Clinical effectiveness of patella mobilisation therapy versus a waiting list control for knee osteoarthritis: a protocol for a pragmatic randomised clinical trial

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ABSTRACT

Introduction Knee osteoarthritis (KOA) is a common, disabling and costly medical condition. The patellofemoral joint is a critical source of pain in individuals with KOA, and coexistence of patellofemoral osteoarthritis (PFOA) and tibiofemoral osteoarthritis (TFOA) is sometimes observed. The identification of subgroups with PFOA and customised interventions to correct underlying pathomechanics is beneficial for individuals with KOA. This study aims to evaluate whether a clinic-based patella mobilisation therapy (PMT) leads to significant improvement in pain, physical function and quality of life of individuals with KOA.
Methods and analysis A total of 208 participants with coexistence of PFOA and TFOA will be recruited. A pragmatic randomised clinical trial will be conducted, and participants will be randomised into the PMT and waiting list groups. For the PMT group, three manual mobilisation sessions, along with home-based vastus medialis oblique muscle exercise, will be conducted at 2-month intervals. The waiting list group will continue to receive their usual care, and as an incentive the waiting list group will be offered PMT after the study period is over. The primary outcome is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, and secondary outcomes include the WOMAC function and stiffness subscales, scores for objective physical function tests (the 30 s chair stand, 40-metre fast-paced walk test, the Timed Up and Go Test), and the EuroQol-5D scores. All outcomes will be evaluated at baseline and 6 months using intention-to-treat and incorporating covariate analysis.
Ethics and dissemination Ethics approval has been obtained (CREC no: 2014.379). Results of the trial will be submitted for publication in a peer-reviewed journal.
Trial registration number ChiCTR-IPC-15006618; Pre-results.

Strengths and limitations of this study

► The pragmatic design of this randomised clinical trial will determine whether patella mobilisation therapy, a simple clinic-based procedure, is effective for knee osteoarthritis (KOA) in clinical settings.
► The primary and secondary outcomes are in accordance with the clinical trial recommendations of the Osteoarthritis Research Society International.
► The intervention targets the subgroup of patellofemoral osteoarthritis and tibiofemoral osteoarthritis, which is an important but under-recognised subgroup of KOA.
► This is an open-label study, and one of the limitations of this study is the lack of participant and physician blinding.

33.6% of the US population and 31% of the Chinese population have osteoarthritis.[3 4] It is a costly disease, causing significant socioeconomic burden because of its high prevalence, worker absenteeism and expensive healthcare services.[5 6] It was ranked as the 11th highest contributor to global disability in 2010.[7] The management of KOA is multidisciplinary, and non-pharmacological strategies are still considered the first-line treatment.[8]

The knee joint is a complex tricompartmental joint consisting of a patellofemoral joint (PFJ), which articulates the patella with the femoral condyle, and the tibiofemoral joint (TFJ), which articulates the medial and lateral tibial plateau with the corresponding femoral condyles. The biomechanics of the PFJ are unique. Patellar alignment relies on passive (osseous configurations and soft tissue restraints) and active (medial and lateral quadriceps) structures. The osseous anatomical anomalies, which most likely affect the alignment and motion of the

INTRODUCTION

Knee osteoarthritis (KOA) is the most common form of chronic arthritis and the major cause of pain and disability worldwide.[1] KOA is age-related,[2] and by the age of 65 years,

patella, occur because of shallow femoral trochlea groove and patella alta.[9–11] Tension from soft tissues, medial and lateral retinaculum, particularly the two distal expansions of the iliotibial band (ITB),[12] the joint capsule, and ligaments, maintain patellar alignment.[13] Vastus medialis obliquus (VMO) and vastus lateralis (VL) are quadriceps muscles that are important in patellar alignment.[14] The imbalance of muscle strength or force vectors can lead to PFJ malalignment and increased compression pressure between the patella and femur during weight bearing, causing pain and structural damage, such as OA.[15–17]

Epidemiological and clinical studies of KOA have focused on the status of the TFJ, and the PFJ has often been disregarded despite the fact that it causes pain in individuals with KOA.[18] The current management of patellofemoral osteoarthritis (PFOA) remains controversial because of the limited trials evaluating customised treatments. Studies targeting treatment of PFOA through use of medial taping or a patellar brace to align the patella have shown positive outcomes in terms of structural improvement and pain reduction.[19 20] Manual therapy is recommended by the National Institute for Health and Care Excellence (NICE) as an adjunctive therapy to exercise for OA.[21] However, only a few clinical trials have evaluated manual therapy that targets PFOA,[22 23] with strength of conclusions limited by small sample size, lack of methodological rigour[22] or heterogeneous interventions (exercise, education, manual therapy and tapping).[23]

Coexistence of PFOA and tibiofemoral osteoarthritis (TFOA) is observed in 40% of older adults with KOA.[24] Research indicates that the coexistence of PFOA and TFOA is associated with more pain and greater loss of function in individuals with KOA,[24] which is commonly diagnosed and managed in primary care settings,[25] mostly by primary care practitioners (PCPs).[26] Therefore, we aim to conduct a randomised clinical trial that evaluates the clinical effectiveness of a simple clinic-based patella mobilisation therapy (PMT) in a subgroup of patients with coexisting PFOA and TFOA. A pragmatic design will be used for the trial to test whether PMT is effective in clinical settings.[25] The therapy consists of passive joint mobilisation to realign and activate VMO firing to maintain the patellar position. The technique is simple and can be easily performed by trained PCPs. We hypothesise that an improvement in the disrupted biomechanics will reduce pain and improve function in individuals with KOA, although PMT only targets the PFJ.[24]

Aims and hypotheses

1. To assess the clinical effectiveness (primary outcome) of PMT in the intervention and waiting list groups in terms of self-reported knee pain at 6 months.

Hypothesis: PMT can reduce knee pain based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which is the gold standard for self-reported measures in KOA trials.[26]

2. To assess the clinical effectiveness (secondary outcomes) of PMT in the intervention and waiting list groups in terms of functional improvement and quality of life (QoL) at 6 months.

Hypothesis: PMT can improve knee function and stiffness and QoL based on the WOMAC function score, 30 s chair stand, 40-metre fast-paced walk test, Timed Up and Go Test (TUGT) and EuroQol-5D (EQ-5D) results.[27 28]

METHODS AND ANALYSIS
Study design

The study is a 26-week, two-arm, pragmatic, parallel, superiority, open-label, phase II randomised controlled trial that aims to evaluate the effectiveness of PMT versus a waiting list group in clinical settings. The protocol design incorporates the recommendations of the Osteoarthritis Research Society International (OARSI) and Standard Protocol Items: Recommendations for Interventional Trials.[26 29] The study workflow is shown in figure 1.

Eligibility

Participants will be screened by a trained research assistant via phone interview, and potential eligible participants will be examined by the principal investigator (RWSS, a physician) at the study site based on the following criteria:

Inclusion criteria

1. age ≥45 to ≤75 years: the age range is chosen because PFOA is common among elderly individuals and among individuals in the middle-age group[18 30]; we set the upper age limit to ensure participants can understand, remember and follow the exercise prescription
2. diagnosis of KOA based on clinical and radiographic criteria (standing anteroposterior view) as defined by the American Rheumatology Association[31]
3. moderate to severe knee pain for at least 3 months with either stair climbing, squatting or prolonged sitting,[32] with a score of 3 or more (0–6 ordinal response scale) on the question 'What is the average level of your left/right knee pain?'
4. involvement of anterior knee pain and fulfilment of two of the following criteria on initial assessment: (1) pain on direct compression of the patella against the femoral condyles with the knee in full extension, (2) tenderness on palpation of the posterior surface of the patella, (3) pain on resisted knee extension, and (4) pain with isometric quadriceps contraction against suprapatellar resistance with the knee in slight flexion[32 33]
5. presence of osteophytes at the PFJ on standing as shown in the 30 degree flexion lateral radiograph.[34]

Exclusion criteria

1. history of open or arthroscopic operation on the symptomatic knee
2. body mass index (BMI) ≥35 kg/m^2
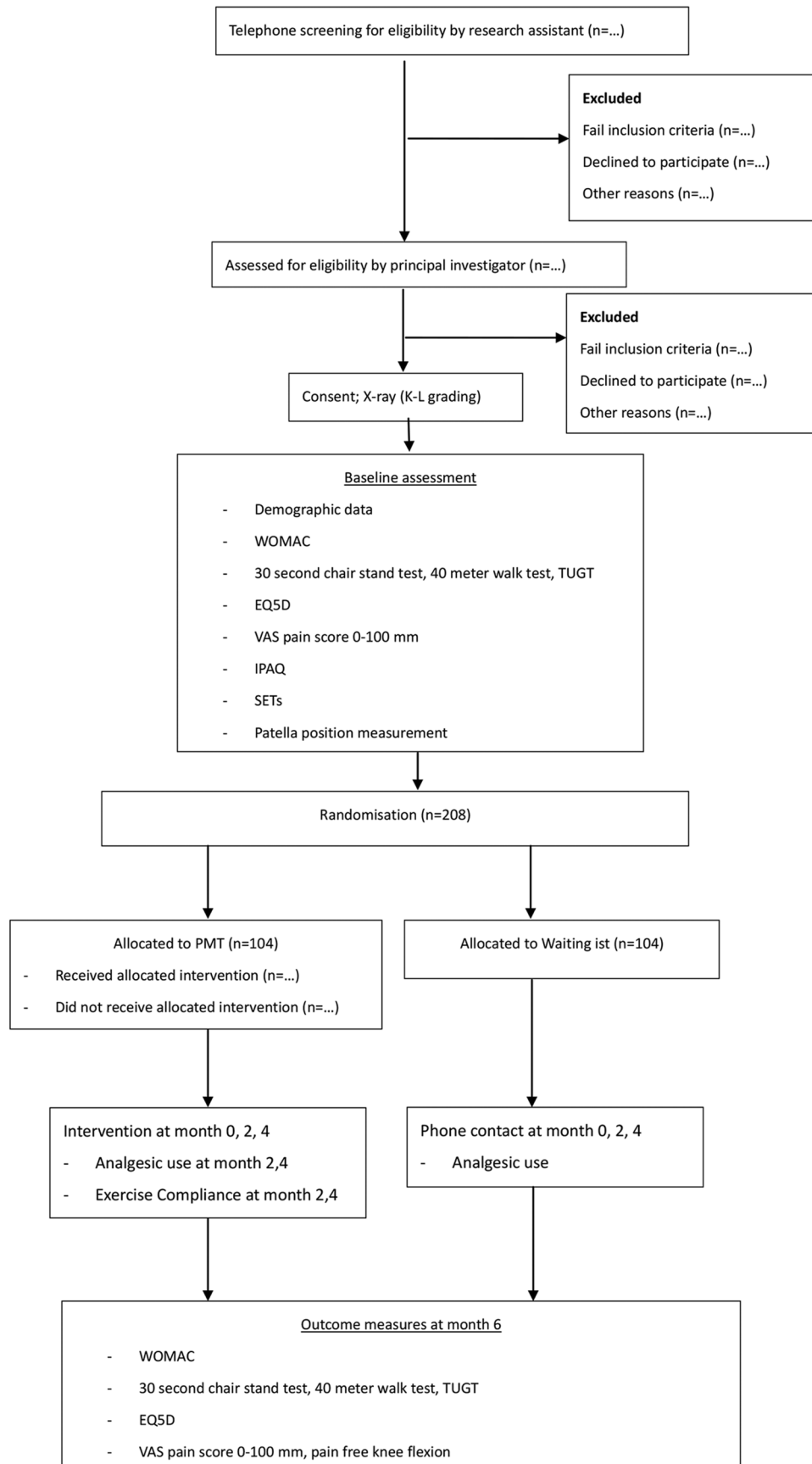3. any knee injections within the preceding month

Figure 1 Workflow of the PMT study. EQ-5D, EuroQol-5D; IPAQ, International Physical Activity Questionnaire; K-L, Kellgren Lawrance; PMT, patella mobilisation therapy; SETs, Stanford Expectations of Treatment Scale; TUGT, Timed Up and Go Test; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

4. history of inflammatory or postinfectious knee arthritis
5. daily use of opioid medication
6. comorbidity severe enough to prevent participation, such as attendance at scheduled appointments
7. fixed flexion deformity >5°, or varus or valgus deformity >15°, which makes realignment of the patella to a normal mechanical position difficult.

Recruitment and informed consent

Participants will be recruited from general outpatient clinics (GOPCs) in the New Territories East (NTE) region of Hong Kong. There are seven GOPCs/family medicine clinics in the NTE region that provide primary care services to a specific population, serving more than 1.2 million people. Participants with KOA will be recruited via poster advertisement in GOPCs and direct physician referral. The study site is a teaching clinic operated by the Chinese University of Hong Kong. After confirming the eligibility of the participants, the principal investigator will discuss the study goals, procedures, activities and possible alternatives for approximately 15 min, and answer all questions. Subsequently, signed written informed consent will be obtained. After enrolment, participants will receive a study identification number and baseline data will be collected.

Randomisation and allocation concealment

Blocked randomisation in a 1:1 ratio will be used by an off-site statistician to allocate patients into two groups,[35] using Random Allocation Software. The allocation sequence is concealed from the researcher enrolling and assessing participants through use of sequentially numbered, opaque, sealed envelopes (SNOSE).[36] The aluminium foil inside the envelope will make the envelope impermeable to light. To prevent the subversion of the allocation sequence, the signature and date of birth of the participants will be written on the envelopes, and a carbon paper placed inside the envelope will transfer the information onto the allocated card inside the envelopes. SNOSE are kept by a person not involved in the care or evaluation of patients or in the data analysis. The treatment allocation process will start when the investigator calls the personnel assigned to keep the SNOSE. The computer database is designed in such a way that treatment allocation cannot be changed after randomisation. The corresponding envelopes will only be opened after the enrolled participants complete all baseline assessment and the time to allocate the intervention.

Blinding

In this open-label study, blinding of physicians and participants will not be possible. However, all data collection will be performed by trained research assistants blinded to the allocation status of the patients via face-to-face interviews. They will receive rigorous training in standardised data collection procedures. A data entry personnel who is not part of the research team will perform data entry such

Figure 2 Manual patellofemoral joint mobilisation.

that the statistician can analyse data without referring to allocation information, thus ensuring blinding.

Intervention group: PMT

We will report the intervention according to the Template for Intervention Description and Replication checklist[37]: Informed written consent has been obtained from the patient who appeared in figures 2 and 3.

Rationale of the PMT

A study has shown that knee joint mobilisation provides immediate local and widespread hypoalgesic effects in individuals with KOA[38] and improves the extensibility of contractile tissues and movement of joints.[39] A recent study by Courtney et al[40] also suggested that joint mobilisation enhances conditioned pain modulation and descending pain mechanisms in patients with KOA. Local mechanical disturbance may modify the chemical environment, thereby altering the concentrations of inflammatory mediators to peripheral nociceptors.[41] In addition, it has been hypothesised that mobilisation involves serotonin and norepinephrine receptors in the spinal cord, which may activate the descending pain inhibitory systems.[42 43]

According to the 2016 Patellofemoral Pain Consensus Statement, combined interventions are recommended to treat PFJ pain.[33] Because the NICE recommended manual therapy as an adjunctive therapy to exercise, we designed our unique protocol for PMT to consists of PFJ mobilisation, followed by supervised VMO exercise. We hypothesised that mobilising and keeping the patella medially can correct the disrupted biomechanics of individuals with KOA, with subsequent improvement in pain and physical function. The interventions will be conducted by trained primary care physicians at the GOPCs (RWSS, KKWC and YHC). Our protocol is designed to fit primary care practice, and is different from traditional mobilisation therapy that consists of multiple treatment sessions at intense frequencies. The technique can be easily conducted by trained PCPs in clinical practice, and the prescribed

Figure 3 Vastus medialis strengthening exercise.

exercise may be followed by patients with KOA. If both knees are painful, both will be treated at the same time.

Step 1: passive PFJ mobilisation (1 session every 2 months for a total of 3 sessions)

A trend towards delayed onset of VMO relative to VL has been demonstrated in those with anterior knee pain, although this dysfunction, as compounded by normal physiological variability in the healthy population, has not been validated.[44] In addition, the patella of individuals with KOA is pulled laterally because of a weak VMO relative to the VL and ITB.[45 46] The participant will be placed on a side-lying position with the knee supported with a wedge. The knee will be flexed to a degree that allows vertical gravitational force to be applied from the palm to glide the patella from the lateral edge to the medial direction, which provides grade 3 stretch to the tight lateral retinaculum.[47] The mobilisation of each knee will take approximately 3 min (figure 2).

Step 2: active non-load VMO exercise

Decreased motor recruitment of the VMO is common in individuals with KOA.[48] To maintain the benefits of the mobilisation, participants will be prescribed VMO exercise primarily to encourage continuous firing of the muscle. The exercise is performed by asking the participants to lie in supine position with the knee extended and the hip in external rotation that is modified by the external rotation of the foot. Subsequently, the participants will be asked to repeatedly perform leg raise exercises with alternate hip flexor contraction (breathing out) and relaxation (breathing in) (figure 3). This non-loaded VMO exercise has been chosen as it is easy to perform, does not require any equipment, and can be performed at home safely by non-athletes and elderly individuals, all of which are important considerations for primary care practice. Moreover, a study has shown that non-loaded VMO training in an open kinetic chain can strengthen muscle architecture based on ultrasound.[49] Participants will be supervised to correctly perform the exercise, and they will be encouraged to continue the exercise at home twice daily with 20 repetitions per session. Those who experience back pain will be instructed to flex the opposite hip and knee to stabilise the lumbar spine before lifting. An exercise pamphlet will be given to reinforce the exercise, and compliance to the exercise will be assessed on follow-up using a 7-day recall diary.

Control group: waiting list group

In the present study, interventions were used in a neutral manner to minimise bias. The waiting list group will continue to receive the usual care from the healthcare team and complete all outcome measures within the

same time frame as the intervention group. All the participants will receive the same PMT after study completion at 6 months.

Cointerventions will be allowed in both groups, such as conventional medication, physical therapy, acupuncture, use of herbal medicines and over-the-counter drugs, and other active treatments. We will neither influence nor restrict doctors, other practitioners or participants from using other interventions during the study period. The use of cointerventions will be retrieved from the Clinical Management System, an electronic system operated by the Hospital Authority in Hong Kong. Participants will be asked to recall their private treatment as well.

Baseline assessment

Demographic data, such as age, gender and BMI, will be collected. The baseline physical activity status will be assessed using the Chinese version of the International Physical Activity Questionnaire.[50] Information on the duration of knee pain and prior knee interventions, such as knee exercise, physiotherapy, hyaluronic acid injection, corticosteroid injection or use of traditional Chinese medicine, will be obtained. All other comorbidities will be documented as potential confounders. The severity of KOA will be graded by a radiologist using the Kellgren-Lawrence classification system,[51] and the presence of radiological evidence of PFOA will be confirmed on X-ray lateral view. Because of limited funding resources, an X-ray skyline view will not be ordered in this study. Instead, the patella position will be examined via ultrasound (GE Logiq e BT11) by measuring the horizontal distance between the centre of the patella and femoral groove, with the knee fully extended (figure 4). The measurement is conducted by the principal investigator (RWSS), with a musculoskeletal sonography certification. Because the patient's response to treatment may be influenced by his or her expectations before the start of

Figure 4 Patella position measured via ultrasound (left knee): (A) femoral groove, (B) centre of the patella tendon and (C) patella position measured using the horizontal distance between (A) and (B).

treatment, reducing the statistical power to detect specific treatment effects, the Stanford Expectations of Treatment Scale will be used to overcome this.[52]

Outcome measurement

All outcome measures will be recorded at baseline and 6 months, which is the primary endpoint.

Primary outcome

The WOMAC is a disease-specific QoL questionnaire used during osteoarthritis clinical trials.[26] It consists of 24 self-reported items, including knee pain (5 items), stiffness (2 items) and function (17 items). The WOMAC pain score will be used as the primary outcome.

Secondary outcomes

The OARSI recommended three core tests for an objective physical function assessment during KOA trials, namely the 30s chair stand performance test, 40-metre fast-paced walk test and the TUGT.[53] The WOMAC function score will be used to assess the self-reported function. Health-related QoL will be assessed using the EQ-5D questionnaire. The EQ-5D has strong construct validity, responsiveness and clinometric profile, and has been used to assess the economic effect of OA.[28] The Visual Analogue Scale of pain on a 0–100mm scale will be used to rate global knee pain. The degree of pain-free active knee flexion will be measured using a goniometer.[54]

Data collection and management

Data will be collected at baseline and 26 weeks. Additional data collection on VMO exercise compliance and analgesic use in the intervention and control groups will be conducted at 8 and 16 weeks. The number of potential candidates, responses received and their resolution, and the number of PMT sessions and assessment sessions attended will be recorded. Follow-up data will include the number of participants completing the trial and the number of withdrawals due to all causes. Data entry, transfer and subsequent maintenance will be performed by a data manager. An electronic database will be used, and the server is in a physically secured location with backup on a weekly basis. Access to study data is restricted to the study research team by the use of username and password.

Fidelity assessment

The observations of intervention sessions will be conducted by Co-investigator (co-I) (KKWC), the physician who primarily designed the PMT protocol. This will provide information regarding the adherence and competency of practitioners (RWSS and YHC) who conduct the PMT.

Safety monitoring

Participants will be advised to call the study coordinator if they encounter any discomfort after the intervention. Standardisation forms will be used for the monitoring and reporting of the side effects and adverse events. The principal investigator will report serious adverse events to the ethics committee within 24hours.
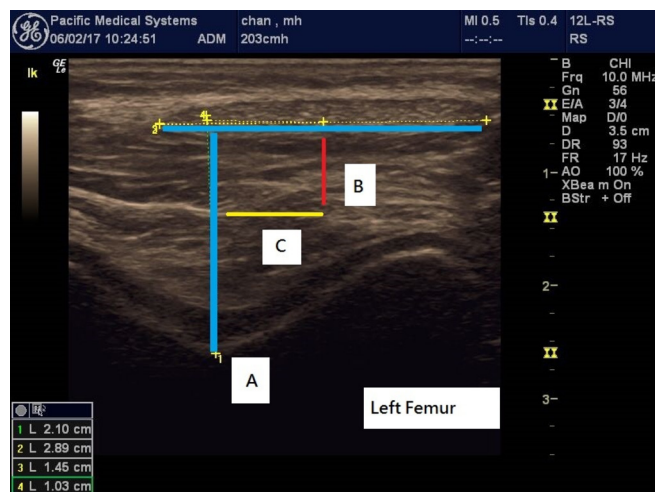
Sample size calculation

The sample size calculation is based on a randomised controlled trial conducted by Abbott *et al*, which compared the intervention (manual therapy, exercise and usual care) versus control (usual care alone) for KOA. The mean change in WOMAC score was 19.3 (SD: 44.70) for the intervention group and 1.6 (SD: 40.48) for the control group, and the calculated effect size (Cohen's d) is 0.42, which favoured the intervention.[55] We use the same Cohen's d, with a two-sided t-test, a type I error at 0.05 of 80% power and a sample size of 90 in each group. Assuming the dropout rate to be 15%, the adjusted total sample size is 208.

Data and statistical analysis

Descriptive statistics will be used to compare the baseline characteristics between the two groups. For the primary analysis, analysis of covariance will be conducted to compare the effects of the intervention versus control in terms of WOMAC values at the end of the study following the intention-to-treat principle; i.e. Baseline WOMAC score, duration of knee pain, number of comorbidities, bilateral knee pain status (yes or no) and the amount of analgesic consumption will be considered as covariates and controlled as confounders in the analysis. Statistical analysis of the primary and secondary outcome measures over time will be conducted. All analyses will be conducted using the R software (StataCorp).

With a clearly defined target population, effectiveness and safety outcomes, and convenient data collection procedures, our trial should maximise the number of participants who are on the protocol-specified intervention until the outcome data are collected. In our sensitivity analysis, we will use multivariate imputation by chained equations to incorporate auxiliary information about the missing data. The imputation model will include prerequisite variables in the data analysis, variables for baseline socioeconomic status and variables considered as outcome predictors. Approximately 10 iterations will be conducted in each imputation process, with more iterations to be considered until the chain reaches convergence.[56] Twenty completed data sets will be imputed with the use of the chain equations. Rubin's rule will be applied to combine the effect estimates.[57] This approach provides estimated SEs and P values that incorporate missing data uncertainty.

Ethics and dissemination

The study complies with the Declaration of Helsinki. Written informed consent will be obtained from all participants. All data will be kept confidential and only accessible to delegated research personnel.

DISCUSSION

PFOA is a critical source of pain, and a coexistence of PFOA and TFOA is sometimes observed. This subgroup is important, but it is an under-recognised subgroup of KOA. Pain and functional impairment in individuals with KOA are associated with a multifactorial set of degenerative intra-articular cartilage, bone and synovial knee structures, in addition to a complex interaction among genetic, psychosocial and other factors.[58] Thus, the identification of the subgroup with PFOA and customised interventions to correct the disrupted biomechanics can potentially reduce the disease burden. The proposed PMT is in accordance with the recommendation from the consensus statement of the International Patellofemoral Pain Research Retreat on PFOA management.[33] The technique is simple and can be conducted safely by trained primary care physicians and other relevant healthcare providers. The home-based exercise also enhances one's responsibility in chronic disease management. If PMT is proven to be effective, it can potentially reduce pain and improve knee function and QoL of patients with KOA in the community.

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