Universitat de Girona

A pain-coping approach for chronic patellofemoral pain syndrome

A randomized controlled clinical trial

Degree final project 2019

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This work would not have been possible without the support and help of Dr Ana Bofill.

I would also like to express my personal thanks to Dr Xavier Castells, for his invaluable contribution and willnigness to teach us critical thinking.

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Abbreviations

PFPS: Patellofemoral pain syndrome

PFP: Patellofemoral pain

PR: Physical rehabilitation

MRI: Magnetic resonance imaging

PFJRF: Patellofemoral joint reaction force

TG: Trochlear groove

VMO: Vastus medialis obliquus

CBT: Cognitive behavioral therapy

CNS: Central nervous system

PS: Peripheral sensitization

CS: Central sensitization

SP: Substance P

PPT: Pressure pain threshold

VAS: Visual analogue scale

KOA: Knee osteoarthritis

CLBP: Chronic low back pain

BMI: Body mass index

RCT: Randomized clinical trial

CEIC: Clinical research ethical committee (*comité ètic d'investigació clínica*)

PMR: Progressive muscle relaxation

EC: Ethics committee

Abstract

Background: Patellofemoral pain syndrome, or PFPS, is a high prevalence condition, especially amongst the young female population, but despite this, diagnose and treatment are not yet well established and as many as 50 % of patients continue to experience symptoms on the long term. Recent research shows patients with long term PFPS have worse overall mental health, as well as hyperalgesia and lower pressure pain threshold, indicating possible centralization mechanisms. These findings pose the question of a multidisciplinary approach to PFPS treatment, with physical as well as psychological interventions.

Objective: To determine if pain coping skills training reduces PFPS symptoms compared to a sham psychological intervention.

Design: This is a randomized, parallel-group, single blind, sham-controlled clinical trial.

Participants: Adults between the ages of 18 and 50, living in the province of Girona, Spain, diagnosed with PFPS with symptoms lasting for longer than 3 months.

Intervention: Pain coping skills training or non-directive counselling. All groups will also receive exercise rehabilitation.

Keywords: *Patellofemoral pain syndrome, pain coping skills training, centralized pain.*

Introduction

Background

Definition of patellofemoral pain syndrome

Patellofemoral pain syndrome (PFPS) is a broad term for pain felt anteriorly around the patella, which increases during loading conditions of the knee, such as prolonged sitting, squatting, kneeling, and stair climbing (1).
It can also be referred as anterior knee pain, patellar chondromalacia or patellofemoral arthralgia.

Epidemiology

PFPS accounts for about 25 % of consultations at orthopaedic and physical therapy clinics (2), but due to the lack of precise diagnose criteria, there's a some variability between studies with regards to prevalence in the general population, with results ranging from 7 % up to 28% (3), while incidence is usually estimated at 9.2% (4).
Patellofemoral pain can appear at any age, but is most common in athletic females (2:1 female to male ratio), in the 15 to 30 age group (5). According to some authors, as much as 50% of the nonspecific anterior knee pain among adolescents may be attributed to PFPS. (1)

Anatomy of the patellofemoral joint

The patellofemoral (PF) joint is complex, and we still lack full understanding of the kinematics during the different loading conditions of movement and exercise.
The patella is a gliding joint that moves in different planes: superior/inferior, medial/lateral, rotation and tilt. During knee flexion, the patella shifts inferiorly, and during knee extension, it shifts superiorly, this movement is called patellar tracking, and it serves to increase the pulling force of the quadriceps during knee extension.
The PF joint is intrinsically unstable because of its large range of motion, the incongruent articular surfaces and the powerful muscles attaching onto the patella from

different directions. Several musculoskeletal systems interact to stabilize the patella along the centre of the trochlea and limit lateral maltracking, here are described the main components:

- Sulcus angle: it is a measure of the depth of the femoral trochlea. The lateral facet of the trochlea is larger than the medial facet, limiting patellar lateral tracking in the first degrees of knee flexion.

  An angle of 150 º or greater is a sign of an abnormally flat articular surface, also known as trochlear dysplasia, which is the main predisposing factor for patellofemoral instability.

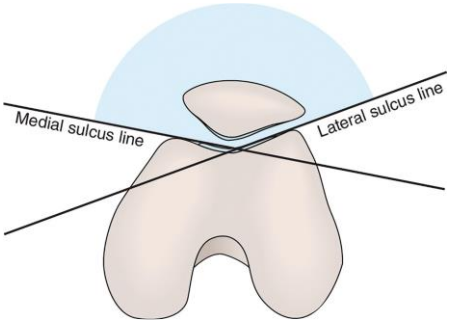


Figure 1 Calculation of the sulcus Angle. Petersen W et al., 2014 (10)

- Q angle: it measures the angle stablished between the femur and tibia using several osseous landmarks. An angle greater than 12 % in males or 18 % in females is indicative excessive knee valgus, which is a predisposing factor for arthritis and PFPS, among others.

  Knee valgus can be permanent anatomical feature of the individual or appear only during loading conditions, which is referred to as dynamic valgus (figure 3).

  Presumably, the much higher incidence of PFPS in women is in large due to anatomical and motor-control differences that cause women to present an increased Q angle during dynamic activities. (6)

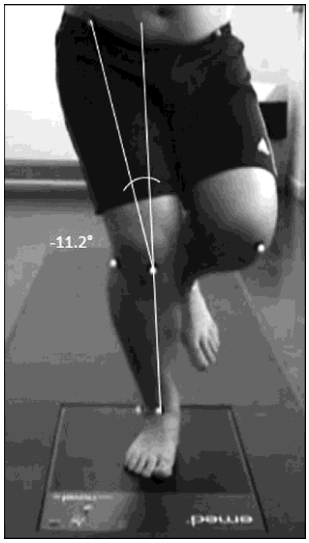


Figure 2 Dynamic valgus during a one-legged squat, and frontal plane projection angle (FPPA). Maclachlan et al. 2017 (17)

- Patellar height: A more proximal patella contributes to patellar instability because the knee requires a greater degree of flexion before the patella is engaged in the trochlea. A more distal patella results in increased posterior forces acting on the patella, which can lead to movement limitation and early patellofemoral arthritis.

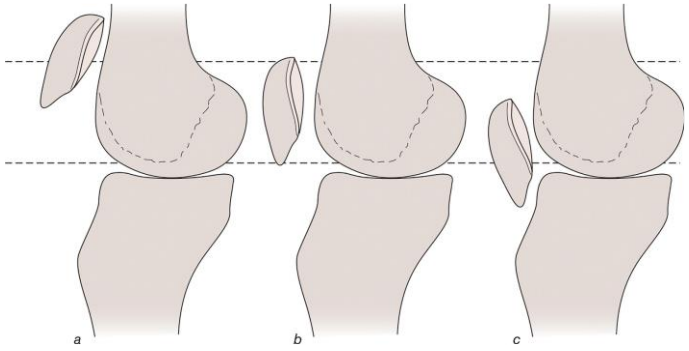


Figure 3 Different positions of the patella. Loudon et al. (9)

- Quadriceps muscles: The quadriceps muscle has four components: the rectus femoris, the vastus medialis obliquus, the vastus lateralis and the vastus intermedius. As knee flexion increases, these muscles pull the patella closer to the trochlea (figure 4), stabilizing it, but as we will discuss later, excessive posterior forces are also related to pain.

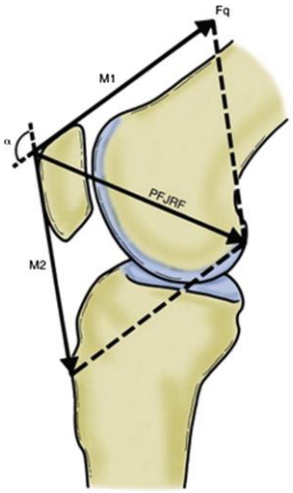


Figure 4 M1 is the quadriceps tendon, pulling the patella proximally. M2 is the patellar tendon, pulling the patella distally. Their resulting force vector (PFJRF) pulls the patella posteriorly into the femoral trochlea. Norman et al. 2012. (66)

The vastus medialis obliquus (VMO) is especially significant in PFPS as it's the main medial restraint of the patella throughout the first degrees of knee flexion (7). Weakness of the VMO, atrophy and decreased activation (assessed with electromyography) have been consistent findings in PFPS patients. (3,8)

- Hip stabilizers: they include the gluteus maximus, medius, the piriformis and deep core muscles. Recent research shows that weakness of hip stabilizing muscles can predispose to PFPS through an internal rotation of the femur, which would promote an increased dynamic Q angle. (6,9)

  The hip stabilizers act on the patella through the fibres expanding from the iliotibial tract to the lateral retinacula. Excessive tightness or retraction of these structures can therefore also increase patellar lateral tilt and patellofemoral pain. (10)

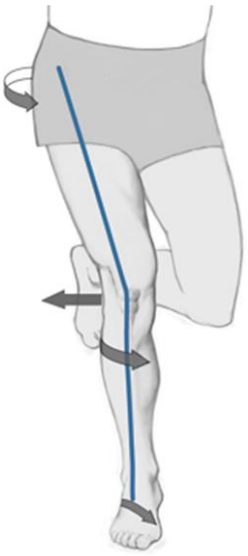


Figure 5 Dynamic valgus of the knee, which can be due to internal rotation of the femur or the tibia. (8)

- The medial and lateral retinacula: they are ligamentous structures attaching at either side of the patella and condensed into two important structures: the lateral and medial patellofemoral ligaments (LPFL and MPFL respectively).

  The MPFL it is especially crucial for lateral patellar stability, accounting for 60 % of lateral restraining forces on the patella during the first degrees of knee flexion. (7) Its injury is one of the indications for surgery in patellofemoral maltracking.

Pathophysiology of patellofemoral pain syndrome

The general opinion on PFPS pathogenesis has largely shifted over the past 40 years, from a cartilage degeneration disease to a purely biomechanical alteration, and although it is not yet fully clear, currently the most widely accepted theory is that PF pain is multifactorial, with structural, biomechanical and neuropsychological factors interacting (figure 9).

Biomechanical alterations

Biomechanical alterations are the result of three main factors that might not all be present at once: structural features of the individual (e.g. trochlear dysplasia), biomechanical dysfunctions (e.g. dynamic Q angle) and overload of the structures (e.g. excessive exercise) (figure 6).

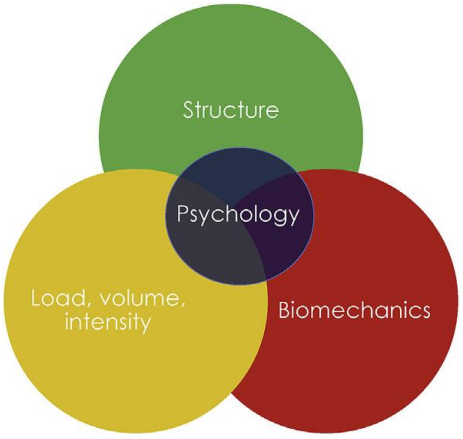


Figure 6 Pathogenesis of PFPS. Lack et al. 2018. (6)

PFP appears as a result of the maltracking of the patella, meaning, instead of being centred in the femoral trochlea, it shifts laterally during knee flexion, causing increased strain on the patellofemoral joint and peripatellar soft tissues (11). The synovium and the subchondral bone are highly innervated tissues, which can be stimulated either mechanically or chemically, by inflammatory substances (12).

Increased joint stress can eventually lead to cartilage degeneration, and according to some authors, to KOA, although this association remains unclear (13).

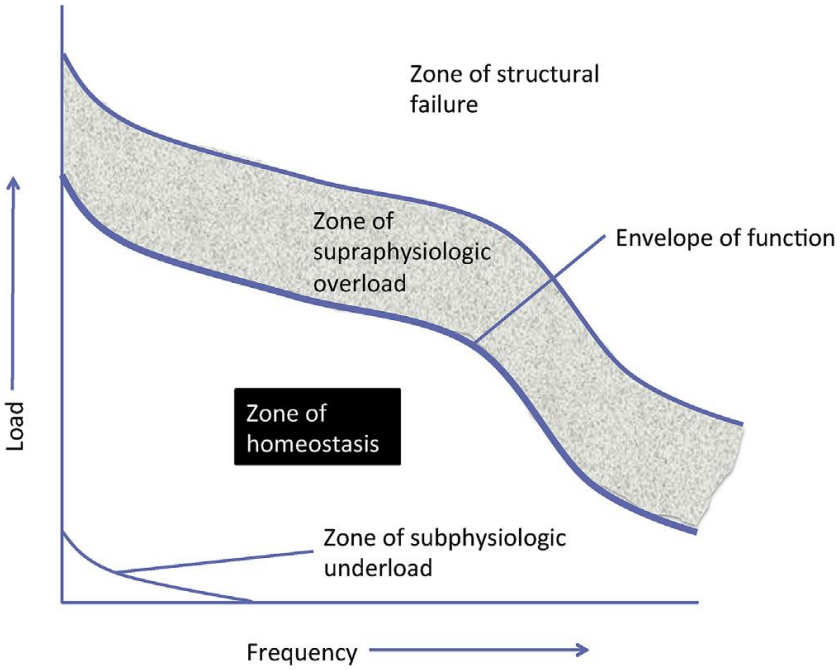


Figure 7 Diagrammatic representation of the zone of tissue homeostasis. Dye et al. 1999. (15)

The "envelope of function" theory, represented in figure 7, represents the pathogenesis of PFPS. The patellofemoral joint can sustain a certain amount of stress or overloading without it resulting in damage or pain. If the stress surpasses the individual's threshold of tissue homeostasis, either after one single acute episode of intense loading or several lesser episodes, the damaged structures are unable to recover, persistent inflammation lowers the pain threshold and they may experience pain during conditions that were previously painless (14,15), generating a vicious cycle. The most frequent triggering activities are running, cycling, and jumping.

Psychological alterations

Pain is subjective and different from nociception, which is the observable response of the nervous system to a stimulus. It is therefore experienced differently by each individual and greatly influenced by personality and past experiences.

Baseline psychological features of the individual account for about 50% of sensitivity to pain, and likeliness to develop chronic pain over the course of their lifetime (16), defined as pain lasting longer than 3 months (17). At the same time, persistent pain can be an accumulative load on the brain, and overtime, through chemical and structural changes, can result in altered psychological processes including cognition, perception and mood (18). Therefore, pain and emotion can be influenced and modified by each other.

The most relevant psychological features, weather pre-existing or developed after the main painful event, that can hinder rehabilitation and facilitate the evolution to chronic pain and depression are summarized in figure 8.

Vulnerability/Exacerbating Factors	Resilience/Protective Factors
• Helplessness • Feelings of no self-control • Low self-efficacy • Catastrophizing • Rigid thinking • Defeated/overwhelmed • Lack or perceived lack of social support	• Resourcefulness • Sense of control • High self-efficacy • Optimism • Psychological flexibility • Resilient • Availability of positive social support

Figure 8 Vulnerability and resilience factors for development of depressive symptoms in chronic pain patients. Okifuji and Turk. (66)

Catastrophizing is the maladaptive understanding of one's condition, with exaggerate negativity and attention towards the pain. It is one of the psychological features that has been most studied in several chronic and acute pain conditions, including rheumatoid arthritis, osteoarthritis and fibromyalgia. Higher levels of catastrophizing are associated with higher pain and disability ratings, more healthcare usage, worse anxiety and poor overall pain management. The current theory behind the mechanism of action is through an increased attention towards the pain stimulus, which diminishes pain-inhibitory pathways, coping efficacy, adherence to treatment, and healthy behaviours like exercise or participation in social activities. (19)

A 2017 systematic review found that individuals with PFP presented general worse mental health, with higher levels of catastrophizing, avoidance behaviour, anxiety and depression (17). These alterations are common to other musculoskeletal pain disorders, including chronic whiplash pain, temporomandibular disorders and chronic low back pain that have well known correlations with centralized pain (20). This observation has led many researchers to consider the possible role of centralized pain in PFPS, which will be further developed in the next sections.

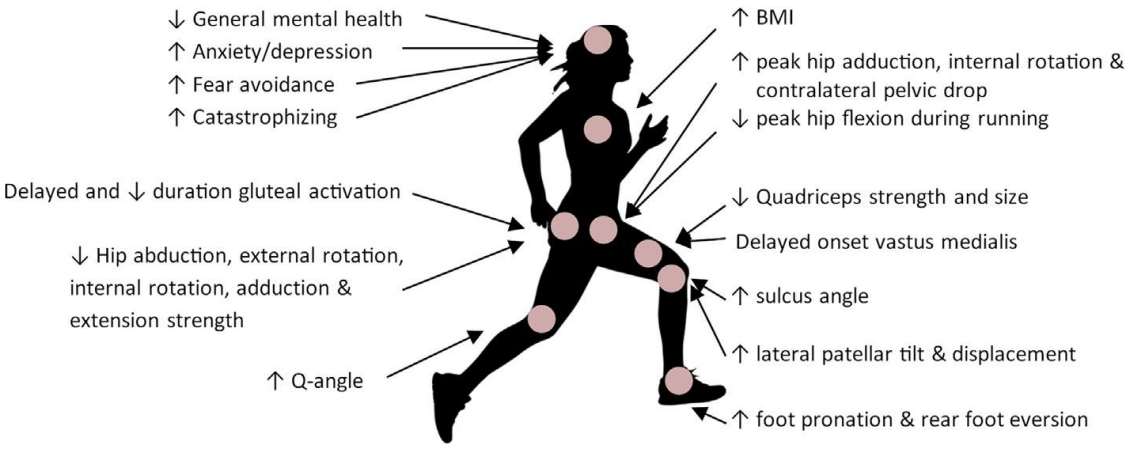


Figure 9 Physical, structural, biomechanical and psychological factors associated with PFPS. Jensen et al, 2007 (21)

It's not yet clear whether the biomechanical and psychological alterations described are pre-existing and facilitate the development of PFPS or if it's the other way around,

where an episode of intense loading leads to a series pathological changes that self-perpetuate the symptoms. (17)

Diagnosis of patellofemoral pain syndrome

The main diagnose criterion for PFPS according to the 2016 international consensus is pain around or behind the patella, aggravated by at least one activity that loads the patellofemoral joint: squatting, climbing or descending stairs, running, and jumping.
Additional criteria that may or not be present are crepitus or grinding sensation during knee flexion, tenderness on patellar facet palpation, small effusion, and pain after sitting for some time. (21)
In PFPS, the routine knee examination can present little to no alterations, whereas dynamic or functional weight-bearing tests are more reliable in eliciting pain or showing dynamic malalignment. The most reliable test is patient-reported anterior knee pain when performing a squat (22).
Something that differentiates PFPS from other causes of knee pain is the lack of structural abnormality, therefore diagnosis is based on exclusion of other causes of anterior knee pain (23), such as meniscal, ligamentous or iliotibial band lesions, usually through physical exam, and sometimes imaging studies, mainly radiographs or magnetic resonance imaging (MRI).
Patient history should also aim to identify the amount and intensity of exercise the patient takes part on, since this will be important to address as part of patient education. (24)
Ideally, evaluation of PFPS should also address psychological factors such as anxiety, catastrophizing or kinesiophobia, to identify those patients that could benefit from a psychological approach.

Standard treatment and prognosis of patellofemoral pain syndrome

Treatment of PFPS is mainly non-operative and consists of four main principles:

- Rest: Evidence suggests that 30 % of anterior knee pain caused by overuse resolves after 4 weeks of decreased activity. (25)

- Pharmacological treatment: Mainly paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs).
- Physical rehabilitation: Evidence shows that exercise focused on strengthening the quadriceps, hamstrings, and the external hip rotators, along with stretching, is the most effective intervention for improving pain and function in these patients (26).

  In the case of patients with maladaptive movement patterns during loading conditions such as running, gait retraining might be more effective than strength training alone (27).
- Education: It is crucial to educate patients on load management in order to change unhealthy exercise habits they may have developed and manage their expectations of full recovery.

The general use of arthroscopy and surgery has no evidence-based support and should be reserved to very isolated cases were there's an identifiable and reparable cause. The most common surgeries are release of the lateral retinacula, excision of a painful synovial tissue and MPFL reconstruction. (28)

PFPS treatment is efficacious in the short-term in 75 % of patients (11), but persistence of symptoms in long term follow up (5-20 years) is reported in more than 50% of patients (24). Some of the factors linked with a poorer prognosis were symptom duration longer than 12 months and worse knee function scores at baseline. (8)

Centralized pain in PFPS

Centralization is characterized by a heightened, diffuse pain state, that lasts long after the initial stimulus has subsided, together with other central symptoms such as fatigue, poor sleep, mood and anxiety disorders. (29)

Initially, centralized pain referred to pain caused by a central nervous system (CNS) lesion, such as a stroke. Afterwards, the term was used to explain functional or idiopathic pain syndromes caused by alterations in pain processing by the CNS, such as fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, headache or interstitial cystitis.

In more recent years, there's been growing interest in the role of centralized pain in chronic pain conditions previously thought to be purely peripheral, such as osteoarthritis or autoimmune disorders. These conditions seem to be more of a "mixed pain" state, with a peripheral nociceptive component, and a central nervous system component that modulates pain transmission by increasing pro-nociceptive substances (glutamate, substance P), and decreasing pain-inhibitory pathways (serotonin, GABA). (29) (figure 9)

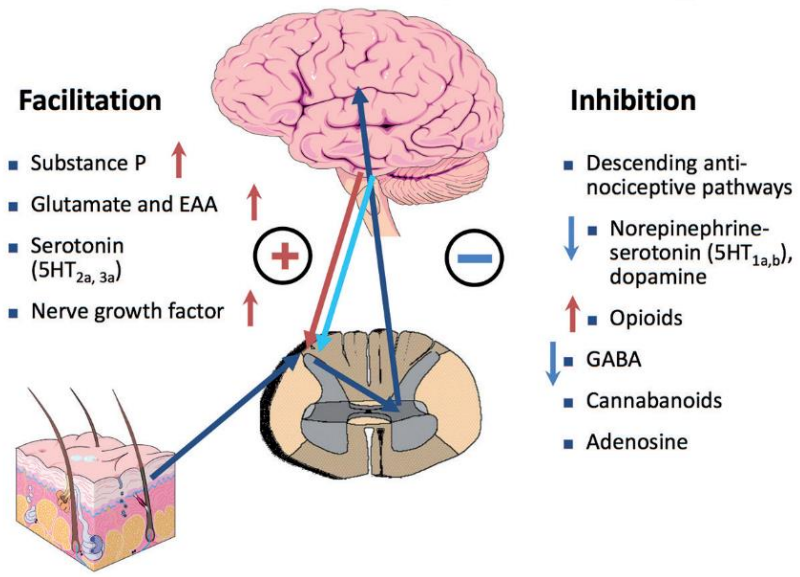


Figure 10 CNS influence on pain and sensory processing. The role of Centralized Pain in Osteoarthritis. Clauw et al. 2017. (30)

The process leading to centralisation can be divided into peripheral (PS) and central sensitisation (CS).

PS begins after tissue injury; if pain persists for a few days, inflammatory substances released by injured tissues and microglia (neurotrophic factors, cytokines, prostaglandins, tumour necrosis factor (TNF)-a, interleukins, substance P, etc.) may lead to sensitisation of peripheral nociceptors, meaning they cause alterations in neuron-specific, voltage-gated sodium channels, increasing membrane excitability and lowering the pain threshold in that area (30–32).

This increase in local pain sensitivity, also known as *primary hyperalgesia*, is a protection mechanism in order to prevent further use of damaged structures and consequent further damage. (20) This heightened response to usually innocuous stimuli can generate fear and avoidance of previously enjoyed activities.

Hyperalgesia can be clinically evaluated either with a pressure algometer (figure 10) or manual palpation of different locations and identifying a decrease in pressure pain threshold (PPT) (33).

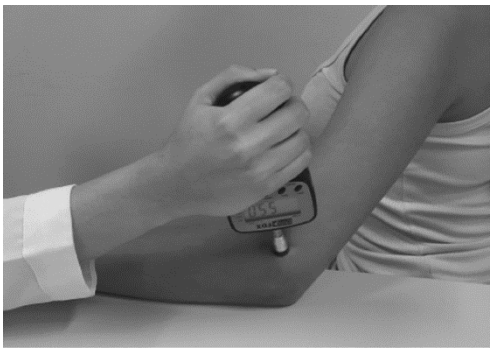


Figure 11 Position of the pressure algometer on the lateral epicondyle of the humerus to assess pain threshold and pain tolerance. (67)

The constant state of peripheral depolarisation can then evolve to central sensitisation (CS) or *secondary hyperalgesia*, referring to the spread of hyperalgesia to undamaged adjacent tissues.

CS can be separated into acute and late phase sensitisation. In acute-phase CS, there's an increased responsiveness of dorsal horn neurons in the spine caused by a rise in glutamate and substance P (20,32). This increase in synaptic glutamate also results in the death of inhibitory neurons that would usually help modulate pain signals (32). (figure 12)

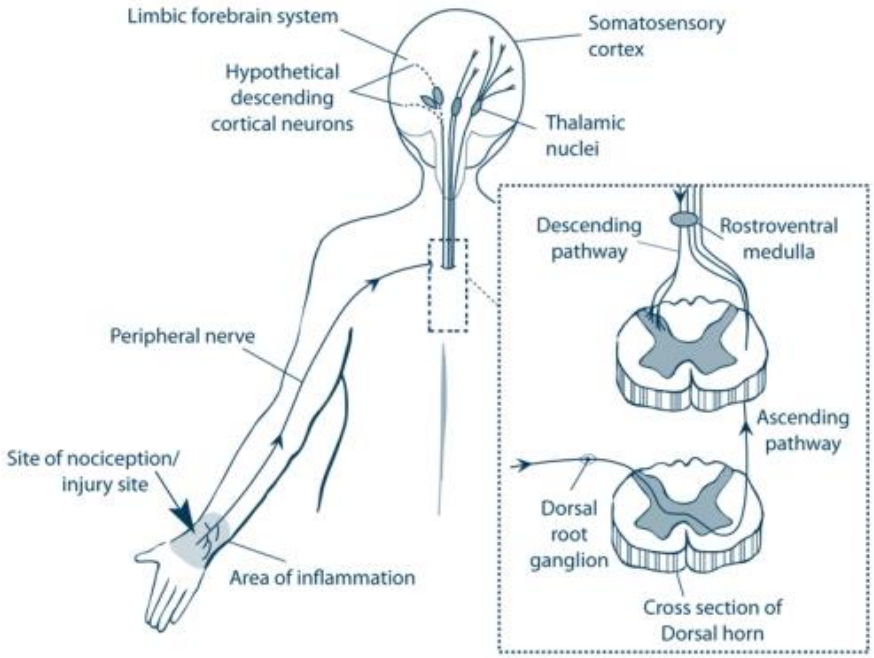


Figure 12 Pain pathways (34)

In late-phase CS there's an alteration of gene expression in dorsal horn neurons and it becomes more difficult to fully recover from hyperalgesia (33). This causes a constant outflow of pain transmission to the insula, the area of the brain responsible for sensory processing.

One of the proposed mechanisms for evolution to chronic pain is the profound impact pain can have on memory through connections with the limbic system (34). For example, in chronic pain, a person may develop a limp or a maladaptive movement in order to avoid pain (negative reinforcement), or even because it generates external attention (positive reinforcement). This can become counter-productive, because it eventually leads to muscle atrophy and imbalances, thus perpetuating and worsening the symptoms.

In order to prevent CS, injury healing and reducing local pain as soon as possible is essential (35).

Treatment approach to centralised pain

Effective therapy for CS should incorporate a multidisciplinary approach that includes physical therapy, pain psychology, and pharmacological agents (18). Here we will only discuss the psychological approach.

The principle of pain coping psychology is to improve the way the patient lives with their chronic condition through a better understanding of it and a realistic, non-judgmental approach to pain. This process is known as cognitive appraisal, or the subjective interpretation one has of life events. In fact, simply educating patients about their condition leads to better attitudes and less functional disability (32).

One of the most famous psychological therapies is cognitive behavioural therapy (CBT), but its principles are common to most pain-coping therapies. In CBT, the therapist encourages patients to become aware of their negative thoughts, and to observe them objectively, without letting them determine emotion. For example, in the face of pain, thinking "I will never get better" versus acknowledging and thinking "I am having a thought that I will never get better". Just a few weeks of CBT-type therapy have been shown to significantly reduce catastrophising in chronic pain patients. (36)

Pain coping skills and the use of "mindfulness" techniques has been used in centralised pain with positive results for almost 30 years (37–39), but it wasn't until recently, that, through the use of functional brain imaging, we've been able to objectify how they work. People with experience in "mindfulness" practices show an increased activation of the prefrontal cortex (in relation to cognition), and decreased activation of the orbitofrontal cortex and the amygdala (pain and stress-related areas). (40)

Justification of the research question

Patellofemoral pain syndrome (PFPS) is a high prevalence condition, especially in young athletic females (4), with a large debilitating impact not only on physical function, but also in social life and ability to take part in recreational activities, which results in worse mental health, with higher levels of anxiety, depression, catastrophising and fear avoidance behaviour (41). This dysfunctional outlook on one's own health can perpetuate pain, act as a barrier for treatment adherence, influence the transition from acute to chronic pain and increase healthcare usage. (17)

Despite its large health impact, PFPS remains a condition with a largely unknown pathophysiology, a difficult diagnosis and poor treatment outcome, with 40% to 57% of patients experiencing an unfavourable long-term outcome, often without any physical findings that might explain the pain. This can become frustrating for both the patient and the therapist. (42)

Recent findings have shown that adolescent females with PFPS have lower pain pressure thresholds (PTT's) both at the patellofemoral joint and at distant locations (1,12), suggesting pain centralisation mechanisms may be present in PFPS.

Pain centralisation is an alteration in the neurological mechanisms for pain sensitivity characterised by a lower pain threshold, as well as sleep, memory and mood alterations.

The treatment of pain centralisation includes psychological therapies like cognitive behavioural therapy (CBT), pain coping skills training (PCST), or biofeedback, amongst others. These have been used in chronic musculoskeletal conditions with centralisation characteristics such as chronic low back pain (CLBP) or knee osteoarthritis (KOA) for over 30 years, with results showing small to moderate improvements in pain, mood and disability according to a 2012 Cochrane systematic review. (43)

There's been very few studies analysing psychological approaches for treatment of PFPS (44,45), and they are largely inconclusive due to small sample size, which is why we value necessary further research on this field.

Based on the literature review, we've designed a multidisciplinary approach that combines physical rehabilitation, which is the most effective treatment for PFPS to date, with pain-coping-skills training (PCST), which is one of the most widely used therapies in chronic pain (46,45).

The aim of this study is to determine if PCST can be effective for those patients whose pain has not subsided after three months, which is considered the cut-off point for chronic pain (47).

Despite the lesser effect that we can expect PCST to have on PF pain, we've chosen pain as our main outcome because it is widely used across chronic pain conditions, making our results more easily comparable to others and applicable for future research. (48) However, PCST seems to have more important effects on reduction of catastrophising and kinesiophobia, which are crucial factors determining inter-individual differences in pain and disability ratings, especially on the long term (44,49).

Finally, a few studies using PCST in chronic pain conditions found that higher education level and greater expectations of treatment efficacy to be important predictors of positive intervention outcome (50,51), so we decided to include these variables in our final analysis.

To conclude, PFPS is a relevant entity with high prevalence and serious impact on quality of life. Determining the effectiveness of psychological therapies on PFPS patients with chronic pain could be beneficial for creating a multidisciplinary treatment plan for these patients. Another more applicable and realistic outcome would be a better understanding of the etiopathogenesis of PFPS, allowing all physicians, specialised or not on knee injuries, to better assess these patients, identifying earlier those with characteristics prone to catastrophising and providing them with some of the simple tools used in PCST. Psychological techniques can often be disregarded or pushed to the background, but when done correctly, they are another helpful tool in our arsenal for treating the full spectrum of repercussions pain has on an individual.

Hypothesis

The primary hypothesis is that the PCST intervention will show slight to moderate improvement for pain measured through the visual analogue scale, in patients with chronic PFPS compared to non-directive counselling; both at 10 week and 6-month follow-up.

The secondary hypothesis is that PCST will show moderate improvement in catastrophising, kinesiophobia and disability compared to NDC in patients with chronic PFPS; both at 10 week and 6-month follow-up.

Finally, with regards to patient education level and expectations of intervention efficacy, we believe both of these variables will directly correlate with greater improvements in outcome measures.

Objectives

The main objective of this study is to compare the effectiveness of pain-coping-skills training (PCST) to a control or "sham" intervention, in this case non-directive counselling (NDC); for pain reduction, measured through the visual analogue scale (VAS); in adult patients diagnosed with chronic patellofemoral pain syndrome (PFPS); at 10 weeks and 6 month follow ups.

Secondary objectives are:

- To assess the effect of PCST on other aspects related to chronic pain: physical disability, perceived improvement with treatment, catastrophising, kinesiophobia, self-efficacy, mental distress and pain elicited during a squat test; all measured through validated self-administered scales.
- To analyse if PCST efficacy on PFPS depends on education level and participants' expectations of intervention efficacy.

Materials and methods

Study design

The study will be randomised, parallel-group, single blind, sham-controlled clinical trial. It will be conducted in a single centre in the city of Girona. The length of the clinical trial phase will be approximately one year.

Population

Inclusion criteria

- Patients diagnosed with PFPS, defined as: diffuse peripatellar and/or retropatellar pain in 1 or both knees, aggravated by squatting, kneeling, or prolonged sitting; having ruled out all other possible causes. (42)
- Symptoms lasting for ≥ 3 months
- Overall average knee pain in the past week ≥ 30 on a 100 mm Visual Analogue Scale (VAS)
- Age ≥ 18 years old
- Living in the region of Gironès, Spain.

Exclusion criteria:

- History of other knee pathology: knee ligament injury, patellar tendonitis, osteoarthritis, patellar tendinopathy, Osgood-Schlatter's disease, recurrent patellar dislocation, etc.
- Previous knee trauma, arthroscopy or surgery in the last 12 months.
- Serious psychiatric comorbidity such as schizophrenia or clinical depression
- Past participation in a PCST program
- Medical condition that doesn't allow for exercising such as uncontrolled hypertension or other heart condition
- Systemic rheumatoid conditions such as rheumatoid arthritis or fibromyalgia
- Neurological conditions such as Parkinson's disease, multiple sclerosis or stroke.
- Age > 50 years

- Unable to follow the protocol and attend the therapy and 10-week follow up sessions at CAP Güell, in Girona.
- Inadequate written and spoken comprehension of neither Spanish nor Catalan.
- Currently taking neuroleptic, opioid or analgesic medication, aside from paracetamol, NSAIDs, or cyclooxygenase 2 inhibitors; which will be allowed.

Sampling

Sample size

We estimated the sample size using the free online software GRANMO, and the setting for two independent means.
We've assumed an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. Estimated loss at follow up was 0.2, based on previous similar studies using CBT intervention and a 12 month follow up period. (45,52)
We found no previous RCTs using PCST for PFPS, so we based our calculation on studies that used an equivalent psychological intervention to PCST (most studies used cognitive behavioural-based therapies) and outcome variable to the VAS (arthritis pain scales, numerical rating scale). A few of these studies were on PFPS, but most were based on other musculoskeletal chronic pain conditions, mainly chronic low back pain and knee osteoarthritis. (26,45,53,54) Since we hypothesize that all these conditions share common centralised pathogenesis and we don't dispose of more trials on PFPS, we assumed the error that may ensue from this approximation.

Based on the literature review, we assumed a standard deviation for our outcome variable (VAS in mm) of 30 and a minimum expected difference of 15.
For these numbers, GRANMO recommended 80 subjects for each of the intervention groups, for a total of 160 study participants.

Sample selection and enrollment

The study will be done in the city of Girona, but sampling will be open to all habitants of the region of Gironès.

Sampling will be consecutive, as patients diagnosed with chronic PFPS in the different public health centres of Gironès are invited to participate.

One month prior to the beginning of sampling, we will send a document explaining the aim and procedure of this study, as well as population characteristics, to orthopaedics services at Hospital Josep Trueta, Hospital Santa Caterina, primary health centres in region of Gironès and private practice doctors of clinics in Girona. The aim of this will be to reach as many health professionals as possible so they can offer their patients the option of participating in our study.

We will also put up advertisements in the form of posters and pamphlets at physiotherapy clinics in the city of Girona and the university of Girona campus. Any interested participants will have to access a website and complete an online survey with their names, address and phone number.

All interested participants will be then contacted by telephone by one of our researchers (not involved in the outcome assessment) and informed of the general aspects of the study. If patients agree and meet general inclusion criteria over the phone, they will be scheduled for the first meeting.

At the first meeting participants will receive all information concerning the study from a researcher not involved in outcome assessment, as well as an information sheet (see annex 1). They will be allowed the necessary time to read the consent form and pose any question to assure understanding, and if they agree to participate, they will be required to sign the informed consent form (see annex 2).

Estimated time of recruitment

According to 2018 population data from the region of Gironès, obtained from the institute of statistics of Catalonia (Idescat), the population between the ages of 18 and 50 was of 89.577 (55).

We weren't able to find data on the prevalence for patellofemoral pain in Girona or Spain; most observational studies have been done in the US or the UK, mostly using young athletic population or military recruits. Prevalence amongst the general population is estimated around 12 to 25 % (56,57), for the purpose of this study, we will

assume a local prevalence of 15 %. With this estimates, there's about 13.000 people with PFPS in region of Gironès.

Ideally, we would require data of rate of PFPS diagnoses in Girona in order to properly estimate time of recruitment, but because this syndrome is often underdiagnosed or if it is, it doesn't appear on open data, we couldn't find any realistic local data on rate of PFPS diagnosis.

Since we will be recruiting patients from several health centres, as well as through publicity, we expect to recruit about 10 cases of PFPS a week, of which 50 % at least will not be eligible or will refuse to enter the study, so we think around 5 patients per week is a more realistic estimate. At this rate, it would take 32 weeks, or about 8 months to recruit all 160 participants.

Randomisation and masking

Participants will be randomised into one of two intervention groups: a) exercise + PCST or b) exercise + NDC in a 1:1 ratio. The randomised allocation will be prepared by the study biostatistician and then revealed by a researcher not involved in outcome assessment or interventions once the participant has signed the consent form. Along with group allocation, each participant will be randomly assigned to one of the study's psychologists, physiotherapists and outcome assessors.

To preserve anonymity and blinding during data collection, every participant will be assigned a personal identification (ID) code at the moment of randomisation by the same statistic.

The researchers in charge of initial participant evaluation, inclusion and allocation, as well as the physiotherapists and psychologists will be by necessity unblinded, but researchers in charge of outcome assessment will be blinded to group allocation.

Participants will also be blinded and told that we are investigating two similar treatment programs, with the same exercise component but a different psychological component. They will be requested not to share details about their treatment with the outcome assessors.

The statistician will be blind to group allocation until completion of the statistical analyses.

Study interventions

Main intervention

PCST intervention. The PCST program used is largely based on a previous 2012 RCT by Bennell et al. using PCST for knee osteoarthritis (45), and is explained in detail in annex 3.

PCST uses behavioural and cognitive techniques aimed at increasing self-efficacy and decreasing pain catastrophising through educating patients on pain neurobiology, and the use of techniques such as progressive muscle relaxation, activity-rest cycling, pleasant activity scheduling, problem solving, identifying negative thoughts, counting backwards, etc.

PCST will be delivered by the two specially trained psychologists. Sessions will take place at Güell centre; they will last 1 h and be scheduled weekly, at a day to convene with the participant. Aside from weekly sessions, participants will be asked to perform a prescribed home PCST practice daily and encouraged to apply the pain coping skills when doing the exercise program.

After the last session on week 10, participants will be encouraged to keep up the practice on their own moving forwards.

During the 6 month follow up, participants will be contacted once a month by telephone or email by the psychologist to discuss their adherence to the pain-coping program and provide motivation and guidance if necessary.

Control intervention: non-directive counselling (NDC). The general idea behind NDC is to provide a control for the attention provided in the PCST group. During the sessions, therapists are told to show a general interest in the participant and encourage them to share their pain experience, but not provide any pain managing strategies or advice. Participants in this group will not do any tasks at home other than the exercise program and will not be given any encouragement to keep up practice past the last session.

Sessions will be scheduled equally and last the same as in the PCST intervention group, but they will be delivered by a psychologist trained only in NDC, and not in PCST, to avoid cross-contamination of the interventions.

In this group, during the 6 month follow up, there will be no additional contact from the psychologist.

Concomitant interventions

Both intervention groups will also be provided with the same exercise program based on the recommend rehabilitation exercises by the Alberta health group for anterior knee pain (58), which is explained in detail in annex 4. It consists of six body-weight, open and close chained exercises aimed at strengthening the quadriceps, hamstrings and hip abductor muscles, plus stretches.

The exercises will be taught and monitored by one of the 4 trained physiotherapists. Physiotherapy sessions will last 30 minutes and be scheduled following the psychological intervention, allowing for a 15-minute break in between. At the first physiotherapy session participants will learn correct form for the exercises, and then on the subsequent sessions corrections or progressions will be recommended based on each participant's abilities.

Participants will be asked to perform the program at home, four times a week, aiming for 3 sets of 10 repetitions for each exercise, which shouldn't take longer than 30 to 45 minutes a day. A descriptive pamphlet with pictures of every exercise will be provided (see annex 4).

After the last session at week 10, all participants will be equally encouraged to keep up an exercise routine, but there will be no additional contact from the physiotherapists.

Intervention quality evaluation

Both the psychological and physiotherapy sessions will be monitored and evaluated through audio tapings by the main researchers, and they will give feedback to psychologists and physiotherapists if needed, in order to assure that treatment is the same between participants and throughout the study duration.

Variables

Main outcome variable

Main outcome variable will be knee pain experienced during the past week, measured using the 100 mm visual analogue scale (VAS), where 0 mm equals no pain and 100 mm equals worst pain possible (see annex 5). The scale will require participants to rate their average pain over the last week, as well as the minimal and maximal pain experienced. The three measurements will be introduced into the data base, and the mean will be calculated automatically.

Pain assessment will be done at the baseline assessment (visit 1) and then every week for the 10-week intervention, always at arrival at the Güell centre, before the psychotherapy session, to evaluate the week prior. The scale will be presented to the participant by a researcher only involved in outcome assessment, and therefore blinded to group allocation. The researcher will then measure the distance marked by the participant using a ruler (in mm) and introduce it into the data base.

One final assessment will be done at the 6 months follow up visit.

Secondary outcome variables:

Assessment of these secondary variables will be done on week 1, week 10 and 6 month follow up, except for overall improvement, which will only be assessed at week 10 and 6 month follow up.

Just like the main outcome scale, these scales will always be administered to the participants at arrival, before the intervention, to assess the week prior. Scales will be presented to the participant one at a time, with no order in particular, by a researcher only involved in outcome assessment and blinded to group allocation. This researcher will also be in charge of introducing the ratings into the database.

- Disability scales: *Kujala Anterior Knee Pain Scale* (AKPS) (Annex). It's a self-administered 13 item questionnaire, on PFPS symptom severity and functional repercussion, with a total rating from 0 (worst possible health) to 100 (no symptoms and no restrictions). The Spanish version has been validated for

diagnosing PFPS (59). Previous studies have found minimal clinical difference to appear with a change of at least 10 points (60).

- Functional or self-perceived health status: *SF-36*. Self-administered questionnaire with 36-items that measures health related quality of life on 8 different aspects: physical health and limitations, pain, emotional and psychological health, social functioning and limitations due to health problems. Final score is 0-100, where 100 is the best health possible. The Spanish version has been validated. (61)
- Mental distress: *Beck depression inventory* (BDI). It's a self-administered, 21 item questionnaire, widely used to evaluate depressive symptoms.(62)
- Kinesiophobia: *Tampa scale for kinesiophobia* (TSK). It's widely used self-administered, 17 item questionnaire to evaluate fear of movement and re-injury. (63)
- Catastrophising: *Pain catastrophising scale* (PCS). It's a short, 13 item, self-administered questionnaire with a 0-52 rating (see annex6). It assesses different aspects of pain catastrophising such as rumination, magnification and helplessness. (64)
- Overall improvement with the intervention: *patients' global impression of change* (PGIC). Participants are asked to rate the overall change in their pain and in physical function after the intervention compared to baseline from 1 (much worse) to 7 (much better). The PGIC has been shown to be a clinically relevant for interpreting truly meaningful improvements from the individual perspective. (65) This scale will only be evaluated at the 10 week and at the 6 month follow up.
- Pain elicited during the squat test, measured with the VAS. This test will only be done at baseline (visit 1), week 10 (visit 11) and six month follow up. An outcome researcher will be in charge of explaining correct form to the participant (feet slightly wider than hip-width apart, toes pointing about 10 º out, knees tracking in the same direction as the second toe, spine straight, sit back by putting body weight through the heels). Participants will be allowed to practice the move 2 times, then the third time they will be asked to evaluate the pain felt at the knee/s through the use of a VAS that the researcher will provide.

Covariates

Baseline data will be collected during the first visit, at week -1, after having signed the informed consent form, through the interview and physical exam the baseline researcher will perform.

- Age: mean ± SD years old
- Gender: male/female
- Height: mean ± SD cm
- Weight: mean ± SD kg
- Body mass index (BMI): mean ± SD kg/m^2
- Duration of symptoms: mean ± SD months
- Affected limb: right/left/both
- Average time a week spent exercising (any kind):
    - Less than 2 hours
    - Between 2-4 hours
    - Between 4-6 hours
    - Between 6-8 hours
    - More than 8 hours
- Education achievements:
    - Less than basic secondary studies (ESO)
    - Basic secondary studies (ESO)
    - Superior secondary studies (Bachillerato)
    - Postgraduate studies
- Expectations on the effectiveness of treatment self-rated as:
    - Not at all effective
    - Somewhat effective
    - Very effective
- Previous knee surgery: yes/no
- Concomitant pharmacological treatment:
    - None
    - Paracetamol
    - NSAIDs (oral or topical)

    - Cyclooxygenase 2 inhibitors
- Employment status:
    - Currently employed
    - Unable to work due to health reasons
    - Retired (not due to health reasons)
    - Not employed
- Living situation:
    - Married/living in couple
    - Living with other family members/roommates
    - Living alone

Data collection

All baseline and outcome data will be introduced into the online database by the baseline or outcome researchers respectively using participant's ID code to ensure anonymity. Data will also be physically stored at research headquarters, in Hospital Josep Trueta, and kept under lock.

A data quality control service will be hired to ensure correct data collection and registration.

Data collection has been summarised in table 2.

Period 1: Inclusion and baseline measures

Phone interview (week -2). A baseline researcher will be in charge of contacting potential participants by telephone in order to evaluate if they fulfil general study criteria (age, symptoms, availability, etc.) and arrange a day for the first visit at Hospital Josep Trueta.

Visit 1 (Week -1). Visit 1 will take place at Hospital Josep Trueta, in a general consultation room, with a baseline researcher not involved in outcome assessment.

After signing of the informed consent form, participants will undergo a medical anamnesis and physical exam to evaluate fulfilment of inclusion and exclusion criteria. If they meet the criteria they will be included in the study and the researcher will then proceed to collecting the rest of the baseline data, corresponding to the covariates.

All participants who have not had a knee X-ray in the past year will undergo a semi flexed poster anterior X-ray of their painful knee at the same Hospital on that same day if possible. X-ray interpretation will be done by two trained researchers.

Period 2: intervention period

Visit 2 (Week 1). Participants will arrive at Güell centre, where a baseline researcher not involved in outcome assessment will be in charge of assigning the randomised allocation previously prepared by the biostatistician to each participant, along with their ID number. Together with the participant they will discuss visit schedule for the coming weeks.

Once allocation has been done, participants will go on to a separate room, where a researcher only involved in outcome assessment (and therefore blinded to allocation) will evaluate the primary outcome (VAS), and then the secondary outcomes (all except PGIC), always in that order. Estimated time for outcome assessment will be 1 h, considering each scale takes about 10 minutes to complete.

Visits 3-10 (week 2-9). For the following 9 weeks of intervention, participants will only be required to evaluate the main outcome variable (VAS), always upon arrival, prior to the intervention, and by an outcome researcher blinded to group allocation.

Visit 11 (week 10). The same procedure as week 1, but this time, all secondary outcomes will be evaluated (PGIC included).

Period 3: follow up

Visit 12 (11 weeks + 6 months). No data collection will take place during the follow up period until the final visit, which will be scheduled 6 months after the last intervention (visit 11).

The exact same procedure as week 11 will be followed, with assessment of primary outcome and all secondary outcomes.

Participants not attending the follow up appointment (or any of the other visits for that matter) will be contacted by telephone. If they missed the appointment, it will be rescheduled as soon as possible, if, on the contrary they want to withdraw from the

study and there's a relevant motive (efficacy, security, availability, etc.), it will be noted.

Data collection chart

*Table 1 Data collection chart and visit schedule. VAS: visual analogue scale. PCST: pain coping strategies training. * only those with no knee X-ray from the previous year*

	Baseline measures			**Intervention**										**Follow up**
Week	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**6 months**
Appointment		**1**	Randomisation	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Phone interview	x													
Information sheet and informed consent		x												
Inclusion and exclusion criteria		x												
Covariate data		x												
Knee X-ray*		x												
Group allocation				x										
PCST Intervention				x	x	x	x	x	x	x	x	x	x	
Control or "sham" intervention"				x	x	x	x	x	x	x	x	x	x	
Concomitant interventions				x	x	x	x	x	x	x	x	x	x	
Primary outcome assessment (VAS)				x	x	x	x	x	x	x	x	x	x	x
Secondary outcome assessment:														
Anterior knee pain score (AKPS)				x									x	x
Self-efficacy questionnaire (SF-36)				x									x	x
Beck depression inventory (BDI)				x									x	x
Tampa scale for kinesiophobia (TSK)				x									x	x
Pain catastrophising scale (PCS)				x									x	x
Patient's global impression of change (PGIC)													x	x
Pain during squat test (VAS)				x									x	x

Statystical analysis

Data will be analysed by a hired statistic using Statistical Package for Social Sciences v.18 (SPSS Inc.).

Statystical plan

In accordance with the main objective, we will compare mean pain score measured with the VAS at week 10 between the two study groups to stablish if there is significant difference between the PCST group and the sham-intervention group.
Secondarily, a comparison test will be performed for each of the secondary variables between the two groups.
Finally, because it was also an objective of the study, we will perform the same comparative analysis for all variables, but this time stratifying for two covariates: participant expectation for treatment efficacy and education achievements.

Descriptive analysis

First, we will perform a descriptive analysis of the sample, using the information for the covariates.
Variables will be first tested for normal distribution using the Kolmogorov-Smirnov test, which we assume they all are.
Categorical variables like gender, education level, employment status, living situation, concomitant treatment, number of affected limbs, previous knee surgery and treatment expectations will be expressed in percentages.
Numerical variables like age, height, weight, body mass index and duration of symptoms will be expressed by mean and standard deviation (SD) if the variable follows a normal distribution or by a median and interquartile range (IQR) if the variable doesn't follow a normal distribution.

Comparative analysis

We will perform an intention-to-treat analysis and the missing data will be replaced using the last observation carried forward.
The input variable in the comparative analysis will be the intervention or placebo group (nominal variable).
The primary outcome measure will be pain (VAS), expressed as a mean ± SD, therefore it's a quantitative variable.

Secondary outcome variables were self-efficacy for pain control (SF-36), self-reported physical function (AKPS), overall improvement with the intervention (PGIC), mental distress (BDI), kinesiophobia (TSK), catastrophising (PCS), and pain elicited during the squat test (VAS); all quantitative variables because they will be expressed as a mean ± SD.

We will test each quantitative variable for normality using the Kolmogorov-Smirnov test. If they are, normal, as we've assumed, we will perform a t-student test for two independent populations, as is the case in this study, with each of the outcome variables.

Multivariate analysis

We assume that with randomisation all covariates and other possible confusion variables will be equally distributed between the two groups, so we initially don't plan to perform a multivariate analysis.

Nonetheless, due to the relatively small sample size, this may not be the case. If any variable is found to be distributed differently during the descriptive analysis, that variable will be a subgroup in the final analysis.

Work plan and chronogram

Personal of the research team

Main research team

The main research team will consist of 6 researchers, made up of traumatologists, general doctors and psychologists.

- All six researchers will be equally in charge of protocol elaboration, intervention design, and general management of the study.
- Two of the main researchers will only be involved in baseline data collection and participant allocation, they will be therefore unblinded.
- Two of the main researchers will be blinded to group allocation and only be involved in outcome assessment. They will receive 1-day training on correct

procedure for scale administration and data registration to ensure maximum internal validity of results.

Additionally, the team will also include 4 experienced physiotherapists and 4 clinical psychologists who will deliver the exercise and psychological interventions respectively but will not be involved in outcome assessment.

- The physiotherapists will receive a 4 h training workshop to deliver the exercise program by one of the main research team members, along with a manual.
- Two of the psychologists will attend a 4-day workshop by a main research team member specialised in PCST. Sessions will cover general theory, detailed PCST procedure and role-playing. The psychologists will be recorded performing a PCST session with an actor and will be accepted into the study if they meet specified criteria for content and quality.
- The other 2 psychologists will attend a 1-day workshop with a main research team member specialised in NDC where they will be taught the principles of non-directive counselling as well as role-play.

Study stages

Stage 0: Preparation

1. **Protocol elaboration**: includes the literature review, and all practical considerations (available population, putting together the research team, choosing a location for intervention development, etc).
   This stage will be carried out by the six main researchers.
   We estimated a period of 3 months.
2. **Ethics committee's (EC) authorisation**: The protocol will be presented to the research ethics committee (CEIC) at Hospital Josep Trueta. We estimate 1 month to receive EC authorisation and 1 month to make any necessary modifications in the protocol.
3. **Management department authorisation** from hospital Josep Trueta and Güell centre. We estimated one month for approval from both centres.
4. **Authorisation from local government** (Generalitat de Catalunya). In accordance to the Spanish legislation (Law 14/2007) this is an invasive

procedure (of psychological nature) and therefore requires authorisation from the autonomous community. We estimated two months to receive approval.

5. **Organisation meeting:** all research team members, (6 main researchers, plus the intervention personnel) will be required to attend a one - day meeting to coordinate all further stages. Thorough information will be provided to ensure the comprehension and equal application of the protocol.
6. **Training of researchers:** researchers involved in intervention will receive specific instructions, as well as researchers involved in data collection, to ensure maximal and equal adherence to protocol stipulations. We estimated a period of 1 month. This will be done by specific members of the main research team.

Stage 1: Data collection

1. **Promotion of the study** to health centres, physiotherapy clinics and universities in the city of Girona and region of Gironès. This will be done one month prior to beginning of participant recruitment, by members of the main research team.
2. **Participant recruitment and randomisation**. Recruitment period has been estimated to last for 8 months.
3. **Intervention, data collection and registration in the database**. It will start once the first participant is recruited and it will end 6 months after the last participant is recruited. In total, we estimated the intervention period to last for about a year.
4. **Data monitoring and quality control**. It will be performed by an external service throughout the data collection process, as well as during final analysis, to ensure all data is correctly collected and registered in the database.

Stage 2: Data analysis and interpretation

1. **Statistical analysis**. It will begin when data from all participants enrolled has been collected and will be performed by an external biostatistician. We estimated 2 months.
2. **Interpretation and elaboration of final report**. It will be done by the main researchers. We estimated 4 months in total.

Stage 3. Divulgation

1. **Publication of the results**: Final report will be presented to several sports medicine and traumatology journals. We've estimated time for publication to be around 3 months.
2. **Dissemination of the results** at national and international congresses. Considering the early inscription that many congresses require, we've estimated a longer period of time of 5 months, but depending on specific dates for that year this schedule could change.

Chronogram

Table 2 Chronogram

	2020								2021					2022							
Month	1	2	3	4	5	6	7	8-12	1- 3	4-9	10	11	12	1	2	3	4	5	6	7	8
Stage 0: preparation																					
Protocol elaboration																					
Ethical committee and government authorisation																					
Centre's authorisation																					
Organisation meeting																					
Training of researchers																					
Stage 1: data collection																					
Study promotion																					
Patient recruitment																					
Intervention, data collection and registration																					
Data monitoring and quality control																					
Stage 2: data analysis and interpretation																					
Statistical analysis																					
Interpretation and final report																					
Stage 3: divulgation																					
Report publication																					
Dissemination in congress																					

Ethical considerations

The study will be performed under the basic ethical principles established by the Helsinki Declaration and the European agreement on Human Rights and Biomedicine with regards to autonomy, risk-benefit ratio and protection of vulnerable individuals.

Since this study consists of a psychological intervention, it falls under regulation of the Spanish legislation for biomedical research ("Law 14/2007, July 3rd, on biomedical research"), as a low risk invasive procedure.

This study will also adhere to the basic bioethical principles stablished in the Belmont report:

- No maleficence: to the researcher's knowledge neither PCST nor sham-intervention NDC have any potential risks for participants. Physiotherapy has the minor risks corresponding to any physical activity, but they are minimal, and it is currently considered the standard, most effective treatment for PFPS.
- Beneficence: All participants will be receiving the standard treatment for PFPS, which is physiotherapy, but for a longer period than is usually mandated in clinical practice. This on itself offers a benefit for participants, and additionally, they will receive a psychological intervention that the researchers have reason to believe will be effective in improving their pain and overall health.
- Autonomy: participants will be informed in detail with regards to study procedures, how their data will be handled, their right to be informed at all moment of any relevant developments and withdraw from the study if desired. This will be done by a researcher who will be available to answer their questions, as well as through an information sheet (see annex 1). To express their accordance and understanding and enrol in the study, participants will be required to sign the informed consent form (see annex 2). Participant autonomy is regulated through the Spanish legislation: "Law 41/2002, of 14 November, regulating patient autonomy and rights and obligations of information and clinical documentation".
- Justice: to ensure a just selection of the sample, we've created very inclusive and exclusion criteria, while taking into consideration that the sample should be a representation of the population that would most benefit from this intervention. Posteriorly to sampling, anonymity and randomising will ensure equal chances for all participants to receive the active intervention.

The protocol for the study will be presented to the clinical research ethics committee of Hospital Josep Trueta as the coordinating study centre. The EC will ensure that the protocol fits de ethical requirements and any modifications proposed will be implemented into a modified protocol.

All personal data and personal information collected during the study will be confidential and used only for the purpose of research and education; therefore, all data will be analysed anonymously, in accordance to the present legislation:

- EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- Spanish data protection legislation: "Organic Law 3/2018, of December 5, on Data Protection and Guarantee of Digital Rights and the royal decree 1720/2007"

All members of the investigation team will have to declare no conflict of interest. They will also have to agree to publish all data and results with clarity and transparency including unfavourable data or events.

Study limitations

There are several limitations to the present protocol that must be taken into consideration for future analysis and extrapolation of results.
First, the impossibility of a double-blind design, since the organising researchers as well as the psychologists will know what intervention every participant is allocated to. In order to reduce detection bias, researchers that administer the outcome scales and perform any outcome assessments will be blinded to the participants' intervention and follow strict rules on assessment procedure. Additionally, in order to reduce performance bias, intervention researchers will only be trained for the intervention they

deliver; they will follow a specific procedure during sessions and will be evaluated through audio recordings to ensure all participants receive equal treatment.

The second bias is in relation with the recruitment of the sample. Consecutive sampling will be used, which is non-probabilistic; therefore, there is a risk of not obtaining the most representative population. To minimise the selection bias and ensure this study has good external validity, inclusion criteria stablished are extensive, and exclusion criteria aim to reduce any possible confusing factors. Still, we are aware the study population will not be the same as the general population, but we consider it to be closer to the real target population that may benefit from such a treatment.

Additionally, by using advertisements to recruit participants we will be indirectly selecting a population who is more implicated in their pathology or more open to new treatments, which is an important factor for PFPS. We will try to minimise this voluntary bias by having medical practitioners offer this study to all their patients with PFPS and also by evaluating participants' motivation as a covariate and creating subgroups for analysis based upon it.

The third limitation of this study is the component of at home exercise and psychological practice, not only because we realise that not all participants will follow our guidelines the same, but also because it is difficult to accurately measure their performance objectively. To address this problem, during sessions, psychologists will ask participants to rate their adherence to the home exercise program as: every day/most days/some days/no days. If adherence is low, this will be addressed in the session and the therapist will help to find solutions and offer advice. Of course if by the end of the study, we find participants report for program adherence is low, internal validity of the study will be low, and we should evaluate the possibility of further research to improve this aspect of treatment.

The fourth limitation is the use of self-administered outcome scales. On the one hand this avoids detection bias by the outcome researcher, but it also introduces the subjectivity and interpretation every participant has of the scales. We are aware of this

limitation, and in order to reduce it, the outcome will explain the scales to participants to ensure full and equal comprehension. It will also be taken into consideration when interpreting results.

The final limitation is participant loss, which we estimated to be of 20 %. We will try to minimise participant loss by informing participants at the beginning of the follow up period, which will be mainly 10 weeks of intervention, plus a 6 month follow up. Participants who initially predict they will not be available will be excluded from the study. We will perform an intention to treat analysis of results, with the last observation carried forward to account for any loss of follow up.

Budget

For the realisation of this study we will need an estimated investment of 39.750 €.

Of the 6 scales used in outcome assessment, the SF-36, Beck-depression inventory and the pain catastrophising scale are protected by copyright laws. We've estimated a cost of 150 € for the rights of each of the scales, therefore 450 € total.

We estimate that the majority of participants will live within close proximity of the city of Girona, or have easy access, since they will be well informed at the beginning of time and transportation commitment. Still, we consider that 20 % of participants may have to be compensated for transportation to and from Girona if costs suppose a considerable economic expense. We've estimated this cost to be of about 100 euros per participant for the whole of the study; for around 35 people, this comes up to 3.500 €. Assignation of this compensation will be done depending on the participants' address and justification of transportation (participants who already come to Girona for work or other commitments besides the study will not be considered eligible).

We will need to hire a data monitoring service to ensure correct data collection, give assessment and coordinate the medical staff. We've estimated 500 h of work given the length of the study, and a salary of 30 €/h, which sums up 15.000 €.

We will hire a biostatistician to perform initial randomisation and statistical analysis of results. We've initially estimated 150 hours of work, with a salary of 40 euros/hour, which would cost around 6000 €.

For the publication in national and international journals we have assigned 4000 €, and for dissemination at two congresses, one at national level and the other at international level for two of the researchers with the travel and the food also computed, a total of 5000€.

Because this study uses an intervention very similar to current medical practice, it is not considered an invasive procedure, and therefore there is no need to hire additional insurance for participants aside from the general health coverage. Nonetheless, this decision is to be determined by the EC, and if they decide otherwise, current budget will have to be accordingly adjusted.

Other costs that have not been taken into consideration because they are already covered by the national health system are the salaries of all the researchers involved, the accommodations used at both the Hospital Dr Josep Trueta and Güell primary health centre (exercise material, consultation rooms, computers, printers, etc.) and the X-rays that will be done at hospital Josep Trueta as part of the usual diagnosis procedure for knee pain.

Table 3 Budget

	Price	Quantity	Total
Staff and services			
External statistic	40 €/h	150 h	6.000 €
Data monitoring services	30 €/h	500 h	20.000 €
Material and follow up			
Participant transport compensation	100/participant	35	3.500 €
Scale copyright	150 €/scale	3	450 €
Publication and dissemination			
Publication expenses	4.000 €	1	4.000 €
Inscription to national congress	300 €	1	300 €
Inscription to international congress	500 €	1	500 €
Travel accommodation and food	2.500 €	2	5.000 €
		Add up	39.750 €

Feasability

We have considered this study feasible from different perspectives.

First of all, the main research team as well as the collaborators that will conduct the interventions will be sufficiently qualified for their role in this study. Their salary, as professionals working for the public health system will already be covered.

The trial will mainly take place at the Güell primary health centre, which disposes of consultation rooms and rehabilitation rooms where the different interventions and outcome evaluations will take place. The first meeting is the only one that will be done at Hospital Josep Trueta because some of the participants will require a knee X-ray to be performed and the hospital disposes of the necessary equipment.

The recruitment and intervention period is estimated to last for a year, which we deem feasible considering the high prevalence for PFPS in general population.

Annexes

Annex 1: Information sheet

(Available in Spanish and Catalan)

HOJA DE INFORMACIÓN AL PARTICIPANTE

TÍTULO DEL ESTUDIO: Pain-coping approach for chronic patellofemoral pain syndrome (o Abordaje de manejo del dolor en el síndrome patellofemoral crónico)

PROMOTOR:

Investigador principal: Vicente Basanta, Elena

Centro: Servicio de Traumatología. Hospital universitario Dr. Josep Trueta. Girona. España

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar.

El estudio ha sido aprobado por el Comité de Ética de del Hospital universitario Dr. Josep Trueta, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y la ley de investigación biomédica 14/2007 del 3 de julio, por las que se regulan los ensayos clínicos con intervenciones médicas.

Antes de decidir si desea participar en este estudio, es importante que entienda por qué es necesaria esta investigación, lo que va a implicar su participación, cómo se va a utilizar su información y sus posibles beneficios, riesgos y molestias. Por favor, tómese el tiempo necesario para leer atentamente la información proporcionada a continuación y consulte con los investigadores cualquier duda que le surja al respecto.

Participación voluntaria

Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria.

Objetivo del estudio

Este estudio consiste en evaluar la eficacia de una técnica específica de terapia psicológica para la mejoría de los síntomas del dolor de larga evolución del síndrome patelofemoral o dolor anterior de la rodilla.

Descripción del estudio

En este estudio participan personas de entre 18 y 50 años, sin otra patología de rodilla a parte de un dolor anterior diagnosticado de síndrome patelofemoral y de más de 3 meses de evolución.

Se prevé un total de 160 participantes en el estudio, que serán divididos en dos grupos, un grupo recibirá la terapia de estudio mientras que el otro recibirá una terapia psicológica destinada a actuar como "placebo", es decir, sin las técnicas psicológicas en estudio, y por tanto de la que no se espera eficacia. Usted como participante no sabrá a que intervención ha sido asignado, y tampoco lo sabrá el investigador que recoja resultados, sin embargo, habrá investigadores, que sí lo sabrán, como por ejemplo el responsable de impartir la terapia.

Actividades del estudio

La intervención dura un total de 10 semanas, con una sesión de terapia a la semana, de aproximadamente 2 h de duración. A continuación, se dejará un periodo de 6 meses sin visitas, tras el cual se le volverá a citar para una última evaluación.

Ambas intervenciones psicológicas se realizarán además de la fisioterapia pautada habitualmente para este tipo de dolor, de forma que todos los participantes seguirán un tratamiento de terapia física rehabilitadora y otro de terapia psicológica.

Tanto las terapias psicológicas como la fisioterapia serán impartidas por profesionales con experiencia.

Además de las sesiones semanales, se requerirá de usted que realice algunos ejercicios a domicilio, los detalles le serán explicados en la sesión semanal, pero no debería llevarle más de 30 minutos-1 h al día.

Como parte del estudio se le realizará una entrevista médica habitual sobre su patología, así como una exploración física traumatológica al inicio. En el caso de que no pueda presentar una radiografía de la rodilla afectada de menos de un año de antigüedad, se le realizará una en el mismo momento de su inclusión en el estudio, en el hospital Josep Trueta.

El seguimiento de sus síntomas a lo largo de la intervención se evaluará a través de escalas que usted mismo completará durante las visitas.

Table 4 Participants' chronogram

	Evaluación inicial		**Intervención**										**Seguimiento**	**Post-intervención**
	Agosto 2020-Agosto 2021													**Agosto 2021-Marzo 2022**
Semana	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**6 meses**	
Visita		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Entrevista telefónica	x													
Primera entrevista, recogida de datos e inclusión		x												
Radiografía de rodilla		x												
Asignación de grupo			x											
Intervención psicológica # 1			x	x	x	x	x	x	x	x	x	x		
Intervención psicológica # 2 (placebo)			x	x	x	x	x	x	x	x	x	x		

Intervención de fisioterapia general			x	x	x	x	x	x	x	x	x		
Evaluación inicial de escalas			x										
Evaluación final de escalas # 1											x		
Evaluación final de escalas # 2												x	
Interpretación de resultados y publicación													x

Riesgos y molestias derivados de su participación en el estudio

En los estudios realizados hasta el momento, se ha observado que la terapia psicológica de manejo del dolor en otras patologías similares al síndrome patelofemoral, como es el dolor lumbar crónico o la artritis de rodilla puede aportar ciertos beneficios respecto al tratamiento farmacológico o rehabilitador usado habitualmente.

En el síndrome patelofemoral este tipo de terapias no han sido ampliamente estudiadas, aunque sí se han realizado unos pocos estudios piloto en los últimos años que mostraban resultados alentadores.

No se espera ningún tipo de efecto adverso derivado de la intervención psicológica.

Las responsabilidades a las que deberá atender como participante son las siguientes:

- Asistir a las visitas semanales donde se realizará la sesión de psicoterapia (1 h aproximadamente) y seguidamente la fisioterapia (30 min aproximadamente)
- Realizar los ejercicios pautados en la visita semanal durante el resto de la semana
- Completar las escalas de evaluación de los síntomas
- Notificar de cambios en su situación clínica, modificaciones de su medicación o cualquier otra sustancia o terapia “medicinal” que reciba

Posibles beneficios

Los beneficios de participar son recibir una terapia física más intensiva que en un contexto clínico habitual, junto con un abordaje psicológico personalizado.

También es posible que usted no obtenga ningún beneficio a raíz de su participación en el presente estudio.

Advertencia relativa al embarazo

No se conoce ningún riesgo de la psicoterapia o fisioterapia pautada en este estudio de cara al embarazo.

En caso de producirse un embarazo durante su participación en el estudio debe informar a su médico de inmediato para recibir la asistencia médica adecuada.

Tratamientos alternativos

El tratamiento actual del síndrome patelofemoral consiste en la fisioterapia, uso de rodilleras o bandas adhesivas, y en casos muy reservados, cirugía.
Si desea más información, consulte al médico investigador.

Protección de datos personales

El promotor de este estudio se compromete al cumplimiento de la Ley Orgánica 3/2018, de 5 de diciembre, de protección de datos personales y garantía de los derechos digitales (BOE núm. 294, de 6 de diciembre de 2018) y al Real Decreto que la desarrolla (RD 1720/2007).
Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no incluya información que pueda identificarle, y sólo los investigadores del estudio podrán relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a nadie salvo en caso de urgencia médica o requerimiento legal.
El acceso a su información personal quedará restringido a los investigadores del estudio, las autoridades sanitarias, al Comité de Ética de la Investigación y personal autorizado por el promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.
De acuerdo con la legislación de protección de datos, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio.
Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido.
Los datos codificados pueden ser transmitidos a terceros y a otros países, pero en ningún caso contendrán información que le pueda identificar directamente, como nombre y apellidos, iniciales, dirección, nº de la seguridad social, etc.

Gastos y compensación económica

El promotor del estudio es el responsable de gestionar la financiación de este y ha firmado un contrato con el centro donde se va a realizar.
Usted no tendrá que pagar por las terapias ni por pruebas específicas del estudio. Su participación en el estudio no le supondrá ningún gasto adicional y le serán reintegrados los gastos extraordinarios (como traslados) que la participación en el mismo le generen.

Otra información relevante

Cualquier nueva información referente a la terapia utilizada en el estudio y que pueda afectar a su disposición para participar en el estudio, que se descubra durante su participación, le será comunicada por su médico lo antes posible.
Debe saber que puede ser excluido del estudio si el promotor o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se

produzca por la medicación en estudio o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio. Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

Debe usted saber que es posible que su médico de Atención Primaria tenga conocimiento de su participación en este estudio.

¿Qué tratamiento recibiré cuando finalice el ensayo clínico?

Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico considere el más adecuado para su enfermedad, pero es posible que no se le pueda seguir administrando la psicoterapia del estudio.

Contacto en caso de dudas

Si durante su participación tiene alguna duda o necesita obtener más información, póngase en contacto con el investigador responsable de informarle.

Annex 2: Consent form

(Available in Spanish and Catalan)

CONSENTIMIENTO DEL PARTICIPANTE

Título del estudio: Pain-coping approach for chronic patellofemoral pain syndrome (o Abordaje de manejo del dolor en el síndrome patellofemoral crónico)

Yo (Nombre y apellidos), _____

- He leído la hoja de información que se me ha entregado sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He podido hacer preguntas sobre el estudio y se me han resuelto mis dudas al respecto
- He hablado con el investigador responsable
- Comprendo que mi participación es voluntaria.
- Comprendo que cualquier hallazgo relevante relativo a mi salud me será comunicado
- Comprendo que puedo retirarme del estudio:
    - Cuando lo desee.
    - Sin tener que dar explicaciones.
    - Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio.

Recibiré una copia firmada y fechada de este documento de consentimiento informado

Firma del participante: Firma del investigador:

Fecha: / / Fecha: / /

Deseo que me comuniquen los resultados obtenidos en la investigación:

☐ SÍ ☐ NO

Firma del participante: Firma del investigador:

Fecha: / / Fecha: / /

Annex 3: PCST intervention

(Available in Spanish and Catalan)

Table 5 Pain coping skills training (PCST) (45)

PCST session	Content	Home practice for the week
Session 1: progressive muscle relaxation (PMR)	-Introduction to psychological and neural aspects of pain -Explain general pain coping skills methods and objectives -Train in PMR: consists on tightening and then relaxing each part of the body consecutively.	2 PMR practices per day (about 5 minutes per practice)
Session 2: Mini-practices	-Review the previous week -Train on mini PMR practices	10 or more mini PMR practices per day (2 minutes per practice)
Session 3: activity-rest cycling	-Review the previous week -Explain activity-rest cycling: overdoing an activity on days when pain is lower can cause more pain on following days, perpetuating the chronic condition. Instead this technique aims to limit activity and schedule resting periods in between.	Use technique twice per week
Session 4: pleasant activity scheduling	-Explain how pleasant activity scheduling can help control and decrease pain -Create pleasant activity goals with the participant	3 pleasant activities per week
Session 5: identifying negative thoughts, keep a diary	-Explain the ABC model of CBT and how it leads to automatic thoughts: our emotions and behaviors (C: Consequences) are not directly determined by life events (A: Activating Events), but rather by the way these events are cognitively processed and evaluated (B: Beliefs) -Teach how to use a thought diary to monitor negative thoughts	Record negative thoughts daily
Session 6: challenging negative thoughts and calming self-statements	-Work with participant to challenge negative thoughts -Develop calming self-statements	Practice developing alternative coping thoughts daily
Session 7: problem solving I, pleasant imagery and distraction techniques I	-Training in problem solving -Training in pleasant imagery -Training in counting backwards	1 problem solving activity per day 2 pleasant imagery per day
Session 8: distraction techniques II, review of skills	-Train use of focal points and auditory stimulation as distraction methods -Review skills from previous weeks	3 distraction techniques per week

Session 9: problem solving II applying pain copying skills in problem situations	-Identify problem situations -Develop coping plans	Record situations and thoughts daily
Session 10: coping skills maintenance, developing a plan	-Review principles of relapse prevention -Identify warning signs of reduced coping -Develop plans to address lapses in coping	

Annex 4: Exercise and stretching program

Table 6 Exercise program (58)

Physical rehabilitation		
Exercise	**Description and progressions**	**Example**
Lying external rotation	1. Begin lying on your side on a soft surface, hip flexed at 45º and knees flexed at 90º º, feet stacked on top of each other. 2. Perform an external rotation of the superior leg while stabilising the hips so that both hip bones are looking forward at all times. 3. Hold position for 5 s and return to start. 4. Perform 10 on each side for a total of 3 sets Progression: add resistance band around the legs, below the knees.	
Leg raises lying on the side	1. Begin lying on your side on a soft surface 2. Tighten your thigh muscles, and then lift the leg that is on top straight up until it is at shoulder height. 3. Hold at least 6 s, keeping your hip and your leg straight in line with the rest of your body, and keep your knee pointing forward. Do not drop your hip back. 4. Slowly lower the leg back down, and rest a few seconds. 5. Do 10 repetitions for 3 sets Progression: add resistance band around the ankles	
Bridge	1. Being lying face up on a soft surface, both knees flexed and feet flat on the floor at hip width apart. Arms lying at either side, 2. Press down on the feet to engage the posterior muscles of the legs and lift hips up slowly until the upper body and lower body are aligned. 3. Hold 5 s and descend slowly to start position. 4. Repeat 10 times for a total of 3 sets Progression: after each set of then, hold a	

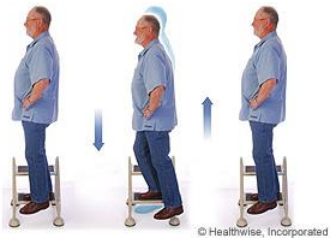
	bridge position and perform 10 additional small “pulses”.	
Wall mini squat with knee adduction	1. Standing back to a wall, place your feet about hip-width and 30-40 cm away from the wall. 2. Place a ball about the size of a soccer ball between your knees and squeeze your knees against the ball 3. Lean against the wall and slide down until your knees are bent 20-30º 4. Squeeze the ball for 6 seconds at a time, resting a few seconds in between for a total of 10 times, then return to standing. 5. Repeat a total of 3 sets	
Straight leg raises	1. Begin lying on your back with one knee bent and the foot resting flat on the floor, the other leg is lying straight. Make sure that your low back has a natural curve, enough that your hand could fit flat between the floor and your low back. 2. Tighten the thigh muscles in the straight leg by pressing the back of your knee flat down to the floor. Hold your knee straight. 3. Tighten the quadriceps muscles of your straight leg and lift the leg 30 to 45º. Hold for about 6 seconds, then slowly lower the leg back down and rest a few seconds. 4. Do 10 repetitions 3 times	
Single leg step up on a box	1. Stand on a step (no higher than your knee), on the leg you want to exercise. Let your other leg hang down off the step. 2. Slowly bend your knee so the foot hanging down moves down toward the floor, then slowly straighten your knee again. 3. Do 10 repetitions on each leg, making sure the knee is tracking straight in line with your middle toe and you can see your toes at all moment.	

Table 7 Stretch program (58)

Stretches		
Stretch	**Instructions**	**PIcture**

Standing quadriceps stretch	1. Stand holding a chair or wall for stability 2. Bend the knee and hold the front of your foot with the hand on the same side. 3. Keeping your knees next to each other, pull your foot toward your buttock until you feel a gentle stretch across the front of your hip and down the front of your thigh. Your knee should be pointed directly to the ground, and not out to the side. 4. Hold the stretch for at least 15 to 30 seconds. Repeat 2 to 4 times.	
Hip rotator stretch	1. Lie on your back with both knees bent and your feet on the floor. 2. Put the ankle of the leg you are going to stretch on your opposite thigh near your knee. 3. Push gently on the knee of the leg you are stretching until you feel a gentle stretch around your hip. 4. Hold the stretch for at least 15 to 30 seconds. Repeat 2 to 4 times.	
Hamstring stretch in doorway	1. Lie on the floor near a doorway, with your buttocks close to the wall. 2. Let the leg you are not stretching extend through the doorway. 3. Put the leg you want to stretch up on the wall, and straighten your knee to feel a gentle stretch at the back of your leg. 4. Hold the stretch for at least 15 to 30 seconds. Repeat 2 to 4 times.	
Iliotibial band and buttock stretch	1. Sit on the floor with your legs out in front of you. 2. Bend the knee of the leg you want to stretch, and put that foot on the floor on the outside of the opposite leg. 3. Twist your shoulders toward your bent leg, and put your opposite elbow on that knee. 4. Push your arm against your knee to feel a gentle stretch at the back of your buttock and around your hip. 5. Hold the stretch for at least 15 to 30 seconds. Repeat 2 to 4 times.	

Calf stretch	1. Stand facing a wall with your hands on the wall at about eye level. 2. Put the leg you want to stretch about a step behind your other leg. 3. Keeping your back heel on the floor, bend your front knee until you feel a stretch in the back leg. 4. Hold the stretch for at least 15 to 30 seconds. Repeat 2 to 4 times.	

Annex 5: VAS scale

(Available in Spanish and Catalan)

1. **Por favor, indique con una raya la severidad del dolor que ha sentido en la rodilla de media en la semana anterior:**

2. **Por favor, indique con una raya la MÍNIMA severidad del dolor que ha sentido en la rodilla en la semana anterior:**

3. **Por favor, indique con una raya la MÁXIMA severidad del dolor que ha sentido en la rodilla en la semana anterior:**

Annex 6: Pain catastrophising scale

PCS

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

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.

… Total

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