (feasibility RCT).

Possible physiotherapy treatments	Treatments offered by treating physiotherapist	
	Loaded Self-Managed	Usual Physiotherapy
Specific pain education*	23	0
Loaded exercise*	26	0
Self-management strategies*	25	0
Closed chain exercise	21	27
General advice	21	20
Open chain exercise	1	23
Orthotics	1	0
Movement re-training	0	11
Hip specific exercise	0	9
Stretches	0	3
VM exercises	0	2
Referral on	0	1
Electrotherapy	0	0
Acupuncture	0	0
Patella taping	0	0
Massage	0	0
Mobilisations	0	0
Other	0	0

*, three-point checklist outlining important details and components of the intervention; VM, vastus medialis

6.3.1.4 Patient-reported outcome measures

At three-month follow-up, participants who had not returned questionnaires were telephoned and reminded. At this stage, one participant (3%) from the loaded self-managed exercise group withdrew, and two participants (7%) from the usual physiotherapy group withdrew.

Differences in loss to follow-up were demonstrated with the return rate of participants' questionnaire booklets. At three-months, 27 questionnaire booklets were returned (nine in the loaded self-managed group, 18 in usual physiotherapy), with a total retention rate of 45%. At six-months, 25 questionnaire booklets were returned (nine in the loaded self-managed group, 16 in usual physiotherapy), with a total retention rate of 42%.

Of the returned forms, all were completed fully, apart from one participant omitting the Tampa Scale for Kinesiophobia at three-months, with the completeness of data indicators of 99.7%.

6.3.1.5 Resources & study management

The mean participant processing time, from the initial date the research team sent out the recruitment pack to date of participant consent, was 18 days.

The mean number of physiotherapy appointments was 2.4 for the loaded self-managed group, over a mean duration of 3.1 months, compared with 3.2 appointments over 3.8 months for the comparator group.

Fidelity rate in the loaded self-managed group, measured by the three-point checklist was 95% (Table 16). Measuring for contamination, this checklist recorded 0% in the usual physiotherapy group. All participants' physiotherapy notes were reviewed.

6.3.2 Patient-reported outcome measures

At three-months follow-up 44% (4/9) of respondents in the loaded self-managed group were classified as recovered, compared with 39% (7/18) in the usual physiotherapy group. At six-months 56% (5/9) of respondents in the loaded self-managed group were classified as recovered, compared with 56% (9/16) in the usual physiotherapy group.

The loaded self-managed group demonstrated greater improvements in average pain (VAS), kinesiophobia, pain catastrophizing, general self-efficacy and general health VAS (see Table 17).

Table 17 - Clinical outcomes. Mean (SD) unless otherwise stated (feasibility RCT).

Outcome	Group	Baseline (SD)	3-months (SD)	6-months (SD)	Mean difference (LSM-UP, 6-months) (95% CI)	ES (*d*) (LSM-UP, 6-months)
Average pain VAS	LSM	4.8 (1.9)	2.9 (1.4)	2.1 (2.2)	-1.2 (-3.4, 1.1)	0.43
	UP	4.8 (2.1)	3.0 (2.8)	2.4 (2.6)		
TSK	LSM	40.8 (6.6)	34.7 (6.2)	31.3 (8.8)	-4.3 (-10.9, 2.3)	0.51
	UP	38.3 (7.1)	34.1 (8.6)	31.6 (6.3)		
PCS	LSM	22.0 (13.8)	16.0 (10.5)	12.6 (9.1)	-4.0 (-14.8, 6.8)	0.29
	UP	20.0 (9.4)	16.6 (13.5)	14.1 (10.4)		
GSES	LSM	30.6 (3.2)	29.9 (3.4)	32.3 (2.4)	1.8 (-1.0, 4.6)	0.53
	UP	31.6 (3.5)	31.2 (3.5)	31.8 (3.2)		
EQ-5D-5L*	LSM	0.65 (0.53 – 0.73)	0.75 (0.54 – 0.82)	0.74 (0.64 – 0.92)		
	UP	0.71 (0.62 – 0.79)	0.80 (0.69 – 1.00)	0.84 (0.73 – 0.87)		
Health VAS	LSM	60.9 (18.4)	67.8 (16.0)	64.4 (26.4)	8.5 (-8.1, 25.2)	0.51
	UP	72.1 (19.4)	80.6 (17.0)	79.8 (17.4)		
Sport Participation*	LSM	3.0 (1.0 – 5.0)	2.0 (1.5 – 4.0)	3.0 (2.0 – 6.0)		
	UP	2.0 (0.0 – 4.0)	3.5 (2.0 – 4.3)	3.5 (2.0 – 5.0)		
GROC	LSM		44.4% (4 / 9)	55.6% (5 / 9)		
	UP		38.9% (7 / 18)	56.3% (9 / 16)		
GROC**	LSM		100% (9 / 9)	77.8% (7 / 9)		
	UP		77.8% (14 / 18)	87.5% (14 / 16)		

LSM, loaded self-managed; UP, usual physiotherapy; CI, confidence interval; TSK, Tampa Scale for Kinesiophobia; PCS, Pain Catastrophizing Scale; GSES, General Self Efficacy Scale; EQ-5D-5L, EuroQol 5-dimensions; VAS, visual analogue scale; GROC, global rating of change scale; ES, effect size.
*, Median (interquartile range); **, sensitivity analysis.

Table 18 - Thresholds for feasibility outcomes – results.

Outcome	Indicator	Successful	Result	Feasible	Suggested modifications
Recruitment & eligibility	Recruitment rate (participants per month)	> 4	5.0	Yes	
	Consent rate (%)	> 75	98.6	Yes	
Adherence & acceptability	Adherence to appointments (%)	> 75	86.8	Yes	
Outcome measures	Retention rate (%)	> 75	41.7	No	Reduce the number of outcome measures, use of IT (e.g. text message), improve communication between treating physiotherapist and participant, relax criteria for success, entry into a prize draw, telephone consultations.
	Completeness of data (%)	> 75	99.7	Yes	
Resources & study management	Adherence to intervention delivery (%)	> 75	94.9	Yes	

6.4 Discussion

The results of this study confirm that it is feasible and acceptable to deliver a loaded self-managed exercise programme to adults with PFP in an NHS physiotherapy outpatient setting (Table 18). The loaded self-managed group demonstrated greater improvements in average pain (VAS), kinesiophobia, pain catastrophizing, general self-efficacy and general health VAS, compared with usual physiotherapy. However, differences in loss to follow-up and poor exercise diary completion mean there remains uncertainty on some feasibility aspects, with the potential for systematic bias. Further feasibility work may be needed to address these issues, before supporting a larger clinical trial which will evaluate the clinical and cost-effectiveness of a loaded self-managed exercise programme for people with PFP compared with usual physiotherapy.

6.4.1 Process

The observed recruitment rate was 5.0 participants per month at the single site over 13-months. It had been expected to be able to recruit 4.6 patients per month but deemed a recruitment rate of 3.7 feasible. The initial recruitment strategy was an estimate based on the referral rate (after full screening by a physiotherapist) of 23 per month (based on the inclusion and exclusion criteria), which was observed in the department between January 2013 and October 2013. However, the observed number of referrals during the study was less than the rate observed in 2013, with 16.8 potentially eligible patients referred each month (before full screening). Therefore, any future definitive trial should consider a lower referral rate than was initially anticipated.

6.4.2 Resources

This feasibility study used exercise diaries as a measure of self-reported exercise adherence. The three diaries returned indicated exercise adherence of 42% of the time (40% in the loaded self-managed exercise group compared with 43% in the usual physiotherapy group). However, with such a low return rate, the reliability and validity of the data are limited, which greatly restrict any conclusions about adherence to the intervention from the quantitative data.

6.4.3 Management

The fidelity assessment highlighted some interesting findings on current practice (Table 16). In contrast to current UK wide physiotherapy treatment, and international best practice guidelines [51,281], very few physiotherapists provided movement retraining exercises, VM muscle exercises, hip-specific exercise or stretches; and no physiotherapists in the usual physiotherapy group offered

patella taping, joint mobilisations or orthotics. Nonetheless, 95% of patients received the intervention as described in the protocol, indicating intervention fidelity was not an issue in this study.

The overall level of missing data for the returned patient-reported outcome measures was negligible (0.3%). However, the return rate was below the feasibility threshold, with a retention rate of 42%. The telephone and postal reminder for non-returned questionnaires did not improve the response. The researcher also asked treating physiotherapists to prompt participants to complete their outcome measures, should they still be receiving physiotherapy management; this accounted for four receipts of outcome questionnaires, each one being completed in the physiotherapy department during a follow-up appointment. It remains unclear why such a large loss to follow-up occurred. This compares to 97% and 96% (at 12-months) in the largest PFP RCT trials to date in the Netherlands and Australia respectively [26,27]. These trials optimised collection of the main outcome measure by telephone follow-ups and e-mail, rather than relying solely on postal mail.

The retention rate was uneven. Twenty-one participants were lost to follow-up (70%) in the loaded self-managed group compared with 14 (47%) in the usual physiotherapy group at six-months. Of note, is the four participants who were prompted by the treating physiotherapists to complete their six-month outcome data during their follow-up appointments were all in the usual physiotherapy group. One further possible explanation for the uneven loss to follow-up rate could be “therapeutic alliance”.

Therapeutic alliance can be described as the working relationship between a patient and a therapist; it is a positive social connection built upon collaboration, communication, and mutual respect [465]. A 2017 systematic review into characteristics of therapeutic alliance in MSK physiotherapy and occupational therapy practice included 130 studies [465]. It concluded that higher levels of therapeutic alliance might result in greater adherence [465]. However, therapeutic alliance is a relationship and therefore develops over time [466]. Participants in the loaded self-managed group received, on average, fewer appointments and for a shorter period – in line with the self-management aim of reducing healthcare burden. Ten per cent (3/29) of participants in the loaded self-managed group were still under physiotherapy care at the six-month follow-up, compared with 55% (14/28) in the usual physiotherapy group. The mean number of appointments were 2.4 in the loaded self-managed group compared with 3.2 usual physiotherapy; this considerably lower than the 7.7 appointments seen elsewhere in the UK [445]. A future definitive trial should make modifications to address participant engagement with the study, particularly after they have been discharged from physiotherapy. Strategies could include weekly telephone calls, frequent newsletters, and the use of e-mail or text messaging for measuring adherence or patient report outcome measures. Future studies may also need to consider measuring therapeutic alliance.

6.4.4 Strength and limitations

The principle strengths of this research are the comprehensive use of a mixed-methods approach, which was based on the recommendations of the MRC for the evaluation of complex interventions [4]; the use of concealed random allocation, and its pragmatic evaluation of physiotherapy assessment and interventions.

- The overarching benefits of a mixed-methods approach based on the recommendations of the MRC [4] have been discussed in detail in Chapter 1 of this thesis.

- A lack of randomisation in medical research trials is a real challenge for selection and confounding bias [467]. Without concealed randomisation, there is a high risk of bias from unequally distributed known and unknown characteristics [468], and a high risk of bias from researchers knowing the group allocation of a participant before they are recruited [469]. Certain study design methods can minimise the risk of bias, such as prospective design, concealed allocation, and adjustment of baseline results with respect to confounders [467]. However, the gold standard method for reducing selection and confounding bias it concealed randomisation [470]. The method employed by this feasibility RCT was a web-based randomisation service using random variable block-size and represented an acceptable method for concealed randomisation, with comparable baseline patient characteristic.

- A pragmatic design was undertaken with this trial. The inclusion criteria used to select participants is widely accepted and required no specific orthopaedic tests [2]; hence participants in this study represents similar patients that could be identified in routine clinical practice within the NHS. Furthermore, the intervention was designed to align with current NHS clinical settings and could be delivered in typical physiotherapy NHS appointment times, without any special equipment or resources. Also, as the intervention was pragmatic in design, it allowed clinical judgment and decision making by the treating physiotherapist, such that exercise prescription was individualised based on examination findings and the patients' response to exercise and progressive load. Since pragmatic trials are designed to inform clinical decisions about an intervention, for a broad range of patients, in a broad range of usual care settings [471], the expected heterogeneity of the participants addressed by the individuality of treatment, is considered a strength [472].

In addition to the high loss to follow-up and poor exercise diary completion, which has been considered in detail in the previous sub-section of this discussion, study limitations included, one

researcher being responsible for the whole study; the research being conducted at a single centre and baseline patient-reported outcome measures being completed in front of an unblinded assessor.

- One researcher was responsible for the whole study. This included overall responsibility for the planning, designing and delivering of all stages of the research. These are elements which may increase the risk of bias; for example, systematically over or understating the truth due as a result of hope of expectations [473]. However, specific characteristics were incorporated into the design of the study. For example, utilising second and third reviewers in the background systematic reviews; periodic trial steering group meetings involving all stakeholders with a clear governance structure; the use of a medical statistician's help to double check statistics; and internal and external peer-review of all stages of the research represented in this thesis.

- The study was conducted at one NHS physiotherapy outpatient clinic, at a large teaching hospital in the East Midlands. It is therefore unclear to what extent the validity of the data holds across other settings [474], with variations in NHS organisations, patient populations and physiotherapy populations; thus reducing the study's external validity. Whilst baseline demographics, symptom duration and average pain scores were comparable to previous trials in PFP [74,475]; a definitive RCT would be required to be multicentred to improve generalisability [474].

- It is well recognised that unblinded assessors in medical research trials can introduce bias. For example, if a researcher has a strong predisposition towards one group or another in a trial, they may misclassify results, characterised by "optimism error" or "intervention preoccupation" [476]. Future trials should introduce blinded assessors to reduce this risk of bias [474].

6.5 Conclusion

A loaded self-managed exercise programme designed around: pain education; a loaded exercise programme; and self-management strategies, is feasible and acceptable to deliver in an NHS physiotherapy outpatient setting. However, the present study demonstrates that further feasibility work may be needed to address differences in loss to follow-up and poor diary completion. These methodological issues need addressing, before supporting a larger clinical trial which will evaluate the clinical and cost-effectiveness of a loaded self-managed exercise programme for people with PFP compared with usual physiotherapy.

The next chapter will discuss the findings on the qualitative embedded component investigating implementation barriers and facilitators of a loaded self-managed exercise programme in an NHS setting. The results from all components of the research will then be synthesised in Chapter 8 which provides an overall discussion and conclusions, concerning the main aims of the thesis as a whole, discussed in Chapter 1.

Chapter 7 - Phase Three: Qualitative Interviews

Summary

This chapter reports the findings of the embedded qualitative study in the feasibility RCT discussed in the previous chapter (referred to as Phase Three in the protocol, Appendix C). The aims of this study were to explore the possible implementation barriers and facilitators of a loaded self-managed exercise programme in an NHS setting, from the perspective of patients and physiotherapists.

7.1 Introduction

With respect to the aims of the thesis as a whole, this chapter aimed to explore the possible implementation barriers and facilitators of a loaded self-managed exercise programme and to understand the feasibility of delivering a multi-centred RCT. The rationale for this exploration relates to the background previously discussed in this thesis. Firstly, the synthesis of self-management interventions for chronic MSK pain provides a foundation that rehabilitation programmes should aim to reduce pain catastrophising and improve physical activity levels to improve patient outcomes [477]. So far, no previous exercise-based intervention within the PFP field has successfully investigated that or explored the feasibility of delivering a multi-centred RCT. Secondly, protocols that use loaded exercises are typically painful to perform [333], with pain thought to predict poor exercise adherence [478] and does not align with current UK physiotherapists' preferred treatment approach [281]. Thirdly, pain education and increasing physical activity require a certain level of self-management and personal responsibility on the part of the patient and are also strong predictors of poor exercise adherence [478]. Moreover, a key aspect of the loaded self-managed exercise programme is the single exercise method, which physiotherapists and patients historically viewed with a degree of scepticism, when used in treating shoulder pain [282,479], and again does not align with current UK physiotherapists' preferred treatment approach for PFP [281].

A secondary aim of this study was to explore participants' experience and thoughts of study design parameters. To fully examine the aims of this study, patients and physiotherapists receiving and delivering both the intervention and usual physiotherapy were interviewed.

This research was undertaken within a framework of mixed-methods, embedded within the feasibility

study presented in the previous chapter.

7.2 Method

A qualitative study was conducted embedded within a mixed-methods feasibility study. The framework approach was the most appropriate method for inquiry, as the objectives of the investigation were set *a priori* [480].

This study has been reported in line with the COREQ [312].

The authors took an epistemological position described as “contextualist” by Braun and Clarke [311]. Through this, the beliefs and perceptions of a person generate experience at an individual level, with any meanings attached, whilst considering the wider context within a sociocultural perspective. This position has been discussed in detail in relation to this mixed-methods study design in Chapter 4 of this thesis and sits centrally on the spectrum of realism and constructivism.

7.2.1 Participants

A purposive sample of ten patients with PFP were recruited from the 60 patients who were recruited to the feasibility study; this included patients in the intervention group and those receiving usual physiotherapy. Based on similar studies, it was anticipated this sample size would be sufficient to reach data saturation [282,479]. Patients were selected based on representation of a spectrum of population in terms of: intervention delivered (both the intervention, and usual physiotherapy), age, gender, return of outcome forms, and clinical outcome, as determined by a global rating of change at follow-up measured on a 7-point Likert scale ranging from “completely recovered” to “worse than ever” [333]. Clinical responders were defined as “completely recovered” or ”strongly recovered” [333]. Attempts were made to interview those lost to follow-up and non-responders in both groups.

Initial recruitment to the feasibility study included gaining consent for taking part in future qualitative investigations. Participants were initially followed up by a telephone call. If they agreed, a convenient time was arranged to complete an interview. Participants were given the opportunity to discuss what the interview involved before they started.

Ten physiotherapists were purposively sampled, this included those delivering the intervention and those delivering usual physiotherapy. Based on similar studies, it was anticipated this sample size would be sufficient to reach data saturation [282,479]. Again, physiotherapists were selected based on characteristics to represent a spectrum population regarding intervention delivered, age, sex and length of time qualified. The physiotherapists initially agreed to take part in the research when briefed

during the study intervention training sessions. They were subsequently approached about the qualitative component of the study via team meetings. Participants were given the opportunity to read the participant information sheet and to ask any questions before the consent form was signed.

7.2.2 Recruitment

All participants were interviewed at a convenient time in the hospital-based physiotherapy department. The researcher (BES) introduced himself as a physiotherapist working in that department, and as a researcher conducting a PhD. The researcher explained the aims of the study. Verbal consent was taken to start recording.

7.2.3 Data Collection

Semi-structured interviews were designed by the researchers (BES and FM) using topic guidelines with prompts to explore barriers and facilitators to taking part in a loaded self-managed exercise intervention. Patients from both treatment groups were asked about the response to treatment, beliefs and attitudes to pain, beliefs and attitudes toward physical activity, treatment expectations and protocol parameters. Only those in the intervention group were asked about their engagement with the loaded self-managed intervention. All physiotherapists were asked about their usual practice, personal development, beliefs and attitudes to pain, beliefs and attitudes toward physical activity and protocol parameters. Only those delivering the intervention were asked about their engagement with the loaded self-managed intervention, including the training package. The interviews ranged from five to 21 minutes (mean time: 11 minutes) in duration.

For pragmatic reasons, the interview guide was not piloted. However, the researcher maintained a reflective journal, noting down initial thoughts and ideas after each interview [309]. This identified that the first two interviews raised matters relating to responsibility and locus of control around a return to physical activity. This was incorporated into subsequent interview schedules for both patients and physiotherapists.

7.2.4 Data Analysis

All audio files were collected and transcribed verbatim.

The data were analysed using a thematic Framework Method [480], which was the most appropriate method for inquiry, as the objectives of the investigation were set *a priori* [480]. Furthermore, data analysis can be conducted systematically, allowing the data to be explored in depth while simultaneously maintaining an effective and transparent audit trail [480]. During transcription, initial

thoughts and ideas were noted in the reflective journal. Audio files were listened to several times to check for accuracy, and transcriptions were read and re-read a number of times; this data familiarisation further informed the development of a thematic framework. Following familiarisation, both authors agreed on the initial thematic framework. Data coding then identified and coded pertinent features of the data giving equal priority over the whole dataset. These steps were independently conducted by two researchers (BES & FM) who met to compare codes. This formed a working analytical framework upon which the data were examined. The transcripts were then indexed using the categories and codes on the working framework. During this process, the data were organised according to the defined thematic framework. Charting was then used to summarise and display the data by category and theme for each transcript [480,481]. Indexing was initiated by one researcher (BES), prior to charting, and subsequently developed and verified by a second researcher (FM).

Data were organised and analysed using QSR International's NVivo 11. After ten interviews per group, it was determined by the researchers that data saturation had occurred as no new thoughts or concepts were generated in the later interviews.

7.3 Results

The ten patients included three men and seven women, aged between 26 to 37 years (mean: 30.6 years), with a diagnosis of PFP for a mean duration of 25 months (range: 3 months to 10 years). The ten physiotherapists included two men and eight women, aged between 24 to 58 years (mean: age 39.4 years), with a mean of 16 years qualified (range: 3 years to 37 years). Full patient and physiotherapist characteristics are presented in Table 19 and 20 respectively.

In respect to barriers and facilitators to delivery of the intervention, the five major overlapping themes that emerged from the data were: (1) locus of control; (2) beliefs and attitudes to pain; (3) treatment expectations and preference; (4) participants' engagement with the loaded self-managed exercises; and (5) physiotherapists' clinical development. With regards to trial feasibility, the final theme to emerge was (6) research parameters. Locus of control was one overarching theme that was evident throughout the data.

Table 19 - Characteristics of patients (qualitative interviews phase 3).

Participant Number	Gender	Age	Duration of symptoms (m)	Intervention Received	Clinical Responder
P1	M	22	120	Intervention	Responder
P2	M	30	12	Usual Physiotherapy	Non-responder
P3	F	33	5	Usual Physiotherapy	Non-responder
P4	F	33	18	Usual Physiotherapy	Responder
P5	F	31	3	Intervention	Responder
P6	F	36	18	Usual Physiotherapy	Non-responder
P7	F	35	12	Usual Physiotherapy	Responder
P8	F	26	36	Intervention	Non-responder
P9	M	37	9	Intervention	Responder
P10	F	36	12	Intervention	Responder

F, female; M, male; m, months; Physio, physiotherapist

Table 20 - Characteristics of patients (qualitative interviews phase 3).

Therapist Number	Sex	Age	Length Qualified (y)	Intervention Delivered
T1	F	39	17	Usual Physiotherapy
T2	F	30	5	Intervention
T3	M	29	7	Intervention
T4	F	45	22	Intervention
T5	F	56	36	Usual Physiotherapy
T6	F	50	30	Usual Physiotherapy
T7	F	58	37	Intervention
T8	M	25	3	Intervention
T9	F	38	3	Usual Physiotherapy
T10	F	24	3	Usual Physiotherapy

F, female; M, male; y, years

7.3.1 Theme 1: locus of control

Locus of control is a psychological construct about the degree people believe they have control over their actions and outcomes [482]. A key feature of the intervention being evaluated in the RCT is the self-dosing of exercise, based on the symptomatic response, and the self-managed approach to physical activity. This could be conceptualised as the internalising locus of control with the patient and is thought to predict treatment compliance, acting as a barrier or facilitator to implementation [478]. Patients within the intervention group described narratives that could be conceptualised as a greater internal locus of control, compared with patients in the usual physiotherapy group.

R: And how did you feel about being in charge of that [the exercise]?

P8: Yeah. I think it was empowering in a way. [Loaded Self-Managed]

Early interviews raised matters relating to whose authority it was to give the "permission" to return to, or increase, physical activity; including when and how this should be done. Again, apparent differences between usual physiotherapy and the intervention could be seen, particularly with physiotherapists' management approach to physical activity.

"Ultimately up to the patient really. They should feel in charge of what they do. They need to have control of the situation. If they're just waiting for somebody else to dictate that, then they haven't got very good control. But they might need some encouragement or reassurance that it's okay to actually, if you want to get back to these activities you can. You don't need to ask me permission really." [T2 – Loaded Self-Managed].

"I would usually kind of bat it back to them and say, 'Well, what do you think you can do?' And using the same principles as with the exercises, if you're getting some discomfort at the time, it doesn't mean to say you then stop. And just see how it is afterwards, and then modify how much you're doing in response to how much pain you're experiencing afterwards." [T4 – Loaded Self-Managed].

Contrasting the push for an internal locus of control with the intervention was a narrative discussed by some patients receiving usual physiotherapy. For example, Participant 4 had indicated she was "strongly recovered", had minimal pain and had returned to almost all of her usual activity. However, she had not returned to the gym yet and had booked a follow-up appointment with the treating physiotherapist for after the interview where she hoped to receive the "go-ahead" to return.

And this patient narrative was reinforced by the treating physiotherapists' understanding of their role:

"I'd assess them functionally. So, you kind of break down that hobby or that activity into sections. So, if it's a sport, look at part of it… and if you can't do two or three of them, it's not just your knee that's letting you down. Generally, you're not quite ready for that." [T10 – Usual Physiotherapy].

A few of the physiotherapists within the usual physiotherapy group viewed their role more of a partnership with the patient, where decisions about return to activity were agreed mutually.

"Well, it'd be a mutual thing. A lot of them weren't sporty, but they would ask, and we discussed the suitability." [T5 – Usual Physiotherapy].

Locus of control is interrelated to the psychological construct of self-efficacy, where it relates to the power of thinking in achieving treatment outcomes [483]. The loaded self-managed exercise programme is designed around optimisation of self-management and self-efficacy. For example, the progressive hierarchy of the exercise demonstrates and provides evidence to the patient that they are systematically approaching their clinical and personal goals [409]. Some patients within the intervention group expressed views that could be contextualised as self-efficacious in line with this hierarchy.

"That sense of just you know how much progress you made. A week ago, you did 20, and now you did 30 or 40." [P9 – Loaded Self-Managed].

"When I hit the target and I then thought, "Oh, I can actually do a few more," and it's comfortable to do, I did do that." P5 – Loaded Self-Managed].

7.3.2 Theme 2: treatment expectations and preference

Previous qualitative work has identified unmet treatment expectation as a potential barrier to treatment adherence [484,485]. Therefore all patients were asked to reflect upon their expectations, with physiotherapists invited to discuss their usual practice. The predominant patient expectation was that they would receive some form of exercise programme from their physiotherapist and that this would probably involve some level of pain.

A small number of patients discussed an expectation of hands-on passive treatment.

"I was more expecting sort of a hands-on approach, more like physio massage when I came." [P8 – Loaded Self-Managed].

Furthermore, in keeping with themes found in other PFP qualitative work [477], several patients

established a clear wish for questions to be answered, in relation to causative factors around their pain:

> *"For me, I wanted answers on why my knee was painful. Because I think, going back ten years ago, when I first went to my doctor's, I was told it was ligament damage. And it didn't clear up, and when I went back, it was like, "Well, the waiting list for physio is so long, by the time you get there, you'll be recovered." And then, when I went back again, it was like, "Well, you're too young to have steroid injections." And then, I just always felt I was like, in a sense, sent packing without any answers. And then, I wanted some answers as to why it's hurting so I could understand it." [P10 – Loaded Self-Managed Group]*

Previous qualitative work in patients with PFP found a dominant negative view of physiotherapy [477], with one patient similarly expressing an initial negative view of seeing a physiotherapist.

> *"The physio-- I don't know, I was a bit sceptical, to be honest. But yeah, it has given me the result I wanted." [P10 – Loaded Self-Managed].*

All physiotherapists reported that their current practice and preference for treating PFP included an exercise programme. However, in contrast to the majority of UK physiotherapists [281], they all reported an expectation that exercises would be performed with a degree of pain. Though there remained a large amount of heterogeneity regarding language choice, and what parameters were used, when discussing optimal exercise dosage with patients.

> *"But if you think about a VAS or something like that … probably you wouldn't want your pain to be greater than maybe a three or a four out of ten." [T1 – Usual Physiotherapy].*

> *"Quite oftentimes I tell people to do reps to kind of fatigue, but not to pain. So, people are getting a bit of a niggle, if they can manage it, and they can bring the pain level back down quite quickly afterwards. So, if they can do exercises, it aggravates it, but within about a half an hour, symptoms have settled, then that's fine." [T10 – Usual Physiotherapy].*

Dissonance between the single exercise approach used in the intervention and treating physiotherapists' preference was evident. The single exercise approach was not favoured by any of the physiotherapists interviewed:

> *"I think possibly the intervention was simpler to do in the fact that it was geared, sort of guided around one exercise. And probably, what I would have done before is perhaps give more exercises and chop and change them maybe a bit more frequently." [T7 – Loaded Self-*

Managed].

Additionally, some physiotherapists were very prescriptive with their exercise dosage.

"Initially I might start with them with 15 repetitions and work to three sets, two-minute break in between". [T9 – Usual Physiotherapy].

Again, in contrast to the majority of UK physiotherapists [281], and similarly to the experimental intervention, many of the physiotherapists interviewed in this study (from both groups) would try to encourage the patient to self-dose their exercise:

"I'm a little less strict on sets and reps. I'm more do what you feel you can. If you're happier, push on a little bit more." [T3 – Loaded Self-Managed].

As identified above, most patients were content with the anticipation that exercises would be painful, and this matched current clinical practice with the physiotherapists interviewed, despite not aligning with UK wide current practice [281]. Where departmental practice did align itself more closely with UK wide practice, was with regards to the number of exercises prescribed, in clear contrast to the single exercise approach with the intervention.

7.3.3 Theme 3: beliefs and attitudes to pain

Interlinked to all the themes, particularly locus of control were patients' and physiotherapists' beliefs and attitudes to pain. There is a growing body of evidence suggesting that physiotherapists with a biomedical orientation to pain are more likely to advise patients to limit their physical activity due to pain [76–78]; and consequently may induce fear-avoidant behaviours onto their patients [78,89], acting as a clear barrier to implementation. There were examples in the usual physiotherapy group of biomedical models of diagnosis and management with misconceptions of "tissue damage":

"She [the physiotherapist] gave me exercises to do. I've always been keen on the gym. I go to the gym. I was a doing a lot of the stuff she's asking me to do, anyway. Or it's probably more about my technique. I was maybe not doing it as well as I could have done. So, I fell back. …So, she referred me for scans on both knees-- well, referred me back to my doctor. My doctor referred me to an orthopaedist. They referred me for a scan on both knees. The MRI scan showed this knee's absolutely fine - which it's not." [P3 – Usual Physiotherapy].

R: So, if they're not achieving that, would you advise them not to run then?

T10: Probably. Yes. I'd probably have a look at them, and if they were really antalgic on their

gait, then yeah, tell them not to bother, to work on their weaknesses, and then reassess it a bit later down the line. Because otherwise, they might just end up making their knee ten times worse because they're running on a weakened, less-controlled knee. [Usual Physiotherapy]

Of interest is that the physiotherapist delivering the usual physiotherapy, as described in Theme 2, did describe treatment preference not fully aligned with the majority of UK physiotherapists [281], and the best practice guidelines [51], in as much as they expressed a belief that pain is acceptable during exercise. Certainly, this did identify some fidelity and contamination concerns with regards to usual physiotherapy:

"I think it was sometimes a bit hard to stick to usual physio, because we still keep reading. We try to keep up with what's happening… So, it's just a bit of reading and then I change 'usual physio', it keeps developing as you work." [T9 – Usual Physiotherapy].

Despite this, there were marked differences in the patients' and physiotherapists' beliefs and attitudes to pain in the intervention group, compared with usual physiotherapy, demonstrating some re-conceptualisation of pain. This suggests the training programme did improve contemporary knowledge of pain science.

"Yeah, the pain wasn't excruciating or anything. At no point did I think, "I can't keep doing this." It was a fairly normal level, I'd say. It wasn't anything that would make me come back, and say, "I'm worried that I'm doing something wrong," or anything like that. It was fairly normal. I wouldn't say it was too bad." [P1 – Loaded Self-Managed].

P7: The physiotherapist said to go ahead and run if it wasn't going to do any damage. Yes, if it's painful, stop. [Usual Physiotherapy]

"My own thoughts have been, I think, changed definitely with this intervention. I think exercise is-- I've always said to patients that if it's painful, they can still carry on. But again, like I said, I gave that arbitrary figure. If it goes above this, then maybe taper down... But actually, maybe educating them and telling them, "Pain isn't an indicator of damage. You can push through into it a little bit, but it just has to be something that you're comfortable with." And I think the thing that changed with me saying that to patients was I am not the one that's going to dictate that. You're the one has to go through this." [T3 – Loaded Self-Managed].

There was one example of mixed messages from the patient, with regards to acceptable and appropriate levels of pain during exercise and physical activity. This may suggest the heterogeneity in physiotherapy advice, as previously discussed in the second theme with physiotherapists, may have a

negative effect with increasing levels of uncertainty. This is in keeping with the research findings from Chapter 4, demonstrating an iatrogenic effect with physiotherapy treatment for PFP relating to diagnosis uncertainty and fear-avoidance behaviour [477].

> *"He [the physiotherapist] recommend that I didn't run, which is probably the only thing I don't do now. I think it was the impact. Like, my knee with my cartilage. That's why he didn't recommend it at that point." [P10 – Loaded Self-Managed].*

7.3.4 Theme 4: participants' engagement with the loaded self-managed exercises

Only patients and physiotherapists receiving or delivering the intervention were asked to discuss their thoughts about it. Both patients and physiotherapists reported several different ways in which they interacted and connected with the intervention. Firstly, the intervention laid the foundation of re-conceptualisation of pain-related fear where the physiotherapist educated the patient about pain mechanisms [333]. Descriptions of tissue-based pathology models of pain, e.g. patella mal-tracking, or limb mal-alignment were actively discouraged and challenged by the physiotherapist. The aim was for the patient to gain an evidence based understanding of dysfunctional central nociceptive processing as an explanation of chronic and persistent pain and the role and impact of fear.

> *"Once you'd explained-- all the key is in the explanation about pain and how pain works and explaining why they're doing it from that. And in fact, sort of the particular girl I'm thinking about, she'd stopped going downstairs because of the pain. When I reviewed her last time, she said, "Well, I haven't been avoiding the stairs." [with no increase in pain levels] So it's good stuff." [T7 – Loaded Self-Managed].*

Other critical aspects of the intervention discussed by the participants were the self-dosage of the exercise, based on the symptomatic response, rather than being prescribed by the physiotherapist. These aspects were all discussed positively, with no negative features identified.

> *"I think for me I've got results a lot quicker, so because I was kind of going through the pain with all that. And I definitely stuck with the exercise more, because when I first started with one exercise I might get a bit bored. But I've definitely stuck to it more." [P9 – Loaded Self-Managed]*

The simplicity of a single exercise approach was discussed by all the interviewees, predominantly in a positive manner.

> *"So, I think it's quite simple, so if I do ever get-- the problem starts to occur again, it's no real*

problem to just start." [P1 – Loaded Self-Managed].

However, one physiotherapist admitted to being initially sceptical that one exercise would be enough.

"And using that single exercise as that treatment. So, in terms of my thoughts before, would that be enough for my patients? And the ones I've seen, have seemingly done well with just one exercise, rather than having four or five different exercises to do." [T3 – Loaded Self-Managed].

The key feature of patients self-dosing their exercise, based on the symptomatic response, is an understanding of when and how to progress or regress the exercise. Patients recognised the role of "trial and error" in this process, and the relevance of the pain education prior to the exercise programme being implemented.

"I do remember, initially, there being kind of a week or two, maybe, where I was kind of finding kind of the right amount [of the exercise to do]." [P9 – Loaded Self-Managed].

"I think what you tend to do as physios, we very often tend to be quite prescriptive. And patients do ask that. They want to know how many they should do, how many times a day, whereas this is actually giving them much more their own power of making them decide what they're going to do. So actually, hopefully, then they're going to carry on with it in the future." [T7 – Loaded Self-Managed].

Interlinked to self-dosing was the expected pain flare-ups when patients overdosed their exercise or physical activity. The physiotherapists' training programme at the start of the feasibility study covered this topic, with physiotherapists aiming to discuss self-management approaches at preventing and dealing with flare-ups. Despite this, flare-ups did occur and were a cause of concern for several patients; suggesting this topic needs additional emphasis in any future training programme.

R: Did it worry you when you had those flare-ups?

P1: Yeah. There were kind of back-of-your-head thoughts, like, "What if this time I have done it a bit too far? If it lasts a bit longer, am I going to have to go back in case I've damaged it a bit?" or anything like that. But most of the time, again, was two days tops. So, I did have kind of a little niggling worry, but nothing to kind of cause me to do anything or anything like that. [Loaded Self-Managed]

Both patients and physiotherapists were asked to reflect upon the intervention and their clinical response. For patients, quantitatively, the global rating of change at follow-up (measured on a 7-point

Likert scale ranging from “completely recovered” to “worse than ever”) was used to identify responders and non-responders. The scale was dichotomised so that responders were defined as “completely recovered” or “strongly recovered” [333], and patients were purposively sampled to ensure that responders and non-responders were included. However, one patient (Participant 8) who received the intervention identified quantitatively as a non-responder. However, qualitatively all five patient participants interviewed from the experimental arm reported improvement and satisfaction with the loaded self-managed intervention.

> *”Yeah. I'm playing football again. Yeah. I'm just kind of…sometimes I can tell I've got a little bit of tension there. But I'm not getting pain. It's not stopping me doing nothing at all. So yeah.” [P9 – Loaded Self-Managed].*

And this corresponded from the feedback from the treating physiotherapists, with all physiotherapists reporting favourable outcomes with the intervention.

The primary emphasis on patients’ and physiotherapists’ narrative was the simplicity of the exercise, the loaded element of the exercise, and the self-dosage of the exercise.

7.3.5 Theme 5: physiotherapists’ development

It is thought that difficulties accessing and understanding research, and professional isolation may act as barriers to implementation of research into practice [486]. Therefore, treating physiotherapists, in both the usual physiotherapy and intervention groups, were asked to reflect upon their clinical development; particularly on beliefs around pain and exercise, and how they have developed their management approach to PFP. There was a common theme amongst all physiotherapists of clinical development over the preceding few years, with concomitant changes within their management approaches. This reflection attributed some of this development, in part, to working within a department where clinical trials were being undertaken, with exposure to contemporary thinking and practice.

> *“I don't think I ever would have said to people, "Don't push into any pain." I think over the years I've probably got-- as research projects and things we've done where we're kind of talking more about it being okay to push into pain, I've got more relaxed with it… I think maybe as a junior I might have done, to be honest. So probably when I did my first rotation, I might have been saying more, "Very, very low," or, "It needs to be virtually pain-free." But as the years have gone on, probably got more and more relaxed with saying it's okay, on the back of, I*

suppose, of the things that have happened in our department and changes in practice generally." [T1 – Usual Physiotherapy].

"I think from when I first started practice, it would have been different. So, when I first started, I would often tape the knee, or if they came back and said that it was painful, I asked them to kind of back off. Almost think about off-loading the knee if it was painful. So, trying to reduce activity if it was sore. And then I think just as I became more experienced and read more about that type of thing, I got more confident in not using adjunct and trying to use loaded exercise and reassurance about pain. So, I think it fits more with my current practice, and I don't think it was that different. Obviously, I do a lot of pain education with back patients, so I think that was quite easily transferable." [T8 – Loaded Self-Managed].

Department culture has been identified in previous qualitative work as a facilitator or barrier to change, over and above research evidence and clinical guidelines [487,488], and the physiotherapists within this study also reflected upon department culture as a driver of practice.

"I guess in this department we're quite used to doing that sort of intervention for these patients, so it wasn't particularly ground-breaking to me, in a nice way [laughter]. It's your [the researcher's] fault." [T2 – Loaded Self-Managed].

*"Oh, it is working in a different environment as well. So, when I was in ** I was most of the time by myself in a GP clinic. And you don't get a lot of interaction. That influence, when you actually have a bigger [department]. We talk about loading as well. So, we talk about Achilles or tendons and we just keep talking about how everything changes, and you just do your own research and you think, "Okay." How to make it better." [T9 – Usual Physiotherapy].*

Two physiotherapists discussed that being part of the research challenged their current practice and resulted in clinical development to both patients with and without PFP: one told how the training package and personal reflection of treating study patients challenged him, the second revealed how it sparked a general interest in research.

"I think if you tell them, "Actually, how do you feel about it. You're in control," gives them the onus to take what they do. That's definitely changed massively. And I kind of do that with other patients now as well, not just the knee patients. I'm a little less strict on sets and reps. I'm more do what you feel you can. If you're happier, push on a little bit more." [T3 – Loaded Self-Managed].

7.3.6 Theme 6: research parameters

All participants, both patients and physiotherapists, were asked to reflect and discuss their thoughts on the design of the feasibility RCT, considering: recruitment and randomisation, outcome measures and the training package (intervention group physiotherapists only).

7.3.6.1 Recruitment and Randomisation

All patients' comments about the information sheets and letters sent to their home were positive, with no concerns raised.

> *"Yeah, they really helped me to decide [to take part]." [P2 - Usual Physiotherapy].*

Also, patients were generally positive about the recruitment process to the feasibility RCT, including receiving a telephone call, the appointment and randomisation process.

7.3.6.2 Outcome Measures

Participants reflected upon appropriateness, ease of filling in and returning, and time taken to complete the questionnaire booklets. All, patients were positive about them, with seven patients happy to give no feedback.

> *"Yeah. The questions, I mean, all seemed fairly normal. I wouldn't have any issues understanding what it was actually asking me or anything." [P1 - Loaded Self-Managed].*

Three participants provided feedback about the clinical outcome measures; including recommendation on the addition of a text-box to write open text, if needed; less ambiguity about if the questions were being asked in relation to just their knee pain, or their whole body; wording of the physical activity questions that one patient felt implied they were not already physically active; and use of the word "accident" in a patient group where the pain usually developed insidiously.

Five participants were contacted who had failed to return any outcome measures. All five initially agreed to be interviewed; unfortunately, four failed to attend. Of the ten patients who were interviewed, five returned all outcome measures, four returned one, and one patient failed to return any outcome measures. Of the patients who failed to return all of their outcome measures, four of them stated that they had, suggesting some problem with the pre-paid envelopes and return of the paperwork back to the physiotherapy department at the hospital.

> *"I did send them both back." [P10 - Loaded Self-Managed].*

However, the one participant who did acknowledge failing to return one of their outcome measure packs reported that it was due to forgetting, with some difficulty regarding living in different places as a university student.

> *"Think I might have forgotten it and then ended up leaving it at home before I came. Because I live in halls here." [P1 – Loaded Self-Managed].*

7.3.6.3 Overall Study Design

Participants were also asked to reflect on the ways in which study design could be improved. In addition to the feedback already mentioned about the outcome measures and diaries, other improvement ideas were: the use of text message reminders (filling in and returning the outcome forms) and information concerning what would happen if they did not respond to treatment whilst in the study.

Finally, physiotherapists were asked to reflect upon, and discuss, their thoughts on the training package delivered at the start of the feasibility RCT. No major concerns or improvements were mentioned; however, the physiotherapists did reference the moderate frequency of other clinical trials running in the department, particularly ones incorporating pain science, suggesting a practised competence at interpreting new information and implementing into clinical practice, that departments not accustomed to clinical trials may find difficult.

> *"No, it wasn't a culture shock or anything that I felt I needed to kind of do very differently." [T4 – Loaded Self-Managed].*

> *"It depends on what your experience is of pain education prior to that. I knew quite a lot about pain education before, so it wasn't new information that you were trying to have to absorb and then impart. And I think it is a skill that people have to practice." [T7 – Loaded Self-Managed].*

7.4 Discussion

7.4.1 Main Findings

In respect to barriers and facilitators, the five major overlapping themes that emerged from the data were: (1) locus of control; (2) beliefs and attitudes to pain; (3) treatment expectations and preference; (4) participants' engagement with the loaded self-managed exercises; and (5) physiotherapists' clinical development. With regards to trial feasibility, the final theme to emerge was (6) research parameters. Locus of control was one overarching theme that was evident throughout the data.

This qualitative study aimed to identify barriers and facilitators to the implementation of a loaded self-management exercise programme, which included education and advice on physical activity. Contrary to popular concerns relating to adherence to painful exercises [281,439,478], all patients in the intervention group reported positive engagement. However, occasionally flare-ups from overdosing happened, with some patients expressing concern over reoccurring thoughts of "tissue damage"; this may be relevant to all patients receiving an exercise programme. This topic needs additional emphasis in any future training programme delivered to the physiotherapists. Previous research has identified physiotherapists' negative beliefs around pain and exercise as a potential barrier to loaded exercises [282], but this was not apparent with the physiotherapists from both groups interviewed in this study; this may be due to department culture where the research team also works clinically. However, despite physiotherapists stating they were happy with exercises being painful, the data demonstrated a degree of heterogeneity in terms of what is considered acceptable, both in terms of what the physiotherapists said, and the participants understanding of what they were told; in the same way the results from Chapter 3 demonstrated heterogeneity for pain and exercise for a larger UK sample of physiotherapists.

A key aspect of the loaded self-managed exercise programme is the single exercise method. Previous research with a similar approach in patients with shoulder pain identified this as a potential barrier to implementation, with physiotherapists and patients viewing this with a degree of uncertainty and scepticism [282,479]. However, contrary to this research, and despite not aligning with the physiotherapists' usual practice, both physiotherapists and patients generally viewed the single exercise approach positively. Furthermore, there was a general underlying acknowledgement of the key benefits of a single exercise approach, from both patients and physiotherapists, regarding a time-saving approach aimed at optimising adherence, and improved dosage monitoring.

Locus of control is thought to predict health-related behaviours and physical activity [489], with an important concept that it may predict healthcare utilisation [490]. Locus of control and the psychological construct of self-efficacy has overlapping meaning, where it relates to the power of thinking in achieving treatment outcomes [483]. The loaded self-managed exercise programme is designed around optimisation of self-management and self-efficacy. For example, the progressive hierarchy of exercises [409]; self-dosage of the exercise; mastery of a single exercise approach; and self-management strategies for physical activity engagement, providing the foundations for self-management of flare-ups, are intended to reduce the need for direct physiotherapy intervention. It has been shown that the lack of belief in one's own ability to manage and function despite pain is a significant predictor of which individuals with pain become disabled or depressed, with regression

analysis showing that self-efficacy mediates the relationship between pain and disability [332]. Within the context of this study, patients in the intervention group described narratives that could be conceptualised as self-efficacious with greater internal locus of control, compared with patients in the usual physiotherapy group. This could be seen particularly with return to physical activity; beliefs and attitudes to pain; engagement of the intervention with self-dosage of the therapeutic exercise; and self-management.

7.4.2 Implications for this thesis

Previous qualitative work has suggested that department culture is a key driver or barrier to change [487,488], and there were clear examples of department culture within this study directly driving recent changes in physiotherapists' clinical practice. This matched previous physiotherapy qualitative work that has identified reflexion of practice and implementation of change, perhaps expeditiously, in physiotherapists who are directly engaged in research [282]. With recent research demonstrating that research-active hospitals have better patient outcomes [491], this may be considered a good thing. However, the results of this qualitative study suggest that in departments which are actively engaged with research, clinical practice may be driven by members of the research team, in lieu of definitive research results or clinical guidelines. Considering the lead researcher works in the department where the interviews were conducted, and may in part drive department culture, implementation of the intervention in other departments may be more complicated.

Another example of how department culture can affect the research was identified in relation to the training package delivered to the physiotherapists; the interviews identified no barriers or issues with the delivery of the training package. However, positive reference was made to the physiotherapy department's frequency in participating in clinical trials, suggesting the staff were more willing and able to adapt to the suggested evidence based training package than, perhaps, a department less experienced in clinical trials.

Implementation fidelity refers to the degree by which the delivery of an intervention adheres to the protocol and description [491]. Physiotherapists delivering usual physiotherapy differed from the UK's usual practice, and best practice guidelines, largely with regards to the advice given on tolerable levels of pain during exercise and physical activity, and how the number and repetitions of the exercises are prescribed [51,281]. Cluster randomisation is one way of overcoming this problem.

This research demonstrates that even though physiotherapists have certain expectations around management and exercise prescription, their approach was adaptable to the intervention with only two, two-hour training sessions; enabling patients to self-manage and make sensible decisions about

their treatment and return to physical activity. The results of this study establish a skill set needed to deliver the intervention, including complex MSK assessment; anatomy; tissue healing and remodelling; pain biology; peripheral and central sensitisation; psychological and social factors that might affect pain perception; self-management strategies; and education skills. Currently, in the UK, these skills form part of the degree training programme for physiotherapy, further supplemented by the research training package.

7.4.3 Study limitations and strengths

Two authors independently coded all transcripts and used a clear, transparent and reproducible methodological approach to data analysis. The author's clinical and research experience lie within the biopsychosocial framework of MSK pain. It is worth noting that the interviewer made it explicit to the participants that he was a physiotherapist working in the department conducting the research.

Despite efforts to the contrary, the main limitations of this study were the difficulty in interviewing patients lost to follow-up (from both treatment groups) and those classed as non-responders in the experimental intervention group. Therefore, the embedded qualitative component was likely to have a biased sample of participants who had largely positive feelings towards the study. Furthermore, they knew they were being interviewed by the main researcher and may have felt obliged to answer questions favourably. Strategies to reduce this risk such as conducting interviews with an independent researcher or collecting anonymised questionnaires may be considered in future research.

The study population comprised of a single clinical setting, where the researcher was also a clinician and where clinical trials are often undertaken; it is unknown how transferable the intervention is without the relevant physiotherapy training package.

7.5 Conclusion

This qualitative study has identified some of the barriers and facilitators with participants (physiotherapists and patients) with the delivery of a loaded self-managed exercise programme, education and advice on physical activity.

From the patients' perspective, facilitators to engagement included effective education around self-management on exercise dosage; physical activity; and flare-ups. This facilitation may have been mediated, in some part, to enhancements of self-efficacy and internalised locus of control. From the physiotherapists' perspective, these results highlight the importance of "control" and self-management during their assessment and management of patients with PFP.

For most physiotherapists, there was some similarity between their usual practice and the loaded self-managed intervention with regards to the advice given on tolerable levels of pain during exercise and physical activity, with a large degree of heterogeneity of precise terminology used. However, this study demonstrated that members of the research team might have driven the department's recent changes in the clinical practice. Therefore, despite these findings, it may be astute to consider this in the context of the UK's usual management approach for PFP, which showed that a large proportion of practising physiotherapists would advise a patient to cease exercise or physical activity if they experience pain. Therefore, implementation into general clinical practice may be challenging, but, as has now been demonstrated, ultimately feasible.

The results from all three components of the research will now be synthesised in Chapter 8 which provides an overall discussion and conclusions, concerning the aims of the thesis as a whole.

Chapter 8 - Discussion and Conclusion

Summary

This chapter presents the final discussion and conclusion for this programme of study. It draws together the results from the six chapters: the systematic reviews; the survey of current UK practice; the pre-intervention qualitative interviews; the development of the exercise intervention; the feasibility RCT and the embedded qualitative interviews. It provides a summary and synthesis of the results, in relation to the aims of the thesis presented in Chapter 1, and suggests further research in this field.

8.1 Aims of the thesis

8.1.1 Summary of main findings

With respect to the main aim of the thesis as a whole, the results of this thesis confirm that it is feasible and acceptable to deliver an evidence-based novel loaded self-managed exercise programme to adults with PFP in an NHS physiotherapy outpatient setting. However, differences in loss to follow-up and poor exercise diary completion mean there remains uncertainty on some feasibility aspects of study design, with the potential for systematic bias. Further feasibility work may be needed to address these issues, before supporting a larger clinical trial which will evaluate the clinical and cost-effectiveness of a loaded self-managed exercise programme for people with PFP compared with usual physiotherapy.

Chapter 1 summarised the current state of the art on PFP as a burdensome problem with little consensus on the cause. It highlighted significant knowledge gaps concerning the role of anatomical variations and dysfunction in PFP with lack of association between pathology and pain, with traditional pain models that described tissue pathology as a source of pain being insufficient in the assessment and treatment of PFP. It suggested, based on the available evidence, that PFP had much in common with other MSK disorders. It proposed that physiotherapy prescribed exercises designed around contemporary pain models (where exercises are designed to load and temporarily aggravate patients' symptoms), self-management strategies and improvements in physical activity levels may have a role in improving pain and function in people with PFP; this was referred to as a loaded self-managed exercise programme.

In an attempt to generate new knowledge and expand the evidence-base, the primary aim of this programme of research was to establish the feasibility and acceptability of conducting a definitive RCT which will evaluate the clinical and cost-effectiveness of a loaded self-managed exercise programme for people with PFP, compared with usual physiotherapy.

Three discrete but overlapping components of research were proposed to address this aim.

1. Systematic reviews to explore the epidemiology of PFP in the UK; the evidence-base of loaded/painful exercises on all MSK disorders; and a survey of current physiotherapy practice.

2. A qualitative investigation to explore the lived experience of people suffering from PFP.

The first two components of this programme were used to develop the intervention and protocol for the final component of this programme.

3. A feasibility study with a controlled trial component to examine the acceptability and feasibility of the intervention within an NHS outpatient setting. This would contain another qualitative component, embedded within it.

The first systematic review was presented in Chapter 2, part one. Four databases were searched, and 23 papers were included that reported incidence or prevalence data for PFP populations. The review demonstrated high incidence and prevalence levels for PFP, across adolescent, adult, military and athletic populations; within the context of this, and poor long-term prognosis and high disability levels, it concluded that PFP should be an urgent research priority.

The second systematic review was presented in Chapter 2, part two, and started with the premise that, to review the evidence-base for loaded painful exercise for PFP, it would be necessary to not only search for studies focusing on PFP but also to include studies with populations comprising any MSK pain. It focused on RCTs on the understanding that these are perceived as the gold-standard evaluation methodology for treatment effectiveness. The review searched seven databases, and nine papers (seven separate trials) were identified comparing the effect of exercises where pain is allowed or encouraged compared with non-painful exercises on pain, function or disability in patients with any chronic musculoskeletal pain. The meta-analysis found that protocols using painful exercises offered a small but significant benefit over pain-free exercises in the short term, with a moderate quality of the evidence for outcomes of pain. However, there was no difference at medium-term or long-term follow-up, with a moderate to low quality of evidence. For all patient-reported outcomes, clinically significant improvements in measures were reported across all interventions and control exercises, and all time points. It was not clear from the data if one approach was superior to the others. The

review concluded that pain during therapeutic exercise need not be a barrier to successful outcomes and was able to offer some preliminary guidance in relation to contextual factors of pain and exercise prescription. In addition to the aspect of pain, an important difference between the intervention arm and the control arm is the higher loads, or levels of resistance, employed with the painful exercises; and it is unknown if the difference in responses could be attributable to these two elements.

The cross-sectional online questionnaire survey was presented in Chapter 3 and was designed to understand the current management strategies undertaken by UK physiotherapists treating PFP. One hundred were asked to take part, and 99 surveys were completed. The five most common management strategies were identified, and an understanding of physiotherapists' approach to pain and exercises was discussed. The review concluded there was no standardised management approach for PFP in the UK, and there was large variability in response to pain with exercise and leisure activity. Strikingly, 55% of all physiotherapists would advise patients against an exercise if it was painful, and 31% of all physiotherapists would advise patients not to continue with leisure or sporting activity if they experienced any pain. This is an important finding - given that 23% of patients with PFP will stop participating in physical activity or sport altogether, and 50% will drastically reduce their levels [42].

One of the outstanding questions from Chapters 1 to 3, was to the extent to which cultural beliefs around pain and exercise determines behaviour. Chapter 4 presented semi-structured qualitative interviews with a convenience sample of ten participants with a diagnosis of PFP on a physiotherapy waiting list, prior to starting physiotherapy, aiming to address this question. Interviews were analysed thematically using the guidelines set out by Braun and Clarke and covered participants' experience of living with PFP. The participants provided rich and detailed narratives of loss of physical and functional ability; loss of self-identity; pain related confusion and difficulty making sense of their pain; pain-related fear, including fear-avoidance and "damage" beliefs; inappropriate coping strategies and fear of the future. The study suggested the consensus that the best-evidence treatments consisting of hip and knee strengthening alone may not be adequate to address the fears and beliefs identified in this patient population.

The recommendations from the reviews and qualitative interviews were used to develop and evaluate the proposed loaded self-managed exercise programme (Chapter 5). Following this, a feasibility RCT (Chapter 6) was conducted in which 60 patients with PFP were randomised to receive either a loaded self-managed exercise programme (*n*=30) or usual physiotherapy (*n*=30). Feasibility indicators of process, resources, and management were collected through follow-up of standardised questionnaires three and six months after recruitment and semi-structured interviews (Chapter 7) with ten participants and ten physiotherapists.

New knowledge has been generated in relation to the development phase and feasibility testing. This includes:

- understanding incidence and prevalence data;
- producing preliminary guidance of contextual factors with loaded exercise protocols for all MSK pain;
- identifying the current UK physiotherapy management strategies for PFP;
- understanding the experience of people living with PFP;
- synthesising the literature surrounding the mechanisms of effect behind therapeutic exercise for all MSK pain;
- identifying feasibility processes of an RCT, and any implementation barriers and facilitators associated with the intervention and trial parameters.

The secondary aims established in Chapter 1 will now be revisited discussing how this body of research has met these aims, including implications for future practice and research.

8.1.2 Secondary aims 1 and 2

The first and second of the secondary aims of this programme of work were to establish:

1. the scale of the problem of PFP in the UK, and the evidence-base of loaded painful exercise programmes, and identify key components of the programmes in order to refine and develop the intervention;
2. what “usual treatment” is before being able to design the feasibility RCT;

These aims were met in Chapters 2 and 3, with a refinement of the intervention in Chapters 4 and 5; and design of the feasibility RCT in Chapter 6. The results have been summarised in the previous section, 8.1.1.

8.1.3 Secondary aim 3

The third secondary aim was to establish if the devised loaded self-managed exercise programme could be delivered in a UK NHS physiotherapy outpatient clinic. This aim was met in Chapter 6 and Chapter 7. Fidelity, the measure of whether an intervention was delivered as planned [491], was undertaken through qualitative interviews with the participants, and through content analysis of the treating, physiotherapists' notes when marked against a three-point checklist outlining important details and components of the intervention (Table 16).

The qualitative interviews (Chapter 7) highlighted some similarity and contamination of the usual physiotherapy intervention with the loaded self-managed exercise in relation to the exercise delivery. The physiotherapists were happy to instruct patients around pain and exercise. This differs from the usual UK physiotherapist practice for PFP, where the majority of physiotherapists would advise patients not to perform exercises if they were painful (Chapter 3) [281]. However, reassurance can be had from the analysis of the three-point checklist, with 95% of patients receiving the intervention as described in the protocol, compared with 0% in the usual physiotherapy group.

One of the biggest challenges with exercise interventions is treatment adherence and monitoring of adherence. With unsupervised exercises, it is unclear to what degree participants have engaged with the prescribed exercise to obtain a therapeutic benefit — this feasibility study used exercise diaries as a measure of self-reported exercise adherence. However, with such a low return of diaries (5%) the reliability and validity of the results may be limited. Indeed, recent systematic reviews have highlighted the lack of validated and reliable self-report measures for unsupervised, exercise-based rehabilitation adherence [492,493]. Therefore, any future definitive trial may need to consider it unfeasible to monitor adherence through self-reported measures.

8.1.4 Secondary aims 4 and 5

The fourth and fifth aims were to establish if the outcome measures used are feasible and reliable to use within an NHS setting for a definitive RCT. This aim was met in Chapter 6 and Chapter 7 with the threshold for feasibility outcomes for retention not being reached (Table 14), with the overall level of missing data for the returned patient-reported outcome measures being negligible (completeness of data indicators of 99.7%). The retention rate was not only low, but uneven, with 21 lost to follow-up (70%) in the loaded self-managed group compared with 14 (47%) in the usual physiotherapy group at six-months. Patient representatives of the trial steering committee approved the completion time of the questionnaires, and this was confirmed by the qualitative interviews of the participants (Chapter 7). Of the five patients interviewed who failed to return an outcome questionnaire, four stated they

had, suggesting some problem with the pre-paid envelopes. However, internal and external testing of the pre-paid envelopes in the UK and hospital mail system operated correctly. One patient did acknowledge to having failed to return one of their outcome questionnaires saying they forgot.

High participant attrition has been observed in different patient populations, in the same physiotherapy outpatients department, in a large scale RCT (56% at six-months) [113]. A high attrition rate does not necessarily mean that large-scale RCTs are unfeasible [235,494], merely that the sample size calculation and recruitment rate could be adjusted to account for this. Further feasibility work may be warranted to test strategies to improve attrition, including:

- reducing the burden of the number of outcome measures;
- use of technology, e.g. text-messaging for reminders or for using short outcome measures like pain score or GROC;
- asking the treating physiotherapists to remind the participants at three-months;
- relaxing the criteria for success;
- using patient incentives to return forms, e.g. entry into a prize draw;
- using telephone consultations to complete the questionnaires;
- or telephoning participants at evenings and weekends [474].

Interestingly, feasibility studies investigating web-based patient questionnaires have found equally low return rates (33% at 24-weeks follow-up) [495], demonstrating the complexity of finding solutions to this problem.

8.1.5 Secondary aim 6

The sixth aim was to establish a sample size calculation for a definitive RCT, and this was met with the feasibility work in Chapter 6. Further feasibility work may be needed with regards to attrition rates. However, point estimates, confidence intervals (95%), and effect sizes using independent t-tests were presented for all appropriate clinical patient-reported outcome measures in Chapter 6 of the target population, allowing calculation of a sample size when applicable.

8.1.6 Secondary aim 7

The seventh aim was to establish if the intervention is acceptable and tolerable to participants and physiotherapists in the NHS. This aim was met in Chapter 6 and Chapter 7.

Quantitatively, due to the poor return of paper exercise diaries, adherence to the exercise was not adequately measured. However, reassurance can be given from the above threshold adherence to appointments (87%).

Through qualitative interviews with both patients and physiotherapists, an understanding of the acceptability of the intervention was gained; with any potential challenges that may occur with implementation into a large RCT. Patients and physiotherapists perceived some value and benefit from the intervention, which can be seen in the effect sizes of the patient-reported outcome measures (Table 17), though the degree and nature of this benefit were variable, with the aforementioned un-even loss to follow-up. Contrary to popular concerns relating to adherence to painful exercises [281,439,478], all patients interviewed in the loaded self-managed group reported positive engagement. Both physiotherapists and patients generally viewed the single exercise approach positively. A key benefits being a time-saving approach aimed at optimising adherence and improved dosage monitoring.

From the phase three interviews (Chapter 7), patients in the loaded self-managed group described narratives that could be conceptualised as self-efficacious with a greater internal locus of control, compared with patients in the usual physiotherapy group. This could be seen particularly in relation to return to physical activity; beliefs and attitudes to pain; engagement of the intervention with self-dosage of the therapeutic exercise; and self-management. Indeed, as discussed in Chapter 7, locus of control has been shown to predict healthcare utilisation [490], with the mean number of appointments in the loaded self-managed group being 2.4 compared with 3.2 in the usual physiotherapy group; although both considerably lower than the 7.7 mean seen elsewhere in the UK [445].

8.1.7 Secondary aims 8 and 9

The eighth and ninth aim were to establish if it is feasible to recruit and randomise participants and identify any potential barriers to recruitment and, the training package (Appendix D) delivered to physiotherapists. This aim was met in Chapter 6 and Chapter 7. Of the participants interviewed (Chapter 7), both patients and physiotherapists, no barriers to recruitment were identified. However, as the embedded interviews were conducted on recruited participants, it may represent a biased

sample. Furthermore, it may be that the participants interviewed felt inhibited to provide negative feedback because they were interviewed by the main researcher. From a management perspective (Chapter 6), 50 (27.8%) potential recruits were uncontactable via the telephone numbers supplied by the referring healthcare professional. Therefore, any future trial may need to include strategies in the protocol to cross-check potential eligible participants contact details on referrals with primary care databases. However, an observed recruitment rate of 5 per month, eligibility rate of 98.4% and consent rate of 98.4% provide reassurance.

The qualitative interviews identified no barriers or issues with the delivery of the training package to the physiotherapists. Though reference was made to the physiotherapy department's frequency in taking part in clinical trials, suggesting the staff were more willing and able to adapt to the suggested evidence-based training package. The high fidelity rate of 95% provides reassurance that the intervention was being delivered as defined in the study protocol, suggesting the training package was feasible.

8.2 Recommendations for future research

There are a number of different research areas that could be proposed within the field of PFP, including questions around the pathoaetiology; validity and reliability of assessment and diagnosis; understanding risk and prognosis; as well as, conservative management strategies. Some of this research is currently being conducted. For example, research around reliable and valid assessments aiming at identifying relevant "sub-grouping", that might be able to direct specific treatment strategies is currently being undertaken [74]. However, this section will focus on ideas for the conservative management of PFP as defined within this thesis, and the main implication arising from this research is the need for a further powered RCT.

As this thesis was a feasibility study, it was not intended that the results would lead to definitive conclusions on the effectiveness of the intervention, nor lead to changes in practice within the NHS. However, there are several areas of new knowledge that have particular clinical and research implications for PFP, MSK pain in general, with implications for this thesis. These are discussed below.

The patient-reported outcome measures used within the feasibility trial were selected with considerable thought, based on the hypothesised mechanisms of effect around pain-related fear (discussed in Chapter 1 and Chapter 5) and with reference to previous large-scale PFP research [26,27]. However, there are recognised limitations when no standardised outcome set is used within a specific field [496]. Firstly, heterogeneity; the use of different outcome measures at different time points within the same field of research makes it difficult to combine results with other trials in a systematic

review and meta-analysis [496]. Secondly, trials are at greater risk of selective reporting bias; where outcomes are promoted or suppressed during the reporting phase based on the treatment effect size [496]. Lastly, it increases the chance of outcomes not being relevant to the major stakeholders (patients and clinician) [496]; for example, outcome measures chosen to meet the needs of the researcher, such as self-efficacy, with patients not being involved in the decision process, may result in research and interventions not acceptable to the patients. This thesis took steps to minimise these limitations, for example, a named patient representative was involved in the decision-making process around selecting of patient-reported outcome measures, and the trial was preregistered with a trial register (ISRCTN 35272486). However, an important step to a more permanent solution would be the creation of Core Outcome Sets (COS) [496].

A COS is a standardised group of outcomes for reporting in trials for a specific field of research [496], and it is suggested that having clinicians, researchers and patients involved in the process will improve the likelihood of clinically relevant research. To date, work has been undertaken on a COS for PFP [2]. However, this work has not been published and does not have patient or clinician representatives involved. Therefore, further research could be the creation of a more substantial patient and public involvement (PPI) group with one objective being significant involvement in the creation of a COS for PFP. COS have been developed in other MSK disorders, including low back pain [497] and knee osteoarthritis [498]; and have enabled the creation of trial databanks with potential for individual patient data meta-analysis and subgrouping [499,500].

Based upon specific trial processes involved in the feasibility study, and considering a definitive RCT, further feasibility work may need to be carried out. For example, the thesis demonstrated that it is now known that participants can be recruited and physiotherapists can be trained to deliver the intervention, set within a single site where the main researcher worked clinically. What is unknown is:

- if it is possible to recruit sites to a multi-centre study and how the recruitment rate of participants would differ at those sites;

- how local department culture around pain and exercise would affect the fidelity and contamination of the intervention and control, and what form the treatment “manual” or “handbook” would take;

- to what extent could the training package be delivered to multiple sites, and how best to support and monitor those sites through a definitive trial;

- if it is possible, to some extent, to consider the acceptability and feasibility of blinding participants to the group they may be randomised to.

Therefore, in the context of uncertainty, and with regards to the high and uneven drop-out (as discussed in detail in Chapter 6) it may be prudent to conduct further multi-centre feasibility work addressing the above concerns.

As well as considering a COS for PFP, and specific research designs parameters, further research needs to be carried out in respect to medical language and terminology, and its affect on pain and behaviour. Chapter 4 demonstrated how pain-related fear was present in people suffering from PFP and was the first study to demonstrate an iatrogenic effect of healthcare, concerning pain and exercise, in the PFP population. Healthcare for shoulder pain has also demonstrated an iatrogenic effect and recent research has further explained that medical terminology, such as "impingement" may contribute to this [501]. Similarly to shoulder pain, medical terminology is common in the conservative treatment of PFP, such as "weakness" and "patella mal-tracking" [281]. Therefore, further research is warranted into advice given to patients, and the specific language used, and identify any important barriers or facilitators to exercise engagement and good clinical outcomes.

Another consideration within the field of PFP research is the adolescent population. It is well understood that PFP symptoms usually start at a young age, with research suggesting it typically starts between 11 and 13 years of age [24], and continues through adolescence [25], into adulthood [27]. However, within the context of the 2015 IPRR consensus statement [2,30], and research from the APA2011 cohort from Denmark [205] that highlighted differences in the presentation of PFP between adults and adolescents, this thesis presented a body of research explicitly investigating adults. However, a recent novel activity modification and load management intervention, on young adolescents (10-14 years of age), that included advice on pain monitoring, home-based exercises and return to sport guidance demonstrated high rates of successful outcomes; at 12-weeks follow-up 86% of participants who completed the questionnaire reported a successful outcome, based on the same GROC criteria used within this thesis (currently unpublished) [502]. Parallels between the intervention in that trial and the intervention investigated within this thesis can be seen with regards to the pain monitoring component, with participants adjusting the load of activity based on their own assessment of symptoms, to introduce and expose the knee to greater loads gradually. No comparison group and no randomisation limit the usefulness of the results. However, with such a shortage of high-quality research on which to base practice, particularly in adolescents in the UK, and the parallels between the two interventions, further research in the NHS should now progress to include adolescents.

From a public health point of view and considering MSK pain in general, this thesis has generated important knowledge that should be researched further as a priority. For example, (as previously mentioned) it is known that physical inactivity accounts for one in six deaths in the UK [295] and costs an estimated £7.4 billion a year in England through direct costs of treating lifestyle-related disease and indirect costs of sickness absence [296]. This topic remains an outstanding healthcare challenge to address; for example, 32% of participants randomised to a brisk walking programme for type 2 diabetes dropped out after 12-months due to development of MSK pain [503]. Similarly, a cohort study of individuals taking part in a running programme for novice runners showed that 48% dropped out by 26-weeks due to running related MSK pain [504] – a greater understanding on how best to improve adherence to physical activity for people with MSK pain is urgently needed. Indeed, a pertinent question to ask is, what proportion of participants would continue with the programmes if they were given appropriate education and advice from Chapter 2, part two and Chapter 5, part one of this thesis? What form would the education take? How would it be delivered, and to whom? The relationship between MSK pain and chronic disorders is further highlighted by research showing that people have a 17% increased risk of developing chronic disease (cardiovascular disease, cancer, diabetes, chronic respiratory disease or obesity) if they have a long-term MSK condition [505]; further research is needed into the relationship between pain, physical activity and chronic disorders, and suitable preventative and management strategies.

8.3 Conclusion

The results of this feasibility study confirm that it is feasible and acceptable to deliver a loaded self-managed exercise programme to adults with PFP in an NHS physiotherapy outpatient setting. Methodological issues do need addressing prior to conducting a definitive RCT, including, between group differences in loss to follow-up and adherence monitoring. However, given the high prevalence, poor long-term prognosis and high disability levels for PFP, a definitive RCT is warranted.

In the face of the growing numbers of people suffering from MSK pain, chronic disease, and physical inactivity, it is clear there are still many unanswered questions. However, this PhD has offered new insights, generated new knowledge, and expanded the evidence-base, into the understanding and management of PFP, and indeed MSK pain as a whole. Strengths and limitations of the work have been discussed in each distinct component of research; the views and perspectives of key stakeholders have been sought concerning the intervention development and research implementation, and further research priorities have been identified.

Given the public health priority of increasing physical activity levels, and the significance of exercise in the management of chronic disease and MSK pain, the implications of a definitive study are likely to be considerable.

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Appendix A - Exercise prescription in patellofemoral pain: a survey of current UK physiotherapy practice - full protocol

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FACULTY OF MEDICINE & HEALTH SCIENCES

RESEARCH ETHICS COMMITTEE

Application for approval of all studies involving Healthy Human Participants only conducted by Staff and Students of the University of Nottingham

1 Title of Project:

Exercise Prescription in Patellofemoral Pain: A Survey of Current UK Physiotherapy Practice

Short title: PFP Survey

2 Names, Qualifications, Job Titles, Work Address, telephone and email of all Researchers:

Chief Academic/Supervisor: Prof Pip Logan, Division of Rehabilitation & Ageing, School of Medicine. Email: pip.logan@nottingham.ac.uk, telephone: 0115 823 0235

Other key researchers/collaborators: Dr Paul Hendrick, Clinical Sciences Building, Faculty of Medicine & Health Sciences. Email: paul.hendrick@nottingham.ac.uk, telephone: 0115 82 31805

Student's name and course: Benjamin Smith, NIHR/HEE Clinical Doctoral Research Fellow, Division of Rehabilitation and Ageing, School of Medicine. Email: benjamin.smith@nottingham.ac.uk, telephone: 07515 479 736.

3 Type of Project:

PhD Student project; PhD, Rehabilitation & Ageing

Online Survey

4 Location of study:

Online – Bristol Online Survey

Start date: May 2016 (ASAP after ethics approval)

End date: June 2016

Length of study: 1 month

5 Description and number of participants to be studied:

Target of 100 completed surveys in 1 month from UK practising physiotherapists.

6 Summary of Experimental Protocol:

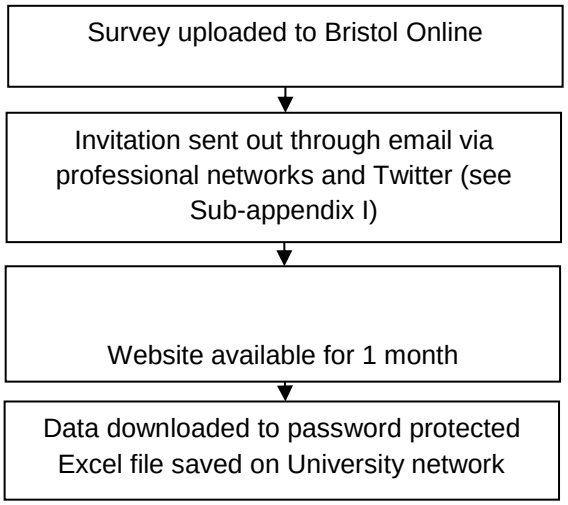
Background: Patellofemoral pain (PFP) is pain affecting the front of the knee around the kneecap and is a common musculoskeletal (MSK) disorder.

A recent review of exercise therapy showed that strong evidence existed for exercise therapy over no treatment, particularly with hip strengthening exercises [1]. However, questions exist as to which exercise modality and dose reduces pain and dysfunction the most [1].

The last survey on UK physiotherapy practitioners for PFP was carried out in 2011[2]. Since then a wealth of information has been published and the understanding of chronic pain states has grown considerably. This survey had no questions relating to the notion of painful exercise or self-management strategies, therefore an updated survey, utilising the recent surge in social media within the profession will be carried out.

Aims: This survey is part of a larger research project looking at effective exercise strategies in the conservative management of PFP. A complex intervention has been developed, titled; "A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study" ("loaded" meaning a weight bearing resistance exercise with some pain or discomfort). The MRC Complex Interventions Framework has been used for the development of this intervention, and an important step in the framework is identifying clearly how the intervention differs from usual practice. Therefore, the aim of this survey is to identify current UK Physiotherapy practice for the treatment of PFP, and particularly the role the exercise.

Protocol / Methods:



Data will be downloaded and stored in a password protected Excel file. This will be stored in an appropriately named folder on the University's secure computer system, within the Division of Rehabilitation and Ageing.

Measurable End Points: Data will be downloaded and imported into Microsoft Excel. Analysis will focus on descriptive statistics for all respondents. Text responses will be summarised.

References:

[1] Clijsen et al. Effectiveness of Exercise Therapy in Treatment of Patients with Patellofemoral Pain Syndrome: A Systematic Review and Meta-Analysis. Phys Ther 2014.

[2] Papadopoulos & Noyes. How do physiotherapists assess and treat patellofemoral pain syndrome in North Wales? A mixed method study. Int J Ther Rehabil 2012;19:261–72

Do not go over the page

7 Lay Summary of project:

Knee pain is a common complaint, with 1 in 6 young people suffering from pain around the kneecap at any one time. The routine treatment is physiotherapy and painkillers, but current long-term outcomes are poor with 91% of patients still reporting pain 4 years after starting treatment. This means that many patients are exposed to potential long-term disability and pain. Patients with this complaint will typically receive a course of physiotherapy. The use of strengthening exercises has been shown to be most promising, but the best 'dose' remains unclear. Resistance exercises, which include painful movements, have been shown to be beneficial for the back and shoulders, but further investigation is warranted to evaluate these.

This survey is part of a larger research project testing the feasibility of conducting a large randomised controlled trial. The potential benefits are to reduce pain and disability, and engaging the patients with appropriate long-term exercise, in order for them to stay in work and have an improved quality of life.

The first component of this research project will identify current physiotherapy treatments within the UK through an online survey.

8 Will written consent be obtained from all volunteers?

N/A

This is an online survey; therefore, alternative procedures will be followed. All potential survey responders will be required to indicate their consent by 'ticking' their agreement to a set of consent statements. If participants do not complete this element they will not be allowed to proceed with the online survey.

9 Will an inconvenience allowance be offered:

No

10 Funding:

No

11 Studies involving NHS Staff, organisations, services:

Does the study involve any staff who hold a contract with a hospital, Primary Healthcare or Social Care Trust? (This does not include investigators with an honorary contract with the NHS but does include staff whose salary is provided by the NHS e.g. Nurse, radiographer, physiotherapist)

Yes

University Sponsor Office has confirmed we do not need sponsor sign off, as recruitment will not be through the NHS but through professional networks and social media.

12 **How will the subjects be chosen?**

Subjects will be approached via Twitter and email via professional networks. Wording of twitter posts and email is in Sub-appendix I.

13 Describe how possible participants will be approached:

The research project will be announced on Twitter through the Nottingham Medical School's official twitter feed. An email will also be sent out through the East Midlands Clinical Research Network and the Chartered Physiotherapy Society website, "iCSP". See Sub-appendix I for wording.

14 What sources of information will be included? i.e, pre-existing research database, student records, visits to other organisation, online resource:

Online survey. See Sub-appendix III.

15 Whose permission will be sought to access this information (eg GP, consultant Head of Organisation)?

None.

16 For interview/focus groups:

N/A

17 What ethical problems do you foresee in this project?

No physical or psychological harm is expected from completing this survey, but participants will have to give up a small amount of their time.

Informed Consent: Participants will be invited to take part in the survey through social media and email via professional networks. However, before participants are able to proceed into the survey they must provide their consent and agreement by 'ticking' their agreement to a set of consent statements. Unlike traditional paper-based questionnaires participants won't be able to see the questions before they provide their consent.

Debrief: At the end of the online survey participants will be reminded about their rights in the research process and again provided with contacts details of the principal investigator.

Withdrawal: Participants will be reminded that their answers can be removed from the study if they choose to withdraw, but only up until a certain point (this is consistent with traditional survey research procedures). After they click the 'finish' button on the final page their answers will be amalgamated into the dataset and removal may not be possible. Given the uncontroversial nature of this study and the questions posed we do not foresee this as a problem.

18. <u>What are the possible limitations of the proposed design of this study?</u>

Not reaching our target of 100 completed responses in 1 month. A 2-week contingency extension has been added to the time table of the main research project, and if we have less than 50 completed responses at the end of 1 month, we will extend the survey for this 2-week period.

DECLARATION: I will inform the Medical School Ethics Committee as soon as I hear the outcome of any application for funding for the proposed project and/or if there are any significant changes to this proposal. I have read the notes to the investigators and clearly understand my obligations as to the rights, welfare and dignity of the subjects to be studied, particularly with regard to the giving of information and the obtaining of consent.

Signature of Lead Investigator: Date:

Benjamin Smith, Room B112, Division of Rehabilitation & Ageing, School of Medicine

benjamin.smith@nottingham.ac.uk

Supervisor: Date:

Pip Logan, Room B108a, Division of Rehabilitation & Ageing, School of Medicine

pip.logan@nottingham.ac.uk

Supervisor: Date:

Paul Hendrick, Clinical Sciences Building, Faculty of Medicine & Health Sciences

paul.hendrick@nottingham.ac.uk

Exercise Prescription in Patellofemoral Pain: A Survey of Current UK Physiotherapy Practice

Full Protocol

Short title: PFP Survey

Study Sponsor: University of Nottingham

Funding Source:Nil

Sponsor: University of Nottingham

Principle Investigator: Benjamin Smith

NIHR/HEE Clinical Doctoral Research Fellow

PhD Student

Division of Rehabilitation and Ageing

School of Medicine

benjamin.smith@nottingham.ac.uk

Study Coordinating Centre: Division Rehabilitation and Ageing,

School of Medicine,

University of Nottingham

SYNOPSIS

Title	Exercise Prescription in Patellofemoral Pain: A Survey of Current UK Physiotherapy Practice
Short title	PFP Survey
Principle Investigator	Benjamin Smith
Objectives	Identify current physiotherapy treatments for patellofemoral pain within the UK
Study Configuration	An online survey
Setting	Internet – web based online survey
Number of participants	100
Eligibility Criteria	UK Physiotherapists that see and treat patients with patellofemoral pain
Description of interventions	Participants will be asked to voluntarily complete an online survey hosted by Bristol Online Surveys (University of Nottingham subscription)
Duration of study	1 month, starting during May 2016
Statistical & data analysis method	Analysis will focus on descriptive statistics for all respondents. Text responses will be summarised.

STUDY BACKGROUND INFORMATION AND RATIONALE

Background

Patellofemoral pain (PFP) is a common musculoskeletal (MSK) disorder and one of the most common reasons why adolescents and young adults seek medical help with 1 in 6 suffering at any one time [1,2]. The main symptoms include retropatella pain, or diffuse peripatellar pain, aggravated by activities that load the patellofemoral joint such as climbing and descending stairs, squatting and sitting with prolonged knee flexion [3–5]. Other symptoms include patella crepitus and giving way sensations [6–8].

Long term outcomes are poor with 91% of patients reporting pain and dysfunction at a minimum follow-up of 4 years post diagnosis [9]; up to 25% will still have symptoms 16 years after treatment [10].

The Chartered Society of Physiotherapy, UK (CSP) has ranked PFP the 3rd most important topic out of 185 in their Musculoskeletal Research Priority Project [11].

A recent review of exercise therapy showed that strong evidence existed for exercise therapy over no treatment, particularly with hip strengthening exercises [12]. However, questions exist as to which exercise modality and dose reduces pain and dysfunction the most [12].

Exercise therapy based upon movements that are painful has been shown to be beneficial for both low back pain [13, 14] and shoulder pain [15-17]. Littlewood et al [18] hypothesised that the response to the painful loaded exercise programme could be attributed to the therapeutic impact upon the central nervous system. Specifically, the exercise prescribed is aimed at addressing fear avoidance and catastrophising beliefs within a framework of 'hurt not equalling harm', and pain described as 'de-conditioned' tissue. This having a positive impact upon the central nervous system with a modified pain output.

It is therefore hypothesised that a prescription of a self-managed high load lower limb strengthening exercise, that is not directed at specific tissue pathology, but rather based upon the neurophysiology of pain, set within clearly defined boundaries, will have a similar positive impact upon PFP patients as with other MSK disorders.

A loaded self-managed exercise programme is a complex intervention; a combination of several components tailored to the individual patient; delivered by different therapists; and targeted at a diverse patient population. The MRC Complex Interventions Framework [19] has been used for the development of this intervention with a feasibility study with a controlled trial component to be undertaken to examine the acceptability, feasibility and tolerability of the intervention.

The last survey on UK physiotherapy practitioners for PFP was carried out in 2011 [20]. Since then a wealth of information has been published and the understanding of chronic pain states has grown considerably. This survey did not include any questions relating to the notion of painful exercise, self-management strategies, or adherence strategies. Therefore, an updated survey is essential in

understanding how the complex intervention differs from the usual practice and the control conditions used in the feasibility control trial.

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[2] Mølgaard C, Rathleff MS, Simonsen O. 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. J Am Podiatr Med Assoc 101:215–22.

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[16] Bernhardsson S, Klintberg IH, Wendt GK. Evaluation of an exercise concept focusing on eccentric strength training of the rotator cuff for patients with subacromial impingement syndrome. Clin Rehabil 2011;25:69–78. doi:10.1177/0269215510376005.

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Study Objectives and Purpose

Research Questions

The proposed project aims to:

1) Understand current UK Physiotherapy management of people suffering from patellofemoral pain. Particularly in relation to:
    a. Passive & non-passive treatments
    b. Dose of any exercise prescription
    c. How exercise is progressed / regressed
    d. Self-management approaches
    e. Attitude to painful exercises

Study Design

Study Configuration

The study will be an online survey which will be advertised on twitter and via email through professional networks. For example, East Midlands Clinical Research Network and the online Chartered Society of Physiotherapy.

Study Management

The Principal Investigator has overall responsibility for the study and will oversee all study management. The survey will be conducted online through the Bristol Online Survey and all data will be downloaded to a password protected Microsoft Excel file. This will be saved in an appropriately named folder on the University's secure computer system, within the Division of Rehabilitation and Ageing. The original data on the Bristol Online Survey server will then be deleted. The data custodian will be the Principal Investigator, Benjamin Smith.

Duration of the Study

The online survey will be live for a period of 1 month. We aim to receive a total of 100 complete responses. We do have a 2-week contingency extension has been added to the time table of the main research project, should we need this. After this time the survey will be closed.

Individual involvement for individuals will be the duration of time it takes to engage with the online survey. It is expected that this should take approximately 5 – 10 minutes.

End of the Study

The online survey will be live for a period of 1 month. We do have a 2-week contingency extension has been added to the time table of the main research project, should we need this. After this time the survey will be closed. If anyone tries to click the link to the survey once it has been closed, they will be redirected to a default page informing them the survey has closed.

Selection and withdrawal of participants

Recruitment

The Principal Investigator will advertise the online survey and its URL 'link' via the University of Nottingham's School of Medicine official Twitter feed, and via email through the East Midland's Clinical Research Network and Chartered Society of Physiotherapy's professional network.

Please see Sub-appendix I for wording of tweet and email.

Eligibility criteria

All UK Physiotherapists that see and treat patients with patellofemoral pain will be eligible to participate in the online survey.

Inclusion criteria

All UK Physiotherapists who see and treat patients with patellofemoral pain are welcome to participate.

Exclusion criteria

None

Expected duration of participant participation

Participants are expected to be participating for 5 – 10 minutes.

Participant Withdrawal

Participants may withdraw from the study at any point during their participation. However, participants will be made aware that once they complete the online survey and click the 'finish' link then should they wish to withdraw the data collected cannot be erased and may still be used in the final analysis. In such cases the Principle Investigator will liaise with the participant and explore their reason, furthermore assurances will be given that answers to open ended questions and comment boxes will not be used.

Informed consent

All participants will be required to indicate their consent prior to taking part in this online survey. As this is an online survey alternative procedures to paper-based surveys will be followed. Each participant, upon clicking the URL web link, will be taken directly to the initial information pages of the survey that contain all the details that would be contained within a traditional participant information sheet (see Sub-appendix II). All potential survey responders will be required to indicate their consent by 'ticking' their agreement to a set of consent statements. If participants do not complete this element they will not be allowed to proceed with the online survey. The mandatory response function of the Bristol Online Survey will ensure only participants that indicate they have read fully the introductory information and agree to each ethical statement will be allowed to continue on to the full survey.

Study Procedures

1. Study goes live, with Principle Investigator acting as point of contact for any queries from potential respondents
2. Principle Investigator will ask the official University of Nottingham University Medical School twitter account to announce the survey and provide the link (permission has already been gained). Please see Sub-appendix I for wording.
3. Principle Investigator will ask the East Midlands Clinical Research Network and the online Chartered Society of Physiotherapy to email their research network. Please see Sub-appendix I for the wording.
4. Interested people follow the URL link and reads the information pages. It not happy they will close their browser and terminate the session. Otherwise the individual will complete the consent process and complete the survey.
5. After 1 month the survey will close. If the total number is below 50 then the survey will remain open for a further 2 weeks.
6. Data screening and analysis and report writing.

Data Analysis

Data will be downloaded and stored in a password protected Excel file. This will be stored in an appropriately named folder on the University's secure computer system, within the Division of Rehabilitation and Ageing.

Data will be downloaded and imported into Microsoft Excel. Analysis will focus on descriptive statistics for all respondents to facilitate development of associated figures and tables. Text responses will be summarised.

Sample Size Calculation

The aim of this survey is to understand the current UK physiotherapy management approaches to people with patellofemoral pain. There is no upper limit to the number of respondents. However, it is hoped that we will obtain 100 responses.

Adverse Events

Adverse events as a result of participation in this survey are not expected, and no adverse event data will be collected.

Ethical and Regulatory Aspects

The key aspects of this online survey are; informed consent, withdrawal and secure data storage. These aspects have already been covered within this protocol. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

Data Protection

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The online survey will only collect the minimum required information for the purposes of the study. The survey data will be held securely, and password protected and stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).

Insurance and Indemnity

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

Study Data

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. Study data and evidence of monitoring and systems audits will be made available for inspection by the Research Ethics Committee as required.

Recording Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. The study documents held by the Principal Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham.

Statement of Confidentiality

It is anticipated no individual personal information will be obtained as a result of this study, but in any case, these data are considered confidential and disclosure to third parties is prohibited with the exceptions of above within this protocol.

Publication and Dissemination

The results of the online survey will be used to prepare a peer reviewed publication. If collected, all personally identifying information will be removed. This also applies to any other dissemination activity.

User and Public Involvement

None. Not appropriate to the study aims.

Study Finances

This study is unfunded.

Participants will not be paid to participate in the study

Signature Pages

Signatories to Protocol:

Signature of Lead Investigator: **Date:**

Benjamin Smith, Room B112, Division of Rehabilitation & Ageing, School of Medicine

benjamin.smith@nottingham.ac.uk

Supervisor: **Date:**

Pip Logan, Room B108a, Division of Rehabilitation & Ageing, School of Medicine

pip.logan@nottingham.ac.uk

Supervisor: **Date:**

Paul Hendrick, Clinical Sciences Building, Faculty of Medicine & Health Sciences

paul.hendrick@nottingham.ac.uk

Sub-appendix I Email and Twitter Wording

Twitter Invitation:

"UK Physios please complete and share this PFP Survey [link]. Thanks."

"PFP: A Survey of current UK Practice [link] please complete and share"

Email Invitation:

Subject:

'Physio Survey Invitation'

Body:

Dear Physio Colleagues

We are seeking UK based physiotherapists to participate in a short survey on the management of patellofemoral pain (PFP). The survey will ask some questions about your management of patients with patellofemoral pain. These questions will be a mixture of 'tick box' style and open-ended questions. Your answers will help us understand current physiotherapy management approaches and help develop future research.

Please share with your colleagues and follow the link below. Thank you for your time

[LINK]

Benjamin Smith

Benjamin Smith
NIHR/HEE Clinical Doctoral Research Fellow
Division of Rehabilitation and Ageing, School of Medicine
University of Nottingham

benjamin.smith@nottingham.ac.uk

Senior Physiotherapist
London Road Community Hospital (LRCH)
Derby Teaching Hospitals NHS Foundation Trust

benjamin.smith3@nhs.net

Sub-appendix II Participant Information Pages

Participant Information Page

I would like to invite you to take part in my research study. Before you decide whether or not to participate, it is important for you to understand the purpose of the research and what it will involve. **Please take time to read the following information carefully**. If you feel that any part of the study is not entirely clear or if you would like more information prior to participation then please do not hesitate to contact the Principal Investigator, contact details below).

What is the purpose of the study?

We are seeking the views of **UK based physiotherapists** on the management of patellofemoral pain (PFP). Exercise prescription is a common intervention in the management of PFP, however it is unclear on the optimal type or dose for treating patients in the long term. You will be asked some questions about your management of patients with patellofemoral pain, particularly in relation to exercises. Your answers will help us understand current UK physiotherapy management approaches and help develop future research. We anticipate the results of this survey will be published.

How long is the study?

The study will take around 5 - 10 minutes.

Do I have to take part?

Your participation in this study is entirely voluntary. If you agree to take part, we will ask you to complete an online consent form. You are free to withdraw from the study at any time without giving a reason, though should you wish to do so, we recommend doing this before finishing the online survey. After that point it may not be possible to remove your data from the study, meaning that it may still be used in our analysis. However, if you have any questions about this please feel free to contact us.

What will I be asked to do if I take part?

If you agree to take part you will be invited to answer some questions about your management of patients with patellofemoral pain. These questions will be a mixture of 'tick box' style and open-ended questions.

What are the possible disadvantages and risks of taking part?

The survey deals with topics about your management of patients with patellofemoral pain and so should not be distressing to you. As an online participant in this research, there is always the risk of intrusion by outside agents, i.e., hacking, and therefore the possibility of being identified.

How will I benefit from participating in this study?

If you are kind enough to participate then your answers will help us understand current physiotherapy management approaches and help develop future research.

If I need to speak to someone about the research, whom should I contact?

If you have any questions, queries or concerns regarding the study, please contact the Principal Investigator using the contact details below.

What will happen if I don't want to carry on with the study?

Your participation in this study is entirely voluntary. You are free to withdraw from the study at any time without giving a reason by clicking the 'exit study' button located on each question page.

How will we use the results of this study?

Your answers will help us understand current physiotherapy management approaches within the UK and help develop future research. We anticipate the results of this survey will be published.

Am I able to know the results of the study?

Yes, if you would like a summary of the results, please contact the Principal Investigator (details below).

Contact details:

This survey is part of research funded by a Clinical Doctoral Research Fellowship from the National Institute for Health Research.

For further information about this survey please contact Benjamin Smith at School of Medicine, University of Nottingham, benjamin.smith@nottingham.ac.uk.

Sub-appendix III Participant Consent Form

I confirm that I have read and understand the information regarding the above study and have the relevant information to contact the researcher to ask any questions.

Please, tick each box to continue:

- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that should I withdraw after completing the survey then the information collected so far cannot be erased and that this information may still be used in the study analysis.
- I understand that my personal details will be kept confidential.
- I understand that I will be asked to complete some questions and that the data from these will be used to understand current UK Physiotherapy management of patellofemoral pain.
- I understand that my data from this study will be anonymised and that only members of the research team will have access to the data and my personal information.
- I agree to take part in the above study.

Please click 'NEXT' to be taken to the survey

Sub-appendix IV Debrief and Thank You

Thank you very much for your time. This work is funded by a Clinical Doctoral Research Fellowship from the National Institute for Health Research and will be invaluable in helping understand current UK physiotherapy management approaches and help develop future research.

If you have any questions about the research please contact the Principal Investigator:

Benjamin Smith
University of Nottingham, UK
benjamin.smith@nottingham.ac.uk

Sub-appendix V - Survey Content

1. Are you a UK based physiotherapist that regularly sees patients with patellofemoral pain?
    a. Yes – please continue
    b. No – thank you for your time, please exit the survey
2. Do you have a specialist interest in treating patellofemoral pain?
    a. Yes
    b. No
3. What is your primary role?
    a. NHS Band 5
    b. NHS Band 6
    c. NHS Band 7
    d. NHS Band 8a or above
    e. Private Practice
    f. Sport Club / Elite Athletes
    g. Educational / Research
4. What management strategies do you use for PFP? Tick all that applies?
    a. No treatment needed
    b. Heat treatment
    c. Cold treatment
    d. Muscle strengthening - closed chain
    e. Muscle strengthening - open chain
    f. VMO exercises
    g. Education / Advice
    h. Stretching
    i. Foot orthotics
    j. Taping
    k. Acupuncture
    l. Electrotherapy
    m. Bracing
    n. Mobilisations
    o. Other (please specify)
5. If you prescribe exercises, how many different exercises to you prescribe at any one time?
    a. 1
    b. 2-3
    c. 4-5
    d. 6+

6. If you prescribe exercises, how often do you ask them to be performed?
    a. Every other day, or less
    b. Once a day
    c. Twice a day
    d. More than twice a day
7. If you prescribe exercises; how many total repetitions do you usually prescribe for an exercise?
    a. Less than 30
    b. 30 – 50
    c. 50+
    d. Patient self-directed

8. If you prescribe exercises, do you encourage patients to continue if they were painful? Please qualify your answer
    a. Yes
    b. No
    c. Other

    Further comments:
9. Do you encourage patients to continue with their recreational / sporting activities?
    a. Yes. But only if pain free.
    b. Yes, regardless of pain.
    c. Yes, but only with pain below a certain level (please qualify)
    d. No
    e. Other

    Further comments:
10. Do you expect patients to (tick all that applies):
    a. Self-Manage after the first appointment
    b. Self-Manage with follow-up appointments for guidance
    c. Self-Manage with follow-up appointments for physiotherapy led treatment
    d. Not self-manage, but attend regular physiotherapy led treatment sessions

11. How many times do you typically see patients with PFP?
    a. Once
    b. Twice
    c. 3 – 4 times
    d. 5 – 6 times
    e. 7 – 8 times
    f. 9 – 10 times
    g. More than 10 times
12. How long would you typically expect to see patients with PFP?
    a. Over 3 weeks
    b. Over 6 weeks
    c. Over 9 weeks
    d. Over 3 months
    e. Over 6 months
    f. Over 12 months
13. Any additional comments:

Appendix B - Survey Ethics Approval

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
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16th May 2016

Dr Benjamin Smith
NIHR/EE Clinical Doctoral Research Fellow
Division of Rehabilitation & Ageing
School of Medicine
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Dr Smith

Ethics Reference No: H10052016 SoM RHA **– please always quote**
Study Title: Exercise Prescription in Patellofemoral Pain: A survey of Current UK Physiotherapy Practice.
Chief Investigator/Supervisor: Dr Pip Logan, Associate Professor in Rehabilitation, Division of Rehabilitation and Ageing, School of Medicine.
Lead Investigators/student: Dr Benjamin Smith, NIHR/HEE Clinical Doctoral Research Fellow, Division of Rehabilitation & Ageing, School of Medicine
Type of Study: PhD Student Project, Online Survey, Current UK Physiotherapy practice
Proposed Start Date: May 2016 **Proposed End Date:** 30 November 2016 6 mths
No of Subjects: 100 **Age:** 18+yrs

Thank you for submitting the above application which was considered by the Committee at its meeting on 10th May 2016 and the following documents were received::

Short Title: PFP Survey:

- FMHS Research Ethics Application Form, version 1.1, Date 26th April 2016
- Full Protocol, version 1.1, Date 26th April 2016
- Appendix A: Email and Twitter wording, version 1.1, Date 26th April 2016
- Appendix B: Participant Information Pages, version 1.1, Date 26th April 2016
- Participant Consent Form, version 1.1, Date 26th April 2016
- Appendix C: Survey Content, version 1.1, Date 26th April 2016
- Appendix D: Debrief and Thank you, version 1.1, Date 26th April 2016

These have been reviewed and are satisfactory and the study is approved.

Approval is given on the understanding that the conditions set out below are followed:

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix C - Study protocol: a mixed methods feasibility study for a loaded self-managed exercise programme for patellofemoral pain

From: **Smith BE**, Hendrick P, Bateman M, Moffatt F, Rathleff MS, Selfe J, et al. Study protocol: a mixed methods feasibility study for a loaded self-managed exercise programme for patellofemoral pain. Pilot Feasibility Stud 2017;4. doi:10.1186/s40814-017-0167-2.

Abstract

Background:

Patellofemoral pain (PFP) is one of the most common forms of knee pain in adults under the age of 40, with a prevalence of 23% in the general population. The long-term prognosis is poor, with only one third of people pain-free one year after diagnosis.

The biomedical model of pain in relation to persistent PFP has recently been called into question. It has been suggested that interventions for chronic musculoskeletal (MSK) conditions should consider alternative mechanisms of action, beyond muscles and joints. Modern treatment therapies should consider desensitising strategies, with exercises that target movements and activities patients find fearful and painful.

High quality research on exercise prescription in relation to pain mechanisms, not directed at specific tissue pathology, and dose response clearly warrants further investigation.

Our primary aim is to establish the feasibility and acceptability of conducting a definitive RCT which will evaluate the clinical and cost-effectiveness of a loaded self-managed exercise programme for people with patellofemoral pain.

Method:

This is a single-centred, multiphase, sequential, mixed-methods trial that will evaluate the feasibility of running a definitive large scale randomised controlled trial of a loaded self-managed exercise programme versus usual physiotherapy. Initially 8 – 10 participants with a minimum 3-month history of PFP will be recruited from an NHS physiotherapy waiting list and interviewed. Participants will be invited to discuss perceived barriers and facilitators to exercise engagement, and the meaning and impact of PFP. Then, 60 participants will be recruited in the same manner for the main phase of the feasibility trial. A web-based service will randomise patients to a loaded self-managed exercise programme or usual physiotherapy. The loaded self-managed exercise programme is aimed at addressing lower limb knee and hip weakness, and is positioned within a framework of reducing fear/avoidance with an emphasis on self-management. Baseline assessment will include demographic data, average pain within the last week (VAS), fear avoidance behaviours, catastrophising, self-efficacy, sport and leisure activity participation, and general quality of life. Follow-up will be 3 and 6 months. The analysis will focus on descriptive statistics and confidence intervals. The qualitative components will follow a thematic analysis approach.

Discussion:

This study will evaluate the feasibility of running a definitive large scale trial on patients with patellofemoral pain, within the NHS in the UK. We will identify strengths and weaknesses of the

proposed protocol and the utility and characteristics of the outcome measures. The results from this study will inform the design of a multicentre trial.

Trial registration: ISRCTN 35272486

Keywords: Mixed methods study, feasibility, patellofemoral pain, anterior knee pain, exercise therapy

Background

Patellofemoral pain (PFP) is one of the most common forms of knee pain in adults under the age of 40 [1–3], with an estimated prevalence of 23% in the general population [1]. Typically, symptoms include retropatella pain, or diffuse peripatellar pain, aggravated by activities that load the joint, such as climbing and descending stairs, squatting and running [4].

The overall long-term prognosis for the majority of patients with PFP is poor [5]. One third of patients are pain-free one year after the diagnosis [5]. Patients will typically withdraw from participation in sport and leisure activities [6, 7], and symptoms can continue for many years [5, 8]. Furthermore, many individuals with PFP develop associated psychological distress, such as fear-avoidance and catastrophising thoughts in relation to their knee pain [9–11]. It is such a common, yet poorly understood condition, that the Chartered Society of Physiotherapy, UK (CSP) has ranked PFP the 3rd most important topic out of 185 in their Musculoskeletal Research Priority Project in 2012 [12].

There remains scientific debate and uncertainty around the underlying aetiology of the condition [13], and it is thought most likely to be multifactorial in its origin [14]. There is currently little high-quality Level 1 evidence on which to base conservative management [15]. Historically, models of clinical reasoning based on the patho-anatomical basis of tissue pathology and differential diagnosis have labelled one major cause of PFP as patellar mal-tracking/malalignment [14, 16–18], with the supposition that various tissue structures could be contributing, such as: general muscle weakness [19], soft tissue tightness [20], lower limb structural abnormalities [21], movement dysfunction [22] and quadriceps mal-timing [23]. It is thought that these deviations from the 'normal' affect patellar alignment, kinematics or joint loading, resulting in greater stress between the patella and femur and the development of pain and dysfunction [14, 16–18]. This biomedical model of pain establishes a direct relationship between tissue structure and pain [24], and traditionally the focus of physiotherapy treatment has been aimed at reducing pain and improving function by addressing these biomedical tissue structures; treatments include taping, stretches, exercises, electrotherapy, joint mobilisations and foot orthoses have all been suggested [16, 17]. However, systematic reviews consistently acknowledge the limitations of included studies when drawing their conclusions on the effectiveness of these interventions [14, 15, 17, 25–27]. Even in relation to exercise therapy, which has the strongest evidence-base [15], there remains insufficient evidence on which to determine the best form and dose of exercise [25].

Exercise therapy designed to load and temporarily aggravate patients' symptoms has shown to be beneficial for tendon pain [28], shoulder pain [29–31], low back pain [32, 33] and plantar heel pain [34]. In agreement with Nijs et al. [35], Littlewood et al [36] hypothesised that the positive response to the painful loaded exercise programme could be attributed to the therapeutic impact upon the central nervous system. Specifically, the exercise prescribed is aimed at addressing fear avoidance and catastrophising beliefs within a framework of 'hurt not equalling harm', with pain rationalised as 'de-conditioned' tissue. Thus, in time, reducing the overall sensitivity of the central nervous system, with a modified pain output.

Exercise interventions for PFP have shown a 'dose response'; characteristically, the more exercise the patient does the better their pain and functional improvement in the long term. A study in Norway (n=42) looked at a high dose regime versus a low dose regime and concluded that there was a

significant benefit in the high dose group over low dose in terms of pain and function at 12 weeks [37]. Strikingly, the one year follow-up showed that the high dose group had continued to improve in terms of pain and function, while the low dose group had deteriorated [37, 38]. This finding is supported by a more recent study looking at supervised exercises and education versus education alone [39]. In this study 121 adolescents were randomised into the two groups, with exercise adherence monitored through attendance and weekly text messages. They demonstrated that successful outcome (defined as 'completely recovered or strongly improved' on a seven-point Likert scale) was directly correlated to the amount of exercise a patient did; if they completed the exercises 0 – 1 x a week 21% recovered compared with 55% who completed the exercises three or more times a week. A recent systematic review and meta-analysis of painful exercises versus pain free exercises for chronic MSK pain found protocols using painful exercises offered a small, but significant benefit over pain-free exercises in the short term; and that protocols using painful exercises typically have higher loads and dose of exercise [40]. The optimal dose of exercise for the greatest improvements in PFP is still unknown [25] and warrants further investigation in relation to load and resistance.

High quality research on exercise prescription in relation to pain mechanisms and dose response (or response to load/resistance) clearly warrants further investigation, particularly when considering the current paucity of high-quality evidence on which to determine the best form of exercise intervention for PFP.

Purpose

The primary aim is to establish the feasibility and acceptability of conducting a definitive RCT which will evaluate the clinical and cost-effectiveness of a loaded self-managed exercise programme for people with patellofemoral pain compared to usual physiotherapy.

Secondary aims include establishing: if the devised loaded self-managed exercise programme can be delivered as planned in an NHS physiotherapy outpatient clinic; if the outcome measures are feasible to use within an NHS setting; if reliable data can be collected; a sample size calculation for an RCT; if the intervention is acceptable and tolerable to participants and physiotherapists; if it is feasible to recruit and randomise participants; the potential barriers to recruitment and the training package delivered to physiotherapists.

Methods

Study Design

This is a single-centred, multiphase, sequential, mixed-methods trial. It incorporates an initial qualitative component; followed by a feasibility randomised controlled trial (RCT); with a final qualitative component. Reporting of this protocol will follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [41].

Phase 1 will recruit 8 to 10 participants and individual interviews will be performed with the purpose of understanding the impact of PFP on their lives. Their physiotherapy will continue as normal.

Phase 2: A clinical trial will then be conducted with 60 further participants (recruited separately to phase 1). These participants will be randomised to the intervention group or to the control group.

Phase 3: A sub group of participants (8 to 10) from phase 2, along with a sub-group of the physiotherapists involved in phase 2 (8 –10), will be asked to take part in individual interviews that will explore the acceptability and feasibility of study design parameters and the intervention from phase 2.

Recruitment

Selection of trial participants for phase 1 and phase 2 will follow the same procedure. Potential trial participants will be identified and triaged from the NHS physiotherapy waiting list at Derby Teaching Hospitals NHS Foundation Trust by the usual department physiotherapists who perform referral triage. Patients are referred from general practitioners and from orthopaedics and rheumatology hospital departments. An introductory letter accompanied by an information sheet and consent form will be sent out to potential trial participants by a member of the clinical team. This will be followed up by a telephone call from a member of the clinical team offering further information and inquiring about participation. Patients showing an initial interest will be asked questions to check they match the inclusion criteria and interview/assessments will be booked with the research team.

Eligibility Criteria

Based on a consensus gained from previous systematic reviews and studies [14, 39] the participants will be recruited from the waiting list according to the following criteria: men and women aged 18 to 40 who are able to give written informed consent; a clinical diagnosis of unilateral or bilateral PFP of greater than three months duration (if bilateral the worst knee will be investigated); anterior or retropatellar pain reported on at least two of the following activities: prolonged sitting, ascending or descending stairs, squatting, jumping and running.

Exclusion criteria include: previous knee surgery; awaiting lower limb surgery; knee ligamentous instability; history of patellar dislocation; true knee locking or giving way; reasons to suspect systemic pathology, or acute illness; pregnancy or breastfeeding; patellar or iliotibial tract tendinopathy; and not able to speak or understand English.

Interventions

Phase 1 – Interviews

Interview participants will explore perceived barriers and facilitators to exercise engagement, the meaning to the participant and impact of having PFP. This may be used to tailor the intervention in phase 2 and to inform the phase 3 interviews, if appropriate.

A convenience sample of the first 10 participants recruited will be invited to discuss factors surrounding the meaning and lived experience of PFP. The interviews will occur in the participant's home or another suitable venue of their choice. There will be an interview schedule to guide (but not lead) discussion.

Phase 2 – Pilot Clinical Trial

Exercise Intervention

The 'experimental' intervention is a loaded self-managed exercise programme for the knee and hip, aimed at addressing lower limb knee and hip weakness [25]. It is set within a framework of reducing fear/avoidance and with an emphasis on self-management and reducing the need for direct physiotherapy intervention.

Before any prescription of exercise, the physiotherapist will spend a period of time educating the participant about pain mechanisms. Descriptions of tissue based pathology models of pain, e.g. patellar mal-tracking, or limb mal-alignment will be actively discouraged and challenged by the physiotherapist. The participant will gain an evidence-based understanding of dysfunctional central nociceptive processing as an explanation of chronic and persistent pain [42], and the role and impact of fear [43]. This period of intense learning is designed to facilitate the reconceptualisation of pain, with an emphasis on descriptions of pain neuroscience rather than psychology [44], and from the perspective and context of the participant and their pain [45]. The education regarding pain mechanisms will take up a large portion of clinical time, such as to address any beliefs or fear within the participant that pain is a sign of tissue damage, and will be delivered in a Socratic teaching style [46]. It is expected that the education period will be complete in the first session, which typically lasts 30 – 40 minutes within the NHS, but participants that require further re-assurance may continue into their second session.

The exercise will be prescribed by the physiotherapist and will typically involve body weight resistance in the form of a modification of the 'Step Down' function test [47]; a single leg squatting exercise sideways on a step. By performing sideways, the participant will be able to use the guide of the wall and/or bannister more easily, as guided by our patient and public involvement feedback. The exercise requires balance, knee extension strength, eccentric control and isometric hip strength. The participant will be advised to exercise to the point of fatigue, such that it reproduces their pain and discomfort, but ensuring the pain is manageable [48–50].

Exercise progression is guided by the symptomatic response, such that the participant is advised that on cessation of the exercise the pain should remain no worse than pre-exercise [48]. Participants with more severe pain will start on a lighter regime, and this will be guided by the baseline functional assessment by the treating physiotherapist. Participants will be advised to exercise at a level they find acceptable and tolerable. Participants are able to start exercising, if they wish, at a very low level, with little or no short-term pain increase, and progress when they feel comfortable and confident. Regression will be in the form of reduced repetitions, or lightening the exercise, for example to double

leg squats 0-30° knee flexion. Progression can be in the form of increased repetitions or increasing the load by moving to plyometric exercises, such as jumping and hopping, for younger participants with higher sporting requirements. The physiotherapist will plan the exercise, motivate and review participant's physical performance and expectations [35].

A single exercise approach will be used for this intervention. Poor levels of exercise adherence are well documented [51], and it has been suggested that a single exercise represents a pragmatic time saving approach [52]. Additionally, as previously discussed, the optimal dosage of an exercise prescription is unknown, and a single exercise approach may allow better monitoring of dosage and adherence. Importantly, it will enable the participant to observe others (the physiotherapist) perform the task successfully, and facilitate the development of mastery of the task. This combined with specific verbal and social persuasion from the physiotherapist, will further promote reconceptualisation of the pain, specific to the participant and their context; all thought to be key modifiers of perceived self-efficacy [53].

The participants will be advised that the exercise should be performed twice a day. The participant will be encouraged to self-direct in progressing/regressing the repetitions, as guided by their pain response, thus further internalising the locus of control and moving towards self-management [53].

Goal setting will be a central part of the intervention. The reconceptualisation of pain through the exercise intervention leads onto the reconceptualisation of pain in the participant's daily activities, including sport and leisure activity, and setting goals helps this transition.

Other self-management strategies employed will be the discussion about managing 'flare ups' and potential or perceived barriers to successful outcomes [35, 52]. This will be through a thorough questioning and discussion with the physiotherapist and participant. Questions such as: Is this safe for your knee? Is exercise good for you? Are you confident of completing this exercise? What do you think will happen? Why do you think that? It is thought that a discussion based on this approach will reveal the participant's perception of exercise, and potential barriers and fears [35].

Keeping the treatment pragmatic, timing over follow-ups, the number of treatment sessions, frequency and discharge, physiotherapy concomitant treatments will be at the discretion of the qualified physiotherapist, but with the aim of the programme being self-management, self-directed exercise and discouraging concomitant treatments. The mean number of sessions for physiotherapy treatment of PFP is eight [54], and the prediction is that self-management strategies should lower the expected number of treatment sessions for the intervention group to three to five sessions. The timings of the follow-up appointments are also pragmatic in nature, and at the discretion of the physiotherapist in discussion with the participant. Following the problem solving and barrier discussion the physiotherapist will have an understanding of the participant's ongoing perception of their pain. Those that require further re-assurance may return sooner, one to three weeks; and those that are comfortable to self-manage sooner will return after a longer period of time, four to six weeks, or not at all in some cases. All participants have the opportunity to telephone for support if required.

To avoid cross-contamination between the two groups, the delivered intervention group will be treated by different qualified physiotherapists, who will be excluded from treating participants from

the comparator group. Furthermore, physiotherapists treating 'usual physiotherapy' will not receive the intervention training package. The intervention training package will be delivered to the treating physiotherapists by the research team. The training package will consist of 2 x 2-hour sessions, scheduled to fit into the usual in-service training slots.

The comparator

Usual physiotherapy typically involves strengthening exercises [55–57], taping [17, 58], stretches [59], and foot orthoses [60], and these are often aimed at restoring the assumed patella malalignment [16, 17]. The comparator will be usual physiotherapy as directed by the normal assessment and clinical decision-making by the treating physiotherapist. Details about the nature of the treatments will be collected.

Phase 3 – Interviews

Potential interviewees will be purposively sampled from the phase 2 RCT with initial contact made via telephone to ask whether they would be willing to participate (information sheet and consent form for phase 2 and 3 are combined). A sample of eight to ten participants will be required with a sample of responders and non-responders, from both intervention arm and comparator group, with 1:2 proportion of males to females to reflect gendered differences in prevalence [1]. Participants lost to follow-up will be telephoned and encouraged to take part. This process will begin 6 months after randomisation. If the participant agrees, a convenient time will be arranged to complete an interview at the participant's home or physiotherapy clinic. Consent for the phase 2 clinical trial will include consent for participation in phase 3.

Treating physiotherapists will be invited to take part in interviews. A purposive sample of eight to ten will be required, with a mixture representing both the intervention group and comparator group, with different grades and length of clinical experience. Consent for this will be taken separately.

The emphasis within the intervention arm is towards self-management and exercises that are performed with pain. Therefore, the aim of the qualitative investigation is to give an insight into the participants' and physiotherapists' perceptions and experiences of the process. There have been recent developments on our understanding of the impact of patients' and therapists' attitudes and beliefs on pain [61], therefore these factors are extremely important to understand. Also, study design parameters will be discussed to explore recruitment and randomisation in this participant group. All interviews will be face-to-face at a location and time convenient to the interviewee. Interviews will be semi-structured and will broadly consider the acceptability and practicality of the exercise programme. For participants, data collection will consider: views on the nature and form of the exercise; perception of its benefits, difficulties and barriers, and perceptions of study design i.e. recruitment, consent, data collection and follow-up periods. For physiotherapists, data collection will consider: views on the nature and form of the exercise; perception of its benefits, difficulties and barriers; views on the delivery of the training package. The interviews will be guided by a semi-structured schedule.

Outcome Assessments

Our patient and public involvement representative has reviewed and approved the outcome assessments and has a total estimated completion time of 10 – 15 minutes. The schedule for assessments is found in the SPIRIT figure (Table 21).

Baseline demographic data will include; age, sex and duration of symptoms. The primary outcome measure that we will test the feasibility of will be a global rating of change at follow-up, the proportion of participants who have recovered (defined as 'completely recovered' or 'strongly recovered'), measured on a 7-point Likert scale ranging from "completely recovered" to "worse than ever" [39, 57, 62].

Secondary outcome measures that we will test the feasibility of using will include: visual analogue scale (VAS) for pain, kinesiophobia, catastrophising, self-efficacy, sport participation and the generic health outcome Euro-QOL (EQ-5D-5L).

Average pain within the last week will be measured on the VAS 0 to 10 cm [63]; 0 represents no pain, 10 the worst pain possible; this scale has been shown to be valid for PFP with a minimal clinically important difference (MCID) of 2 [64].

Fear associated with avoidance behaviours and kinesiophobia will be measured with the Tampa Scale for Kinesiophobia (TSK) [9, 65]. This is a 17-item questionnaire widely used for the assessment of fear of movement and been shown to be reliable and valid for an English-speaking population with spinal pain. Each question is scored on a 4-point Likert scale ranging from 'strongly disagree' (1) to strongly agree (4), giving a total possible score of 17 to 68.

Catastrophising will be measured by means of the 'Pain Catastrophising Scale' (PCS) [66]. The PCS scale is a 13-item questionnaire used to explore participants' thoughts and feelings when experiencing pain. Each question asks the degree with which the participant agrees with the statement and is scored on a 5-point Likert scale ranging from 'not at all' (0) to 'all the time' (4), giving a total possible score of 0 to 52.

Self-efficacy has shown to be a strong predictor of disability in patients with MSK pain [67], therefore the General Self Efficacy Scale will also be used (GSES) [68]. The GSES is a 10-item questionnaire with each question asking the degree with which the participant agrees with the statement, with a 4-point Likert scoring structure ranging from 'not at all' (1) to 'exactly true' (4). The questions are used to explore the participants' perceived belief at coping with a range of stressful and challenging demands; with a total possible score of 10 to 40. The GSES has been shown to have high reliability and validity across multiple languages and settings [69].

Patients characteristically withdraw from participation in sport and leisure activities [6], therefore the number of times the participant has participated in leisure time sport or exercises within a week will be recorded.

The generic Euro-QOL (EQ-5D-5L) is a generic health outcome used widely internationally [70]. The questionnaire has 5 questions about mobility; usual activities; self-care; pain and discomfort; and anxiety and depression. The results are converted into in single summary index and can be used to aid and assist any future economic evaluation planned for the definitive RCT.

Compliance is the act of conforming and following the prescribed dosage, timing and frequency of the exercise. Feasibility outcomes of compliance levels will be monitored through a participant activity diary. Participants will be asked to complete an exercise diary daily for 6 months indicated how many repetitions they completed of their exercise.

Non-responders will be telephoned after seven days to encourage them to complete the forms and return them.

	STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT**	***October 2016 – May 2017***	***October 2016 – May 2017***	***Month 1***	***Month 2***	***Month 3***	***Month 4***	***Month 5***	***Month 6***	***May 2017 – August 2018***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
Loaded Self-Managed			←	—	—	—	—	→	
Usual Physiotherapy			←	—	—	—	—	→	
ASSESSMENTS:									
Diagnosis		X							
Baseline demographic		X							
Seven-point Likert scale					X			X	
Pain VAS (previous week's average)		X			X			X	
Tampa Scale for Kinesiophobia		X			X			X	
Pain Catastrophising Scale		X			X			X	
General Self Efficacy Scale		X			X			X	
Number of leisure sport and exercise in previous week		X			X			X	
Euro-QOL (EQ-5D-5L)		X			X			X	
Submission of Exercise Diary								X	

Table 21 - SPIRIT figure. Schedule of enrolment, interventions and assessments.

Sample size

A formal sample size calculation will not be performed since this is a feasibility study. We therefore envisage being able to recruit 30 participants into each treatment arm, and we consider that this will give a robust and useful amount of information [71]. Part of the feasibility study is to investigate the feasibility of recruitment. However, we envisage recruiting 60 participants in 13 months.

We will use the primary outcome measure, the global rating of change scale, to inform a sample size calculation for a definitive RCT.

Randomisation

Patients who fulfil the inclusion and exclusion criteria, read and understood the patient information sheet and have given written consent to take part in the trial will be randomised to either the intervention or the control. A web-based randomisation service with secure password protected login using random variable block-size will be used.

Due to the nature of therapeutic studies, blinding of the participants and physiotherapists is not possible [72].

Data Collection Methods

Phase 1 & 3

Interviews will be recorded with a digital recorder. The interviews will then be transcribed verbatim and analysed.

Phase 2

Baseline data will be captured prior to randomisation in the physiotherapy clinic. Follow-up assessments will be 3 months and 6 months (by post with a stamped addressed envelope for return). Participants will be asked to post back their exercises diary at the 6-month follow-up.

Planned data analysis

Phase 1 & 3

The qualitative components will follow a thematic analysis approach, as described by Braun and Clarke (2006) [73]. Line by line coding, leading to a thematic analysis (using an abductive research strategy), will be used. Following data familiarisation, initial codes will be generated and peer-reviewed, by a member of the research group, to search for common themes. This will be carried out using the NVivo software (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 11, 2015). For phase 1 the analysis will assess the lived experience of PFP; for phase 3 the analysis will broadly assess acceptability and feasibility of study design, intervention and training package to physiotherapists.

Phase 2

The analysis will focus on descriptive statistics and confidence intervals for the variables we are obtaining. The characteristics of the participants will also be described using means, standard deviations and ranges for quantitative variables and counts and proportions for categorical variables.

As this is a feasibility study we are testing our ability to collect data, therefore no data imputation will be performed to account for any missing data.

Feasibility threshold will be set at 75% for recruitment. Feasibility threshold will be set at 75% to assess reliability and completeness of outcome measures. Data relating to the timing of the return of outcome forms, department referral rate, recruitment rate and numbers lost to follow-up will be recorded. Acceptability and tolerability of the treatment intervention will be assessed through completeness of outcome measures, and feedback from the phase 3 qualitative interviews.

Monitoring

The exercise intervention is low risk and is commonly used in the population. The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

Access to the final trial data set

All available data can be obtained by contacting the corresponding author.

Patient and Public Involvement

This research project has been driven by the views of people suffering from patellofemoral pain (PFP). Patients who receive physiotherapy for PFP have been consulted for their views, including patient members of the Steering Group Committee. Thoughts and preferences to current programmes of therapy and treatment have been requested, and these views have been incorporated into the planning, design, application and dissemination of this study.

Patients stressed the importance of ensuring a minimal number of exercises for improved adherence; the tailoring of the physiotherapy intervention around their usual sport/hobbies (where appropriate); and the capability of telephone support when required at short notice.

The main exercise of the intervention itself was adapted after consultation with patients. Initially the intervention was an exercise based upon the 'Step Down' function test [47]. The feedback from the patients was that performing the same manoeuvre sideways, rather than facing down the step, allowed them to use the guide of the wall and/or bannister with their hands. This has been incorporated into the intervention.

Discussion

We have presented the rationale and design of a mixed-methods feasibility study for a loaded self-managed exercise programme for PFP. The premise that a loaded self-managed lower limb strengthening exercise, that is not directed at specific tissue pathology, but rather based on the neurophysiology of pain, set within clearly defined boundaries, will have a positive impact upon fear-

avoidance, catastrophising and self-efficacy behaviour and patient reported pain levels. The feasibility of a large definitive RCT will either be established, or negated, and the results of the trial will be published when they are available.

Declarations

Ethics Approval

This study has been reviewed and given a favourable opinion by the West Midlands - Black Country Research Ethics Committee (16/WM/0414).

Funding

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Consent to publication
Not applicable

Availability of data and material
Not applicable

Authors' contributions
BES is the chief investigator and drafted the manuscript. PH, MB, FM, MSR, JS, TOB and PL are study investigators who participated in the development of the study protocol. All authors contributed to the editing and revising of the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Acknowledgements
Not applicable

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Appendix D – Physiotherapists' Training Programme

Training 1 – for all physiotherapists (2-hours in duration)

1. Background to PFP
    a. Anatomy and terminology
    b. Burden of PFP
    c. Aetiology of PFP
    d. Rationale for further study
    e. Typical patient presentation
    f. Clinical Examination
2. Overview of research design
3. Qualitative investigation
4. Clinical Equipoise
5. Usual physiotherapy
    a. Best Practice Guidelines (2015) BJSM
    b. International Expert Consensus Statement (2016) BJSM
    c. Survey UK Current Practice
6. Discussion and Q&A

Training 2 – only for physiotherapists delivering intervention (2-hours in duration)

1. Brief reminder on background to PFP
2. Brief reminder on rationale for further study
3. Pain
    a. Contemporary understanding of pain
    b. Why avoid pain
    c. Results of systematic reviews
4. Pain-related fear
    a. Self-efficacy
    b. Pain catastrophising
    c. Kinesiophobia
    d. Physical activity and pain
5. The intervention
    a. Pain education
    b. Loaded exercise
    c. Self-management strategies
6. Discussion and Q&A

Appendix E - Invitation Letter Phase 1

Date:

{*name*} {*address*}

Dear {*name*}

Knee Pain Research

You are being contacted because you were recently referred to physiotherapy with knee pain and we would like to invite you to take part in our research study. We are conducting interviews to try to increase our understanding of how people with knee pain perceive and experience their pain.

Knee pain is a common complaint, with 1 in 6 young adults suffering from pain around the kneecap at any one time. However, not enough is known about this condition at the moment, specifically in relation to its impact on patients' lives. The interviews will aim to find out what problems people with knee pain have and what difficulty they have staying active. We hope to use this information to help find ways to help people with knee pain to improve their pain and activity levels.

Your physiotherapy appointments will continue as normal.

Before you decide if you would like to take part we would like you to understand why the research is being done and what it would involve for you. Please take time to read the information sheet enclosed.

We will telephone you in the very near future to answer any questions you may have.

Thank you.

Yours sincerely

Benjamin Smith
NIHR/HEE Clinical Doctoral Research Fellow
University of Nottingham

Senior Physiotherapist
Physiotherapy Outpatients
London Road Community Hospital (LRCH), London Road, Derby DE1 2QY
Tel: 01332 254631

✂……
……...
If you would like to opt out of receiving a telephone call from us please complete this form and return to the above address, or contact us on the above telephone number.

After reviewing the information sheet I do not want to receive a telephone call or take part in the study.

Name (please print):_____

Signature:_____

Appendix F - Participant Information Sheet – Patients Phase 1

Participant Information Sheet – Patients Phase 1

(Version 2.0 – 06/09/16)

IRAS Project ID: 211417

Title of Study: A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study

Name of Researcher(s): Benjamin Smith

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

Please note that this study is being performed as part of an educational qualification.

What is the purpose of the study?

Knee pain is a common complaint, with 1 in 6 young adults suffering from pain around the kneecap at any one time. The routine treatment is physiotherapy which can include a variety of treatments, e.g. exercise, stretches, massage, ultrasound etc. However not enough is known about this condition at the moment, in particular in relation to its impact on patients' lives.

As part of a larger study, we are conducting interviews to increase our understanding of how people with knee pain perceive and experience their pain.

Why have I been invited?

You are being invited to take part because of the information in your physiotherapy referral letter, and the details you have provided about you and your knee pain. We are inviting 8-10 participants like you to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect your medical care or legal rights.

What will happen to me if I take part?

You will be invited to attend the physiotherapy department to undergo a short examination carried out by a qualified physiotherapist. This is to see if you are eligible to participate in the study. The examination will last up to 30 minutes and will involve taking a little further history, performing an assessment of your spine, hip and knee, as well as feeling the tendons around your knee. If you do not meet for criteria you will not be eligible to participate in the study, and your physiotherapy appointments will continue as normal in line with the usual arrangement within the department.

If you are eligible then you will be asked to stay to participate in an interview lasting approximately 1 hour. The interview will be relaxed and informal and can be arranged in a quiet room at the physiotherapy department or in your own home if you'd rather.

The interview will be recorded and afterwards the recording will be converted into text. This text will be analysed and some quotes may be used in the study report. Any quotes or discussions will be anonymised, so no one will know it was you who made the comments. There will be no other use of the recordings.

After the interview, your physiotherapy appointments will continue as normal in line with the usual arrangement within the department.

Expenses and payments

Participants attending an interview will be offered a £10 intu Derby voucher.

What are the possible disadvantages and risks of taking part?

You will have to take time to attend and participate in the interview. Apart from that there are no expected disadvantages or risks to taking part in this research. However, should you feel uncomfortable with any of the discussions in the interview; you are free to end the discussion at any point.

What are the possible benefits of taking part?

The information we get from this study may help inform future research. You will continue to receive your physiotherapy appointments as normal.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting The Patient Advice & Liaison Service (PALS) at Derby Teaching Hospitals, telephone: 01332 785156

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham and Derby Teaching Hospitals NHS Foundation Trust. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for less than 3 months after the end of the study so that we are able to contact you about the findings of the study

(unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 5 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your medical care or legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

What will happen to the results of the research study?

It is anticipated that the results of the study will be published in peer reviewed journals as well as being presented at relevant conferences. You are entitled to receive a summary of the results if you wish.

Who is organising and funding the research?

This research is being organised by the Derby Teaching Hospitals NHS Foundation Trust and is being funded by the National Institute of Health Research (NIHR).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the XXX Research Ethics Committee.

Further information and contact details

Benjamin Smith, NIHR/HEE Clinical Doctoral Research Fellow / Senior Physiotherapist

Physiotherapy Outpatients (Level 3), London Road Community Hospital, Derby Teaching Hospitals NHS Foundation Trust, London Road, Derby. DE1 2QY

Tel: 01332 254631

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Professor Pip Logan, Professor of Rehabilitation Research and Occupational Therapist

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Tel: 0115 8230235

E-mail: pip.logan@nottinham.ac.uk

Appendix G – Consent Form – Patients Phase 1

CONSENT FORM – Patients Phase 1

(Version 2.0 – 06/09/16)

Title of Study: A loaded self-managed exercise programme for *patellofemoral* pain: a mixed methods feasibility study

IRAS Project ID: 211417

Name of Researcher: Benjamin Smith

Name of Participant:

Please initial box

1. I confirm that I have read and understand the participant information sheet (version 2.0 – 06/09/16) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham and Derby Teaching Hospitals NHS Foundation Trust, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I consent to audio-taping of the interview and agree that anonymous direct quotations may be used for the purpose of this research. ☐
5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Appendix H - Topic Guide Interviews Phase 1

Interview Topic Guide Phase 1

(Final version 2.0 - 23/8/2016)

Introduction and background

- Thank you for agreeing to take part in this study and thank you for agreeing to discuss your experience.
- Tell me about this knee pain that you have been experiencing
- How long has it affected you for?
- How many times have you seen the GP about this?
    - How did you find that experience?
- Have you seen any other NHS Health care professionals?
    - How did you find that experience?
- Have you had any private treatment for this?
    - How did you find that experience?

Interpretation

- Do you have any thoughts on the cause of your pain? Why? Where has this come from?
- What information source have you found most useful in terms of understanding your knee pain?

Beliefs, attitude and behaviour

- How does the pain affect you?
- How does it affect your leisure / sporting activities?
- Does your knee pain affect the distance you're able to walk? How?
- Is it safe for someone with your pain to be physically active? Please explain.
- Does it affect your sleep and rest periods? How?
- Does it affect your social relationships?

Expectation

- How long do you think other people with this type of knee pain take to recover?
- How long do you think you will take to recover?
- Do you think it will recover?
- What are your expectations from physiotherapy?

Emotions

- Do you worry about your knee pain?

Close

- Is there anything further you would like to mention or discuss?
- Thank you for taking the time to discuss your experience.

Appendix I - Invitation Letter Phase 2 & 3

Date:

{*name*}
{*address*}

Dear {*name*}

Knee Pain Research

You are being contacted because you were recently referred to physiotherapy with knee pain and we would like to invite you to take part in our research study. We are conducting a study into different physiotherapy exercises.

Knee pain is a common complaint, with 1 in 6 young adults suffering from pain around the kneecap at any one time. The routine treatment is physiotherapy which can include a variety of treatments, e.g. exercise, stretches, massage, ultrasound etc.

The purpose of this study is to evaluate whether a self-managed weight bearing exercise programme is more effective than usual physiotherapy in reducing pain and improving function in people with pain around the kneecap.

Before you decide if you would like to take part we would like you to understand why the research is being done and what it would involve for you. Please take time to read the information sheet enclosed.

We will telephone you in the very near future to answer any questions you may have.

Thank you.

Yours sincerely

Benjamin Smith
NIHR/HEE Clinical Doctoral Research Fellow
University of Nottingham

Senior Physiotherapist
Physiotherapy Outpatients
London Road Community Hospital (LRCH), London Road, Derby DE1 2QY
Tel: 01332 254631

✂……
……...
If you would like to opt out of receiving a telephone call from us please complete this form and return to the above address, or contact us on the above telephone number.

After reviewing the information sheet I do not want to receive a telephone call or take part in the study.

Name (please print):_____

Signature:_____

Appendix J - Participant Information Sheet – Patients Phase 2 & 3

Participant Information Sheet – Patients Phase 2 & 3

(Version 4.0 – 24/10/16)

IRAS Project ID: 211417

Title of Study: A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study

Name of Researcher(s): Benjamin Smith

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

Please note that this study is being performed as part of an educational qualification.

What is the purpose of the study?

Knee pain is a common complaint, with 1 in 6 young adults suffering from pain around the kneecap at any one time. The routine treatment is physiotherapy, which usually involves a structured assessment, plus typically a variety of physiotherapy led treatments, e.g. exercise, taping, stretches, massage, ultrasound etc.

The purpose of this study is to evaluate the feasibility of running a large scale study into whether a self-managed weight bearing exercise programme is more effective than usual physiotherapy in reducing pain and improving function in people with pain around the kneecap. A self-managed weight bearing exercise programme concentrates on patient led exercises and self-management strategies taught to the patient by the physiotherapy team. Pain during the exercises is expected but should be within tolerable limits for the patient. The programme will be overseen by the physiotherapy team although there will be less physiotherapy led treatments. As part of this study we will also be inviting some people to discuss their experience of physiotherapy.

Why have I been invited?

You are being invited to take part because of the information in your physiotherapy referral letter, and the details you have provided about you and your knee pain. We are inviting 60 participants like you to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect your medical care or legal rights.

What will happen to me if I take part?

You will be invited to attend the physiotherapy department to undergo a short examination carried out by a qualified physiotherapist. This is to see if you are eligible to participate in the study. The examination will last up to 30 minutes and will involve taking a little further history, performing an assessment of your spine, hip and knee, as well as feeling the tendons around your knee. If you do not meet for criteria you will not be eligible to

participate in the study, and your physiotherapy appointments will continue as normal in line with the usual arrangement within the department.

If you are eligible then you will be asked to fill in a few questionnaires to help us understand how the knee pain affects you. This should take 20 minutes. These same questionnaires will be posted to you at 3 and 6 months after you start the study for you to complete again and return in the provided stamped, addressed envelope.

Because we don't know which is the best way to treat patients we need to compare the different treatments. This is the reason why we perform a randomised controlled trial, where we put an equal number of patients into each group and then compare treatments. To make sure that each group is similar, patients are put into their groups by chance (randomly). So once you have completed the questionnaires you will be randomly assigned to a self-managed weight bearing exercise programme under the guidance of a physiotherapist, or usual physiotherapy. There is equal chance you will be treated with one or the other option.

If you are asked to take part in the self-managed weight bearing exercise programme you will be asked to complete a short exercise diary to let us know how much of the exercise you were able to complete. You will be asked to complete the diary daily, and return it at 6 months in a stamped envelope provided.

During the study we will invite 8 – 10 people, once they have completed their 6 months questionnaires, to attend a short interview to discuss their experience of the process. The interviews will be relaxed and informal, may last up to 1 hour and can be arranged either in a quiet room at the physiotherapy department or in your own home.

These interviews are optional and should you wish, you can choose to not volunteer to take part in them while completing the consent form.

Interviews will be audio-taped and recordings will be converted into text and some quotes used in the written up report. Any quotes or discussions will be anonymised, so no one will know it was you who made the comments. There will be no other use of the recordings.

Expenses and payments

Participants will not be paid an inconvenience allowance to participate in the study.

Participants that volunteer to attend the interview and are invited will be offered a £10 intu Derby voucher.

What are the possible disadvantages and risks of taking part?

You will have to take time to complete the questionnaires on 3 separate occasions and attend the initial assessment. Apart from that there are no disadvantages or risks to taking part in this research. Essentially you will be receiving a course of physiotherapy as you would expect following a referral to the physiotherapy department. The physiotherapy exercises in both groups will likely cause some short term temporary pain and discomfort, particularly the loaded self-managed group as the exercises are designed so that the patient pushes themselves to a point where they experience a tolerable level of pain. If invited to take part in the interview, should you feel uncomfortable with any of the discussions; you are free to end the discussion at any point.

What are the possible benefits of taking part?

It is expected that you will gain benefit from the treatment you receive, in terms of pain reduction and improved function. But we cannot promise the study will help you. The information we get from this study may help inform future research and direct future treatment to other patients with a similar complaint.

What happens when the research study stops?

Your involvement in the study will end when you complete and return your questionnaires at 6 months after starting the study, or after completing the interview if you are invited. Your physiotherapy appointments will end at the discretion of your physiotherapist, in agreement with you. When your involvement in the study ends, you should discuss what physiotherapy treatment you wish to continue on with your physiotherapist.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researcher's contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting The Patient Advice & Liaison Service (PALS) at Derby Teaching Hospitals, telephone: 01332 785156

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham and Derby Teaching Hospitals NHS Foundation Trust. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for less than 3 months after the end of the study so that we are able to contact you about the findings of the study (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don’t want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your medical care or legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

What will happen to the results of the research study?

It is anticipated that the results of the study will be published in peer reviewed journals as well as being presented at relevant conferences. You are entitled to receive a summary of the results if you wish.

Who is organising and funding the research?

This research is being organised by Derby Teaching Hospitals NHS Foundation Trust and is being funded by the National Institute of Health Research (NIHR).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the West Midlands - Black Country Research Ethics Committee.

Further information and contact details

Benjamin Smith, NIHR/HEE Clinical Doctoral Research Fellow / Senior Physiotherapist

Physiotherapy Outpatients (Level 3), London Road Community Hospital, Derby Teaching Hospitals NHS Foundation Trust, London Road, Derby. DE1 2QY

Tel: 01332 254631

E-mail: benjamin.smith@nottingham.ac.uk

Professor Pip Logan, Professor of Rehabilitation Research and Occupational Therapist

Head of Division Rehabilitation and Ageing, B108a, School of Medicine, University of Nottingham, Nottingham. NG7 2UH.

Tel: 0115 8230235

E-mail: pip.logan@nottinham.ac.uk

Appendix K - Consent Form – Patients Phase 2

CONSENT FORM – Patients Phase 2 & 3
(Version 4.0 – 24/10/16)

Title of Study: A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study

IRAS Project ID: 211417

Name of Researcher: Benjamin Smith

Name of Participant:

Please initial box

1. I confirm that I have read and understand the Participant Information Sheet – Patients Phase 2 & 3 (version 4.0 – 24/10/16) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham and Derby Teaching Hospitals NHS Foundation Trust, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand that the researchers require access to my personal contact details to send the postal questionnaires to me. ☐
5. **Optional:** I understand that I might be contacted after completion of the treatment to discuss my experience in an interview, which will be audio-taped and I agree that anonymous direct quotations may be used for the purpose of this research. ☐
6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Appendix L - Baseline Questionnaire Pack – Phase 2

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Derby Teaching Hospitals NHS
NHS Foundation Trust

Date:

Age: Gender: Duration of Symptoms:

(months)

On average over the last week, how severe is your pain? Please place a mark on the line below to indicate how bad you feel about the pain.

no pain worse pain imaginable

On average, how many times a week are you participating in sport or physical activity?

Reading the statements below, please indicate whether or not you agree with each of the statements listed.

1 = strongly disagree

2 = disagree

3 = agree

4 = strongly agree

1. I'm afraid that I might injure myself if I exercise	1	2	3	4
2. If I were to try to overcome it, my pain would increase	1	2	3	4
3. My body is telling me I have something dangerously wrong	1	2	3	4
4. My pain would probably be relieved if I were to exercise	1	2	3	4
5. People aren't taking my medical condition seriously enough	1	2	3	4
6. My accident has put my body at risk for the rest of my life	1	2	3	4
7. Pain always means I have injured my body	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9. I am afraid that I might injure myself accidentally	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13. Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17. No one should have to exercise when he/she is in pain	1	2	3	4

Reading the statements below, please indicate whether or not you agree with each of the statements listed.

1 = not at all true

2 = hardly true

3 = moderately true

4 = exactly true

1. I can always manage to solve difficult problems if I try hard enough.	1	2	3	4
2. If someone opposes me, I can find the means and ways to get what I want.	1	2	3	4
3. It is easy for me to stick to my aims and accomplish my goals.	1	2	3	4
4. I am confident that I could deal efficiently with unexpected events.	1	2	3	4
5. Thanks to my resourcefulness, I know how to handle unforeseen situations.	1	2	3	4
6. I can solve most problems if I invest the necessary effort.	1	2	3	4
7. I can remain calm when facing difficulties because I can rely on my coping abilities.	1	2	3	4
8. When I am confronted with a problem, I can usually find several solutions.	1	2	3	4
9. If I am in trouble, I can usually think of a solution.	1	2	3	4
10. I can usually handle whatever comes my way.	1	2	3	4

PCS-EN

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain ...

1□ I worry all the time about whether the pain will end.

2□ I feel I can't go on.

3□ It's terrible and I think it's never going to get any better.

4□ It's awful and I feel that it overwhelms me.

5□ I feel I can't stand it anymore.

6□ I become afraid that the pain will get worse.

7□ I keep thinking of other painful events.

8□ I anxiously want the pain to go away.

9□ I can't seem to keep it out of my mind.

10□ I keep thinking about how much it hurts.

11□ I keep thinking about how badly I want the pain to stop.

12□ There's nothing I can do to reduce the intensity of the pain.

13□ I wonder whether something serious may happen.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

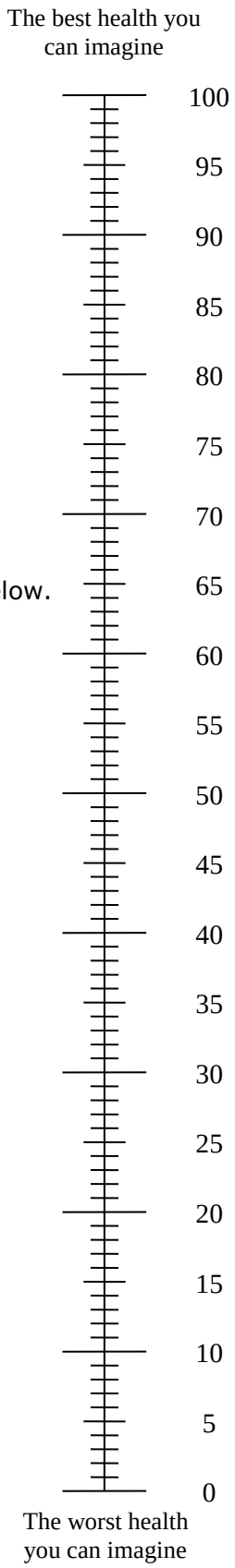
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix M – Exercise Diary

Derby Teaching Hospitals NHS
NHS Foundation Trust

Exercise Diary

Phase 2 Exercise Diary - A loaded self-managed exercise programme for patellofemoral pain V2.0 Date 23.8.2016

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Month 1																															
Month 2																															
Month 3																															
Month 4																															
Month 5																															
Month 6																															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Please record the number of times your exercise is completed

Appendix N - Topic Guide Interviews Phase 3 – Patients

Interview Topic Guide Phase 3 – Patients

(Final version 2.0 - 23/8/2016)

- Thank you for agreeing to take part in this study and thank you for agreeing to discuss your experience.
- Will you begin by briefly describing your knee complaint, how it affected you
- Did you find the physiotherapy helpful / did you get benefit from it?
- What made you decide to enter the study and did the fact it was part of a research study affect your decision?
- How useful were the information sheets (given prior to entering the study) in helping you understand what was involved?
- How did you find the initial research consultation, including consent taking?
- Where you happy to be randomised/ for chance selection of treatment options?
- How have you found the questionnaires?
    - Were they understandable?
    - Were they easy to fill in?
    - Did they take long?
    - Do you think there were important questions that were missing?

Intervention Group Only:

- You were encouraged to carry out your exercises mostly independently. How did you feel about this?
    - Did it feel safe?
    - Did you feel motivated to do them?
    - Did you understand exactly what you had to do?
    - Did you do them?
- Is this what you expected from physiotherapy treatment?
- Did you encounter any problems completing the exercises?
- You were also encouraged to exercises with some discomfort. How did you feel about this?
- Did you expect the exercises to be uncomfortable?
- Did the discomfort worry you?
- Anything that stopped you?

- Is there anything further you would like to mention or discuss?
- Thank you for taking the time to discuss your experience.

Appendix O - Topic Guide Interviews Phase 3 – Physiotherapists

Interview Topic Guide Phase 3 – Physiotherapists

(Final version 2.0 - 23/08/2016)

- Thank you for agreeing to take part in this study and thank you for agreeing to discuss your experience.
- Can you please discuss your physiotherapy experience to date, e.g. length of time qualified, length of time specialist in outpatients?
  What have been your professional experiences of treating patients with PFP?

Intervention Group:

- You were asked to deliver treatment according to the research protocol. Did you find the approach much different to your usual practice?
- Did you have any issues delivering the intervention? For example with regards to prescribing exercises that were painful/uncomfortable, or any issues encouraging the patient to self-manage?
- Were there any other issues that you experienced?

Control Group:

- You were asked to deliver usual physiotherapy. How would you feel about prescribing exercises that were painful/uncomfortable?

- What are your thoughts on patients performing exercises that are painful? Is it safe?
- Would you use that approach to any other MSK problems?
- Did the patients report any problems to you about the trial?
- Thinking about the study procedures, e.g. your recruitment / consent taking / training, how did you find them?
- Any other comments?
- Thank you for your time.

Appendix P - Ethics Approval

NHS
Health Research Authority

West Midlands - Black Country Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

07 November 2016

Mr Benjamin Smith
Senior Physiotherapist / NIHR Research Fellow
Derby Teaching Hospitals NHS Foundation Trust
Physiotherapy Outpatients, London Road Community Hospital
Derby Teaching Hospitals NHS Foundation Trust
Derby
DE1 2QY

Dear Mr Smith

Study title:	**A loaded self-managed exercise programme for patellofemoral pain: a mixed methodsfeasibility study**
REC reference:	**16/WM/0414**
IRAS project ID:	**211417**

Thank you for your submission of 25 October 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair together with another Committee member.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Georgia Copeland, nrescommittee.westmidlands-blackcountry@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above

research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

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Health Research Authority

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [TOPIC GUIDE PHASE 1]	2.0	23 August 2016
IRAS Application Form [IRAS_Form_08092016]		08 September 2016
Letters of invitation to participant [Initial Invitation Letter Phase 1]	3.0	04 October 2016
Other [PHYSIO CONSENT FORM Phase 3]	2.0	06 September 2016
Other [PHYSIO INFO SHEET Phase 3]	2.0	06 September 2016
Other [TOPIC GUIDE PHASE 3 PATIENTS]	2.0	23 August 2016
Other [TOPIC GUIDE PHASE 3 PHYSIO]	2.0	23 August 2016
Other [Phase 2 Baseline Questionnaires Pack]	2.0	23 August 2016
Other [Follow-up Letter Phase 2 Month 3]	2.0	23 August 2016
Other [Follow-up Letter Phase 2 Month 6]	2.0	23 August 2016
Other [Phase 2 Follow-up Questionnaires Pack 3 and 6 month]	2.0	23 August 2016
Other [University of Nottingham Loan Working Policy]		17 July 2012
Other [Derby Hospitals Loan Working Policy]	3	01 May 2016
Other [Initial Invitation Letter Phase 2]	4.0	24 October 2016
Other [PATIENT INFO SHEET Phase 2 & 3]	4.0	24 October 2016
Other [PATIENT CONSENT FORM Phase 2 & 3]	4.0	24 October 2016
Participant consent form [PATIENT CONSENT FORM Phase 1]	2.0	06 September 2016
Participant information sheet (PIS) [PATIENT INFO SHEET Phase 1]	2.0	06 September 2016
Research protocol or project proposal [Protocol]	4.0	04 October 2016
Sample diary card/patient card [Phase 2 Exercise Diary]	2.0	23 August 2016
Summary CV for Chief Investigator (CI) [CV for CI]	1.0	06 September 2016

Summary CV for student [Student CV]	1.0	06 September 2016
Summary CV for supervisor (student research) [CV for Supervisor]	1.0	06 September 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

NHS
Health Research Authority

16/WM/0414	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Dr Hilary Paniagua
Chair

Email:nrescommittee.westmidlands-blackcountry@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Teresa Grieve, Derby Teaching Hospitals NHS Foundation Trust*

Appendix Q - HRA Approval

NHS
Health Research Authority

Mr Benjamin Smith
Senior Physiotherapist / NIHR Research Fellow
Derby Teaching Hospitals NHS Foundation Trust
Physiotherapy Outpatients, London Road Community Hospital
Derby
DE1 2QY

Email: hra.approval@nhs.net

22 December 2016

Dear Mr Smith,

Letter of HRA Approval

Study title:	**A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study**
IRAS project ID:	**211417**
REC reference:	**16/WM/0414**
Sponsor	**Derby Teaching Hospitals NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **211417**. Please quote this on all correspondence.

Yours sincerely

Simon Connolly
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Teresa Grieve, Derby Teaching Hospitals NHS Foundation Trust*

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Interview schedules or topic guides for participants [TOPIC GUIDE PHASE 1]	2.0	23 August 2016
IRAS Application Form [IRAS_Form_08092016]		08 September 2016
Letters of invitation to participant [Initial Invitation Letter Phase 1]	3.0	04 October 2016
Other [PHYSIO CONSENT FORM Phase 3]	2.0	06 September 2016
Other [PHYSIO INFO SHEET Phase 3]	2.0	06 September 2016
Other [TOPIC GUIDE PHASE 3 PATIENTS]	2.0	23 August 2016
Other [TOPIC GUIDE PHASE 3 PHYSIO]	2.0	23 August 2016
Other [Phase 2 Baseline Questionnaires Pack]	2.0	23 August 2016
Other [Follow-up Letter Phase 2 Month 3]	2.0	23 August 2016
Other [Follow-up Letter Phase 2 Month 6]	2.0	23 August 2016
Other [Phase 2 Follow-up Questionnaires Pack 3 and 6 month]	2.0	23 August 2016
Other [University of Nottingham Loan Working Policy]		17 July 2012
Other [Derby Hospitals Loan Working Policy]	3	01 May 2016
Other [Initial Invitation Letter Phase 2]	4.0	24 October 2016
Other [PATIENT INFO SHEET Phase 2 & 3]	4.0	24 October 2016
Other [PATIENT CONSENT FORM Phase 2 & 3]	4.0	24 October 2016
Participant consent form [PATIENT CONSENT FORM Phase 1]	2.0	06 September 2016
Participant information sheet (PIS) [PATIENT INFO SHEET Phase 1]	2.0	06 September 2016
Research protocol or project proposal [Protocol]	4.0	04 October 2016
Sample diary card/patient card [Phase 2 Exercise Diary]	2.0	23 August 2016
Summary CV for Chief Investigator (CI) [CV for CI]	1.0	06 September 2016
Summary CV for student [Student CV]	1.0	06 September 2016
Summary CV for supervisor (student research) [CV for Supervisor]	1.0	06 September 2016

IRAS project ID	211417

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Benjamin Smith

Email: benjamin.smith@nottingham.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor is the single participating NHS organisation. No requirement for statement of activities or schedule of events.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study

Section	HRA Assessment Criteria	Compliant with Standards	Comments
4.3	Financial arrangements assessed	Yes	Study to be completed as part of a PhD. Student has successfully applied for HEE/NIHR Clinical Doctoral Research Fellowship.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	
6.3	Devices – MHRA notice of no objection received	Not Applicable	
6.4	Other regulatory approvals and authorisations received	Not Applicable	

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There will be a single participating NHS organisation where the research activities described in the submission will take place. If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research

management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
This is a single site study sponsored by the site. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
The researcher will be the principal investigator at the single participating NHS organisation. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
Researcher has existing contractual arrangements at the participating NHS organisation.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix R - R&D Approval

SMITH, Benjamin (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST)

From:	RAVIPATI, Parameswari (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST)
Sent:	03 January 2017 17:01
To:	SMITH, Benjamin (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST); BATEMAN, Marcus (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST)
Cc:	SHAW, Anne (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST); BURNS, Jo (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST); PATEL, Ramila (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST); BOATENG, Trish (DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST)
Subject:	DHRD/2016/089_ IRAS 211417_Patellofemoral pain Study_DHFT Confirmation of participation.

On Behalf of Dr Ramila Patel, Research Governance & Clinical Trials Manager

Dear Mr. Smith,

RE: DHRD/2016/089_ A loaded self-managed exercise programme for patellofemoral pain: a mixed methods feasibility study

- **Chief Investigator:** Mr Benjamin Smith
- **Sponsor:** Derby Teaching Hospitals NHS Foundation Trust
- **Funder:** National Institute for Health Research

Further to the above study being issued with HRA/REC approval, this email confirms that Derby Teaching Hospitals NHS FT (DHFT) has the capacity and capability to deliver the above study, DHRD/2016/089. **Please note that the Sponsor may issue their own 'green light' prior to DHFT being able to start recruitment – please do confirm with them prior to any recruitment activities.**

- The 70 day Target* Date for Recruiting the First Subject is **02/03/2017**
- The agreed Recruitment Target for this Study is **60**
- Recruitment end date is **28/07/2017**
- Clinical Trial Agreement **is attached**

Please supply the following information at the appropriate time points to Dr Teresa Grieve, Assistant Director of R&D via (dhft.randdadmin@nhs.net):

- The date of your first patient recruited to the study.
- A report every six months if the study duration is greater than six months.
- Notification of any changes to the local study team, SUSARS, amendments, urgent safety measures or if the trial is abandoned.
- Notification of end of the study and an end of study report.
- Details of any publications arising from this research project.

Please note that approval for this study is dependent on full compliance with all of the above conditions.

*The Government's Plan for Growth (March 2011) announced the transformation of incentives at local level for efficiency in initiation and delivery of research. As a result the NIHR have introduced research performance benchmarks: '***studies must recruit to time and target, and first patient must be recruited onto the study within 70 days of the "Date Site Selected"*** (i.e. from the date of provision of the local information package by the sponsor including the HRA Initial Assessment Letter). Trusts will be fined, otherwise penalised and funding withheld if these metrics are not met.

Please ensure you work towards recruiting the first patient by the 70 Day target, and inform us if you envisage any problems as we will endeavour to help you meet this target.

Also, please find below the list of HRA/REC and R&D approved documents for this study:

Document	Version	Date
TOPIC GUIDE PHASE 1	2.0	23 August 2016
Initial Invitation Letter Phase 1	3.0	04 October 2016
PHYSIO CONSENT FORM Phase 3	2.0	06 September 2016
PHYSIO INFO SHEET Phase 3]	2.0	06 September 2016
TOPIC GUIDE PHASE 3 PATIENTS	2.0	23 August 2016
TOPIC GUIDE PHASE 3 PHYSIO]	2.0	23 August 2016
Phase 2 Baseline Questionnaires Pack	2.0	23 August 2016
Follow-up Letter Phase 2 Month 3	2.0	23 August 2016
Follow-up Letter Phase 2 Month 6	2.0	23 August 2016
Phase 2 Follow-up Questionnaires Pack 3 and 6 month	2.0	23 August 2016
Initial Invitation Letter Phase 2	4.0	24 October 2016
PATIENT INFO SHEET Phase 2 & 3	4.0	24 October 2016
PATIENT CONSENT FORM Phase 2 & 3	4.0	24 October 2016
PATIENT CONSENT FORM Phase 1	2.0	06 September 2016
PATIENT INFO SHEET Phase 1	2.0	06 September 2016
Research protocol	4.0	04 October 2016
Phase 2 Exercise Diary	2.0	23 August 2016

I would like to take this opportunity to wish you every success with this study. Good Luck!

Kind regards

Dr Ramila Patel

Research Governance & Clinical Trials Manager

(To ensure your query is dealt with quickly please ensure you quote the Local Project Reference Number (e.g. DHRD or DEV number) and/or full study title on all correspondence)

Research and Development Office

Royal Derby Hospital

Room 5033, University of Nottingham GEM School

Derby Teaching Hospitals NHS Foundation Trust

Uttoxeter Road

Derby, DE22 3DT

Tel: 01332 789339

E-mail: Ramila.patel8@nhs.net

All general enquiries for the R&D Department should be directed to our admin support address dhft.RandDadmin@nhs.net where we will endeavour to provide a same day response service

Kind regards

Pam

Parameswari Ravipati

Study Support Service Administrator

P please don't print this e-mail unless you really need to

(To ensure your query is dealt with quickly please ensure you quote the Local Project Reference Number (e.g. DHRD or DEV number) and/or full study title on all correspondence)

Research and Development Office

Royal Derby Hospital

Room 5033, University of Nottingham GEM School

Derby Teaching Hospitals NHS Foundation Trust

Uttoxeter Road

Derby, DE22 3DT

Tel: 01332 787224

E-mail: parameswari.ravipati@nhs.net

All general enquiries for the R&D Department should be directed to our admin support address dhft.RandDadmin@nhs.net where we will endeavour to provide a same day response service

Z`Appendix S – Physiotherapy Intervention Record Sheet

Possible physiotherapy interventions	**Tick if documented**
Specific pain education* Loaded exercise* Self-management strategies*	
Acupuncture Closed chain exercise Electrotherapy General advice Hip specific exercise Massage Movement re-training Open chain exercise Orthotics Patella taping Referral on Stretches VM exercises	
*, three-point checklist outlining important details and components of the intervention; VM, vastus medialis	