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Which treatment is most effective for patients with patellofemoral pain? A protocol for a living systematic review including network meta-analysis

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ABSTRACT

Introduction Patellofemoral pain (PFP) affects 1 in every 14 adults. Many treatments for PFP have been evaluated, but the comparative effectiveness of all available treatments has never been examined. Network meta-analysis is the only design to study the comparative effectiveness of all available treatments in one synthesis. This protocol describes the methods for a systematic review including network meta-analysis, to assess which treatment is most likely to be effective for patients with PFP.

Methods and analysis The primary outcome measures of this network meta-analysis are the global rating of change scale at 6-12 weeks, 13 – 52 weeks and >52 weeks. The secondary outcome measures are patient-rated pain scales at 6-12 weeks, 13 – 52 weeks and >52 weeks. Completed published and unpublished randomised controlled trials with full text reports are eligible for inclusion. We will search EMbase, Pubmed (including MEDLINE), CENTRAL, Scopus, Web of Science, and CINAHL, SPORTDiscus, OpenGrey, Worldcat, Conference Proceedings and multiple trial registers for relevant reports. Two researchers will appraise the study eligibility and perform data extraction. Risk of bias will be assessed with the Cochrane Risk of Bias Tool v.2.0.

Bayesian network meta-analyses will be constructed for global rating of change scale and patient-rated pain. Consistency between direct and indirect comparisons will be assessed. Between study variability will be explored and a threshold analysis for the credibility of the network meta-analyses' conclusions will be performed.

Ethics and dissemination This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for Protocols, and PRISMA extension for network meta-analysis. The study commenced at 1 February 2018 and its expected completion date is 15 January 2019.

PROSPERO registration number: CRD42018079502

Keywords: Patellofemoral pain, knee cap, network meta-analysis, evidence synthesis, ranking

ARTICLE SUMMARY

Strengths and limitations of this study

- This living systematic review will include thorough search methods, searching conventional databases, grey literature resources and trial registers.
- Risk of bias in randomised controlled trials will be appraised using the new Cochrane Risk of Bias tool, v2.0, for intervention studies.
- This living systematic review and network meta-analysis enables clinicians to consult a contemporary, comprehensive overview of the comparative effectiveness of treatments for patellofemoral pain.
- The feasibility of this study is depending on the availability and the homogeneity of the trials and the consistency between direct and indirect evidence.

INTRODUCTION

Patellofemoral pain (PFP) affects 1 in every 14 adolescents and 1 in every 8 adults.[1] PFP is characterised by diffuse pain around or behind the knee cap, provoked during activities which load the knee-joint, such as stair climbing, running and jumping.[2] One in every two patients with PFP continue to suffer from knee pain, which can impact their quality of life, and physical activity.[3,4]

Similar to other chronic musculoskeletal pain conditions, there are many different evidence-based treatments available. Patient education, exercise therapy, foot orthoses, gait retraining and surgery are common treatments used for patients with PFP.[2,5] While there are several systematic reviews that focus on different treatments for PFP,[6-10] the comparative effectiveness of all available treatments has never been examined. This is challenging for clinicians and patients, who are faced with uncertainty when presented with so many potentially beneficial treatment options.

Traditional systematic reviews present fragmented pairwise 'head to head' comparisons, e.g. treatment A versus B, and treatment B versus C. The limitation with this approach is that multiple treatments cannot be compared simultaneously (i.e. treatment A versus B versus C). The traditional approach may lead to invalid interpretations regarding the comparative effectiveness of treatments.[11] Clinicians are left to speculate on which treatment is most effective, based on multiple, independent 'head to head' comparisons. Network meta-analyses offer the opportunity to combine both direct and indirect treatment comparisons in a single analysis, which overcomes main limitations of pairwise systematic reviews. They do this by allowing for:

- a coherent comparison of effectiveness of multiple treatments in one statistical model, while maintaining the randomised nature of the evidence, and
- comparison of treatments even if the treatments have not been investigated directly in a randomised controlled trial.[12-14]

Based on the network meta-analysis, a ranking from "most likely to be effective" to "least likely to be effective" treatment (for a given outcome) can be estimated. In this way, the results from the network meta-analysis can directly feed into shared decision-making in clinical practice.

A common critique on systematic reviews is that they are soon out-of-date.[15] Living network meta-analysis are particularly suitable to control for this issue as they are regularly updated, preferably as open access content. This enables clinicians to consult a comprehensive overview of the comparative effectiveness of treatments for a given condition, while ensuring a contemporary evidence synthesis for clinical practice (Table 1).[16, 17].

The comparative effectiveness of all studied treatments for patients with PFP has never been examined. The aim of this living systematic review with network meta-analysis is to evaluate the comparative effectiveness of all available treatments for patients with PFP, providing a comprehensive and up-to-date overview of evidence-based treatments.

	Traditional systematic review + meta-analysis	**Systematic review + NMA**	**Living systematic review + NMA**
Direct comparison between treatments	X	X	X
Indirect comparisons between treatments that have never been compared in a RCT		X	X
Research question • Which treatment is most effective, A or B? • Which of the many available treatments that have been tested in randomised trials are most effective?	X	X X	X X
Always-up-to-date best evidence synthesis to inform clinical practice			X

Table 1. The advantages of a living network meta-analysis compared to traditional systematic reviews

NMA = network meta-analysis, RCT = randomised controlled trial

METHODS

Protocol registration

The protocol for this living systematic review with network meta-analysis is registered on PROSPERO [CRD42018079502]. This protocol follows the PRISMA-P and PRISMA extension for network meta-analysis checklist for reporting systematic review protocols and network meta-analysis.[18-20]

Patient involvement & prioritising outcomes

Patients with PFP (N=7) from a patient reference group have been involved in setting a hierarchy of outcomes (global rating of change scale and pain scales) for this network meta-analysis. Six out of seven (86%) indicated a preference for the global rating of change scale over pain outcomes. Consequently, the outcomes selected are as follows:

Primary outcome measure:

- Global rating of change scale. This scale has 7 descriptors for perceived change: completely recovered, strongly recovered, slightly recovered, unchanged, slightly worse, strongly worse and worse than ever.

Secondary outcome measures:

- Pain intensity, measured by 'worst pain in the previous week' on a visual analogue scale (0-10/0-100) or numerical rating pain scale (0-10)
- Patient-rated pain during activities of daily life (ADL) and during sporting activities. We will synthesie one pain outcome for ADL, and one for sporting activities. The choice for these outcomes will be made based on availability; an outcome that allows for inclusion of the highest number of comparisons. Pain will be expressed a visual analogue scale (0-10/0-100) or numerical rating pain scale (0-10)
- Adverse effects (any, following the original studies)

Research questions

1. Which treatment(s) is most likely to be effective for patients with PFP on global rating of change and patient-rated pain?

2. Which treatment class(es) is most likely to be effective for patients with PFP on global rating of change and patient-rated pain? The study of treatment classes is relevant when more than one subtype for a treatment is available, e.g. multiple types of exercise regimes, which can be grouped together to answer this question.
3. Which treatment (class) is most likely to cause an adverse effect in patients with PFP?

Eligibility criteria

Type of studies

Published or unpublished RCT's (including randomisation through minimisation, or clustering), for which a full-text report or full text protocol of a completed trial is available, are eligible for inclusion.

Type of population

All patients with a clinical diagnosis of PFP are included. Studies will be included if they use synonyms for PFP, but as minimum criterion, should describe patients with retropatellar or peri-patellar pain, of at least 6 weeks duration, and a non-traumatic onset. The diagnostic criteria used in the original studies, will be followed, given that the aforementioned minimal diagnostic criteria are met. Studies examining other conditions are excluded (e.g. patellar dislocations, patellofemoral osteoarthrosis, patellar tendinopathy, Osgood-Schlatter, iliotibial band syndrome, Sinding-Larsen-Johansson syndrome). Trials that include participants diagnosed with PFP, but with concomitant pain around the patella caused by other conditions (e.g. patellar tendinopathy) will be considered eligible for inclusion. No age restrictions will be imposed.

Type of treatments and control treatments

Any treatment, control treatment, placebo, wait-and-see, or no treatment group studied in a RCT is eligible for inclusion. Examples of treatment classes are exercise therapy, orthoses, braces, patient education, pain medicine or surgery.

Type of outcomes

Studies assessing the treatment effect after a minimum of 6 weeks will be included. Studies assessing the following outcomes will be included:

- Global rating of change scale
- Worst pain in the previous week, measured with a VAS (0-10) or NRPS (0-100).
- Patient-rated pain during activities of daily living and sporting activities, measured with a VAS (0-10) or NRPS (0-100).
- Adverse effects (any)

Search strategy

A sensitive search strategy has been developed for each of the data sources by a research librarian and one investigator (MW). We used the Cochrane sensitive search strategy for RCTs and modified this for the purpose of our study.[21] The search strategy includes a mix of indexed and free text terms, where applicable (supplementary file, appendix 1). No restrictions (e.g. language or full-text availability) were applied to the search.

One investigator (MW) will search conventional databases, grey literature databases and trial registers from their date of inception. Supplementary file, appendix 1 provides a detailed explanation of how the search is built, and with source-specific search strategies for each database, grey literature sources and trial registers.

Conventional databases

Conventional electronic databases EMbase, Pubmed (including MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science, and CINAHL and SPORTDiscus (both via Ebsco) will be searched for relevant reports.

Identifying grey literature and ongoing studies

Databases

OpenGrey.eu and WorldCat.org will be searched for studies that have remained unpublished.

Conference proceedings

We will search the conference proceedings from all Patellofemoral Research Retreats (2009, 2011, 2013, 2015 and 2017) for relevant reports and request authors to make available their full reports or protocols for unpublished studies.

Trial registers

We will search the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) Clinical Trials.gov, The European Union Clinical Trials Register and the ISRCTN registry for unpublished or ongoing studies.

Hand searching

We will screen reference lists of all Cochrane Reviews (N=6) on PFP for possible relevant studies that were not identified by our search. We will also screen reference lists of all the reports included in our systematic review.

Study selection

Two researchers will screen titles and abstracts independently, after duplicate removal by one of the investigators. Consensus will be sought in case of initial disagreement. If consensus cannot be reached, the report will be included for full text evaluation.

Both investigators will independently apply inclusion and exclusion criteria to the full text reports. In case of disagreement, consensus will be sought, however, if disagreement persists a third author (AW) will take the decision.

Data extraction

Data will be independently extracted by two researchers using standardised extraction forms adopted from the Cochrane Collaboration (see supplementary file, appendix 2).[22] Disagreements will be resolved by seeking consensus, and by a third reviewer (AW) in case of persistent disagreement. The following data will be extracted:

- Publication and study details: E.g. authors, year of publication, funding source, possible conflicts of interest, aim study, design, unit of allocation
- Population: Number of included patients, population characteristics for age, sex, body mass index, activity level, setting where population was recruited, baseline scores for outcome measures (mean, standard deviations (SDs), standard errors extracted for continuous outcomes, and number and percentage for categorical outcomes)
- Eligibility criteria and diagnostic criteria used for PFP

- Treatments: E.g. number randomised to group, detailed description of e.g. application, dose, intensity, frequency, number of sessions, delivery, tailoring (individual/group), duration of treatment, providers, co-treatments, modification (change to treatment), adherence. We used items from the Template for Intervention Description and Replication (TIDierR) checklist to assure comprehensive data extraction in this section of the extraction form.[23]
- Outcomes: time points measured, and the time points reported upon, outcome definition, person measuring, unit of measurement, scales (upper and lower limits), imputation of missing data. Primary and secondary outcomes used in the original trials.
- Data and analysis: comparisons, outcomes, subgroups, time points, results (central estimates and measures of dispersion; e.g. mean for both groups, mean difference, SD's/95 confidence intervals/standard errors), number of missing patients, statistical methods used and appropriateness of these.
- Other information: key conclusions of study authors

Risk of bias assessment

The Cochrane Risk of Bias Tool 2.0 will be used to assess the risk of bias for each outcome per study, and for outcomes across a (direct) comparison. In this tool risk of bias can be assessed following the "intention-to-treat" principle (i.e. assignment to intervention) or "per protocol" (i.e. adherence to intervention). We will assess risk of bias on the basis of "assignment to intervention". This new tool has a fixed set of items to use for the risk of bias appraisal, i.e. 'bias arising from the randomization process', 'bias due to deviations from intended interventions', 'bias due to missing outcome data', 'bias in measurement of the outcome', 'bias in selection of the reported result', and overall risk of bias judgement for each outcome.[24, 25]

Two experienced reviewers will independently assess the risk of bias for each outcome within the study, for each follow-up. They will trial the approach by assessing 20 RCT's in other musculoskeletal conditions, before the study starts. Each major domain of bias will be appraised in light of each outcome. The tool's signalling questions and criteria will be followed to inform a domain-based appraisal of the risk of bias.[24, 25] The risk of distortion of the outcome estimate by the methodology will be appraised as at 'low', 'some' or 'high' risk of bias. Judgements will be made regarding the direction of distortion 'favours experimental', 'favours comparator', 'towards null', 'away from null', or

'unpredictable'. Each outcome within a study will receive an overall risk of bias judgement based on the individual domains; 'low', 'some' or 'high' risk of bias.[24, 25]

In case of disagreements between reviewers, consensus will be sought through discussions. If consensus is not met, a third reviewer (AW) will take the decision.

Data synthesis and statistical methods

We plan a network meta-analysis to assess which treatment for PFP is most effective. Networks of treatment comparisons will be constructed for the primary and (each) secondary outcome separately. Three authors (MW, SH, MSR) will appraise the clinical homogeneity before any analysis is commenced, by tabulating study and population characteristics and inspecting them for differences in potential effect modifiers. This is to assess the assumption of exchangeability required for network meta-analysis. In addition, treatments will be assigned to a class, e.g. exercise therapy, surgery, drug therapy.

Bayesian network meta-analysis

We will model networks following the Bayesian approach, using Markov chain Monte Carlo simulations in WinBUGS (v1.4, Medical Research Council, United Kingdom, and Imperial College of Science, Technology and Medicine, University of Cambridge, United Kingdom). Direct, pair-wise comparisons will be estimated first. For treatments that are connected in a network of comparisons from our included studies, we will estimate relative treatment effects using network meta-analysis, and hierarchical network meta-analysis using classes if possible.[26, 27] Continuous outcomes will be presented as mean difference (MD), with their 95% credible intervals when outcomes are measured with the same instrument. We will present standardised MDs if different continuous measures are used to evaluate the same construct. We will fit both fixed and random effects models and compare model fit using the deviance information criterion and posterior mean residual deviance. A lower deviance depicts a better model fit. We will group outcome follow-ups based on the available data, seeking the following approximate timeframes; 6-12 weeks, 13 – 52 weeks and >52 weeks. If there are multiple time points available for an outcome, and these are equally close to the time point to be synthesised across studies, the last follow-up in this timeframe will be used. For >52 weeks, a slightly different approach will be followed, where multiple time points will be synthesized following available

data. We will make attempts to model a time-course function for pain scales instead of analysis for multiple timeframes, if possible.

Surface under the cumulative ranking curves (SUCRAs) and probability ranks will be used to estimate the likelihood of individual treatments being superior than the other treatments for the individual with PFP.

Assessing statistical heterogeneity and exploring it with individual patient data

Statistical heterogeneity will be assessed by inspecting the between study standard deviation, comparing fit of the fixed and random effect models. Depending on resources and data availability, individual patient data from a previous randomised controlled trial by our group, will be used together with study level data to explore statistical heterogeneity.[28] Otherwise, only study level data will be used. The following factors are considered for exploration when sufficient data are available (>10 studies/events per variable), in the following order: diagnostic approach used (clinical vs imaging), pain intensity, symptom duration, active or sedentary population, age, sex (male/female), quality of life, uni- versus bilateral pain and publication status (published/unpublished).[29, 30]

Exploring inconsistency in the network

The consistency assumption will be tested for each network. We will compare results from a model that assumes consistency with a model that relaxes the consistency assumption, to assess whether there is evidence of inconsistency. For this purpose, we will compare the models' residual deviance and deviance information criterion to examine model fit. If we identify evidence of inconsistency, we will use the node-split method to identify where in the network the inconsistency is.[31] We will use a Bonferroni correction for interpreting multiple P-values.

Assessing small study bias

Where possible, we will use comparison-adjusted funnel plots to examine small study bias. In this case, we assume that small study bias is consistent across comparisons, and experimental treatments are more likely to be favoured in small studies compared to control treatments/groups. The funnel plot will be evaluated for its distribution, where missing small studies are expected favouring the control treatment in the presence of small study bias. Funnel plots will be generated for each outcome, but

only when ≥10 studies are available. [32] Conventional funnel plots for pairwise comparisons are constructed if comparison-adjusted funnel plots cannot be constructed. [21]

Threshold analysis for credibility of the network meta-analysis' conclusions

Risk of bias in the pair-wise estimates may distort the reliability of the network's estimate, and can, therefore, affect the credibility of the network meta-analysis' conclusion. We will investigate if bias in the estimate for global rating of change and pain would change the posterior mean treatment effect, and hence, the recommended treatment based on the probability ranks.[33] We will perform a threshold analysis where the variance around the bias estimate is assumed to be 0. We assume bias for both measures to over or underestimate treatment effects by maximally 20%, following empirical estimations of bias by Page et al., Wood et al., and Armijo-Olivo et al. [34-36] The threshold analysis will be run with steps of 5%, to detect the level at which bias may attenuate rankings.

Administration, dissemination and updating the living systematic review

The living systematic review will be administered at the Research Unit for General Practice in Aalborg, and we plan to update the network meta-analysis for at least 5 years. The study started at 1 February 2018 and the expected completion date for its first version is 15 January 2019.The search and review process will be updated every 12 months, if needed. When new data has become available, we will update the analysis and present the updated findings at the website of Aalborg University. Here, we will also provide a plain-language summary for patients and clinicians dealing with PFP. If there is a change in conclusions, re-publication will be sought in an international peer-reviewed journal. We will seek presentation of the study results on national and international conferences, and we will submit the full text report for "open access" publication in an international peer-reviewed journal.

PERSPECTIVES

Systematic reviews should inform clinical practice and treatment decisions. When multiple treatments exist, traditional systematic reviews come short handed. Network meta-analysis is the only design that can study the comparative effectiveness of *all* available treatments for a condition. Patients and clinicians dealing with PFP are in urgent need of evidence rather than expert opinion-based guidance for the treatment of this often long-living condition. Network meta-analysis will rank treatments

according to their probability of being the most effective treatment. In this way, it directly informs the clinician and patient when making a shared decision-making on how to treat PFP. The 'living' nature of this network meta-analysis facilitates to make an informed shared dicision in clinical practice based on the latest Level 1 evidence.

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AUTHOR STATEMENT

MW, AW and MSR came up with the study idea. MW, SH, BV, AW and MSR designed the study. MW and CBL designed the risk of bias approach, MW, SH, NJW, DMC and MSR designed the statistical analysis plan. MW, SH and MSR drafted the manuscript. All authors provided feedback and gave important intellectual input. All authors read and consented to the content of the article.

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CONFLICTS OF INTEREST

MW receives funding outside this project from Trygfonden, a non-profit organization in Denmark. The funding body has no influence in the planning, execution or reporting of this study. NJW leads a research project in collaboration with Pfizer plc. Pfizer part-funds a junior researcher. The projects is purely methodological, using historical data on treatments for pain relief. NJW has no other conflicts. All other authors report to have no conflicts of interest.

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Supplementary file

Appendix 1: Sensitive search strategy in conventional and grey literature resources, and trial registers.

We used a mix of indexed and title & abstract terms to construct a sensitive search strategy for all databases, grey literature resources and trial registers and registries. Three team members (a clinical epidemiologist(MW), a physiotherapist(MSR) and a health & performance scientist(SH)) with extended experience in the field of PFP generated terms for PFP. We also consulted previous systematic reviews published in this field to find any relevant terms not identified by our team.[#1, 2]

We built up our search strategy in four steps:

1. Indexed terms for the condition
2. Free text terms for the anatomical region
3. Free text terms for symptoms (e.g. pain/dysfunction/injury/syndrome)
4. Indexed terms for the design (e.g. randomised controlled trials, cohort studies etc)
5. Free text terms for the design.

We used multiple synonyms to identify indexed terms for the condition, for each database if applicable. We scanned the term trees upwards to determine any term that was relevant and overlapping the field more broadly - and more appropriately. The indexed terms for the condition were then used as a first step in the search. The second step was the use of free text term for the condition. An extensive list of possible terms to describe the condition was used. First only the anatomical terms were used (step 2 of the search) which were then combined with synonyms for pain, and syndrome.

Free text terms were individually trialled in each database, to determine if these were actually yielding any hits, and if it yielded any hits, if they were covering patellofemoral pain. After this step we went down the list of conditions terms and built the search strategy.

References:

1. Matthews M, Rathleff MS, Claus A et al. Can we predict the outcome for people with patellofemoral pain? A systematic review on prognostic factors and treatment effect modifiers. Br J Sports Med. Epub 2016/Dec/13. doi: 10.1136/bjsports-2016-096545.
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Terms were removed when they did not yield additional hits to the existing search. The free text terms for the anatomical location were then combined by AND, with the free text terms for pain, syndrome etc.

Finally, we chose to restrict our search by the study design of interest (i.e. (synonyms for); RCT's. We searched for indexed terms for designs in each database. Relevant indexed terms for designs were then combined (with OR) with free text terms for design names. Lastly, this search was then combined with the initial steps of the search for each database.

During the search building process, OR and NOT were used to determine if an indexed or free text term added to the existing search strategy. The number of hits for each search was used to observe if the particular term yielded hits in addition to what was already found with the existing terms. As we aimed to search as sensitive as possible, we used all known terminology for the condition to find relevant papers. We listed our final search strategy for each database and briefly state which terms were left out of the search strategy along with the reasons for doing so.

EMBASE:

1. "patellofemoral pain syndrome"/exp
2. "anterior knee pain"/exp
3. patell*:ab,ti OR femoropatell*:ab,ti OR femoro-patell*:ab,ti OR retropatell*:ab,ti OR retro-patell*:ab,ti OR "anterior knee*":ab,ti OR peripatell*:ab,ti OR peri-patell*:ab,ti OR kneecap*:ab,ti
4. pain*:ab,ti OR sore*:ab,ti OR discomfort*:ab,ti OR arthralgia*:ab,ti OR dysfunction*:ab,ti OR injur*:ab,ti OR syndr*:ab,ti OR chondromalac*:ab,ti OR chondropath*:ab,ti OR disorder*:ab,ti
5. 'clinical trial'/de
6. randomised:ab,ti OR randomized:ab,ti OR randomly:ab,ti OR trial:ab,ti OR groups:ab,ti
7. # 1 OR #2
8. #3 AND #4
9. #5 OR #6
10. #7 OR #8
11. #9 AND #10

Excluded term(s) EMBASE	**Reason for exclusion**
'lateral compression syndrome*':ab,ti OR 'lateral facet syndrome*':ab,ti OR 'lateral pressure syndrome*':ab,ti OR 'lateral hyperpressure syndrome*':ab,ti OR 'odd facet syndrome*':ab,ti	1 irrelevant hit in addition to #1 OR #2 OR (#3 AND #4)
Patellofemoral OR patello-femoral	No relevant hits in additon to #3 - based on title and abstract screening
'knee malalignment'	No relevant hits in additon to #3 - based on title and abstract screening
'randomized controlled trial/de	Included in 'clinical trial'/de

Pubmed (including MEDLINE)

1. "Patellofemoral Pain Syndrome"[Mesh]
2. "Chondromalacia Patellae"[Mesh]
3. patell*[tiab] OR femoropatell*[tiab] OR retropatell*[tiab] OR "anterior knee*"[tiab] OR peripatell*[tiab] OR "kneecap"[tiab] OR patellofemoral[tiab] OR patello-femoral[tiab]
4. pain*[tiab] OR sore*[tiab] OR discomfort*[tiab] OR arthralgia*[tiab] OR dysfunction*[tiab] OR injur*[tiab] OR syndr*[tiab] OR chondromalac*[tiab] OR chondropath*[tiab] OR disorder*[tiab]
5. "controlled clinical trial"[Publication Type]
6. randomised[tiab] OR randomized[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]
7. #1 OR #2
8. #3 AND #4
9. #5 OR #6
10. #7 OR #8
11. #9 AND #10

Excluded term(s) Pubmed	Reason for exclusion
femoro-patell*[tiab]	Does not add to "patell*[tiab] OR femoropatell*[tiab]"
retro-patell*[tiab]	Does not add to "patell*[tiab] OR femoropatell*[tiab]" OR retropatell*[tiab]
peri-patell*[tiab]	Does not add to "patell*[tiab] OR femoropatell*[tiab]" OR retropatell*[tiab] OR "anterior knee*"[tiab] OR peripatell*[tiab]
"knee malalignment"[tiab]	No relevant hits in additon to #3 - based on title and abstract screening
"lateral compression syndrome*"[tiab] OR "lateral facet syndrome*"[tiab] OR "lateral pressure syndrome*"[tiab] OR "lateral hyperpressure syndrome*"[tiab] OR "odd facet syndrome*"[tiab]	1 irrelevant hit in addition to #3

CENTRAL

1. MeSH descriptor: [Patellofemoral Pain Syndrome] explode all trees
2. MeSH descriptor: [Chondromalacia Patellae] explode all trees
3. patell*:ti,ab OR femoropatell*:ti,ab OR retropatell*:ti,ab OR "anterior knee*":ti,ab OR peripatell*:ti,ab OR "kneecap*":ti,ab
4. pain*:ti,ab OR sore*:ti,ab OR discomfort*:ti,ab OR arthralgia*:ti,ab OR dysfunction*:ti,ab OR injur*:ti,ab OR syndr*:ti,ab OR chondromalac*:ti,ab OR chondropath*:ti,ab OR disorder*:ti,ab
5. MeSH descriptor: [Controlled Clinical Trial] explode all trees
6. randomised:ti,ab OR randomized:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab
7. # 1 OR #2
8. #3 AND #4
9. #5 OR #6
10. #7 OR #8
11. #9 AND #10

Excluded term(s) CENTRAL	**Reason for exclusion**
femoro-patell*:ti,ab	Did not add to #3
retro-patell*:ti,ab	Did not add to #3
peri-patell*: ti,ab	Did not add to #3
patellofemoral:ti,ab	Did not add to #3
patello-femoral:ti,ab	Did not add to #3
"lateral compression syndrome*":ti,ab or "lateral facet syndrome*":ti,ab or "lateral pressure syndrome*":ti,ab or "lateral hyperpressure syndrome*":ti,ab or "odd facet syndrome*":ti,ab	Did not add to #1, #2 and #5
knee malalignment":ti,ab	No relevant hits (n= 7) in addition to #3

SCOPUS

1. (TITLE-ABS-KEY (patella*)) OR (TITLE-ABS-KEY (patellofemoral)) OR (TITLE-ABS-KEY (patello-femoral)) OR (TITLE-ABS-KEY (femoropatell*)) OR (TITLE-ABS-KEY (femoro-patell*)) OR (TITLE-ABS-KEY (retropatell*)) OR (TITLE-ABS-KEY (kneecap*)) OR (TITLE-ABS-KEY (retro-patell*)) OR (TITLE-ABS-KEY ("anterior knee*")) OR (TITLE-ABS-KEY (peripatell*)) OR (TITLE-ABS-KEY (peri-patell*)) OR (TITLE-ABS-KEY (peri-patell*)) OR (TITLE-ABS-KEY ("lateral compression syndrome*")) OR (TITLE-ABS-KEY ("lateral facet syndrome*")) OR (TITLE-ABS-KEY ("lateral pressure syndrome*")) OR (TITLE-ABS-KEY ("lateral hyperpressure syndrome*")) OR (TITLE-ABS-KEY ("odd facet syndrome*"))
2. (TITLE-ABS-KEY (pain*)) OR (TITLE-ABS-KEY (sore*)) OR (TITLE-ABS-KEY (discomfort*)) OR (TITLE-ABS-KEY (arthralgia*)) OR (TITLE-ABS-KEY (dysfunction*)) OR (TITLE-ABS-KEY (injur*)) OR (TITLE-ABS-KEY (syndr*)) OR (TITLE-ABS-KEY (chondromalac*)) OR (TITLE-ABS-KEY (chondropath*)) OR (TITLE-ABS-KEY (disorder*))
3. (TITLE-ABS-KEY (randomised)) OR (TITLE-ABS-KEY (randomized)) OR (TITLE-ABS-KEY (randomly) OR (TITLE-ABS-KEY (trial)) OR (TITLE-ABS-KEY (groups))
4. #1 AND #2
5. #4 AND #3

Excluded term Scopus	Reasons for exclusion
TITLE-ABS-KEY ("chondromalacia patellae")	Did not add hits to #1
TITLE-ABS-KEY ("patellofemoral pain syndrome")	Did not add hits to #1
TITLE-ABS-KEY ("anterior knee pain")	Did not add hits to #1

Web of Science

1. TS=(patell* OR femoropatell* OR femoro-patell* OR retropatell* OR retro-patell* OR "anterior knee*" OR peripatell* or peri-patell* OR "kneecap" OR patellofemoral OR patello-femoral OR "lateral compression syndrome*" OR "lateral facet syndrome*" OR "lateral pressure syndrome*" OR "lateral hyperpressure syndrome*" OR "odd facet syndrome*")

2. TS=(pain* OR sore* OR discomfort* OR arthralgia* OR dysfunction* OR injur* OR syndr* OR chondromalac* OR chondropath* OR disorder*)

3. TS=(randomised OR randomized OR randomly OR trial OR groups)
4. #1 AND #2
5. #3 AND #4

Excluded term(s) Web of Science	**Reason for exclusion**
TS=("Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain") OR	Did not add hits to #4

CINAHL (via EBSCOhost)

1. (MH "Patellofemoral Pain Syndrome")
2. (MH "Chondromalacia Patella")
3. TI patell* OR AB patell* OR TI "anterior knee*" OR AB "anterior knee*" OR TI femoropatell* OR AB femoropatell* OR TI retropatell* OR AB retropatell* OR TI peripatell* OR AB peripatell* OR TI "kneecap" OR AB "kneecap"
4. TI pain* OR AB pain* OR TI sore* OR AB sore* OR TI discomfort* OR AB discomfort* OR TI arthralgia* OR AB arthralgia* OR TI dysfunction* OR AB dysfunction* OR TI injur* OR AB injur* OR TI syndr* OR AB syndr* OR TI chondromalac* OR AB chondromalac* OR TI chondropath* OR AB chondropath* OR TI disorder* OR AB disorder*
5. MH "Clinical Trials"
6. TI “randomised" OR AB "randomised" OR TI "randomized" OR AB "randomized" OR TI "randomly" OR AB "randomly" OR TI "trial" OR AB "trial" OR TI "groups" OR AB "groups"
7. S1 OR S2
8. S3 AND S4
9. S5 OR S6
10. S7 OR S8
11. S9 AND S10

Excluded term(s) CINAHL	**Reason for exclusion**
TI femoro-patell* OR AB femoro-patell*	Did not add to #3
TI retro-patell* OR AB retro-patell*	Did not add to #3
TI patellofemoral OR AB patellofemoral	Did not add to #3
TI patello-femoral OR AB patello-femoral	Did not add to #3
TI peri-patell* OR AB peri-patell*	Did not add to #3
TI "lateral compression syndrome*" OR AB "lateral compression syndrome*" OR TI "lateral facet syndrome*" OR AB "lateral facet syndrome*" OR TI "lateral pressure syndrome*" OR AB "lateral pressure syndrome*" OR TI "lateral hyperpressure syndrome*" OR AB "lateral hyperpressure syndrome*" OR TI "odd facet syndrome*" OR AB "odd facet syndrome*	Did not add to #3

SPORTDiscus (via EBSCOhost)

1. DE "PLICA syndrome"
2. DE "CHONDROMALACIA patellae"
3. DE "PATELLA -- Diseases"
4. TI patell* OR AB patell* OR TI "anterior knee*" OR AB "anterior knee*" OR TI femoropatell* OR AB femoropatell* OR TI retropatell* OR AB retropatell* OR TI peripatell* OR AB peripatell* OR TI "kneecap" OR AB "kneecap"
5. TI pain* OR AB pain* OR TI sore* OR AB sore* OR TI discomfort* OR AB discomfort* OR TI arthralgia* OR AB arthralgia* OR TI dysfunction* OR AB dysfunction* OR TI injur* OR AB injur* OR TI syndr* OR AB syndr* OR TI chondromalac* OR AB chondromalac* OR TI chondropath* OR AB chondropath* OR TI disorder* OR AB disorder*
6. TI "randomised" OR AB "randomised*" OR TI "randomized" OR AB "randomized" OR TI "randomly" OR AB "randomly" OR TI "trial" OR AB "trial" OR TI "groups" OR AB "groups"
7. #1 OR #2 OR #3
8. #4 AND #5
9. #7 OR #8
10. #6 AND #9

Excluded term(s)	Reason for exclusion
TI femoro-patell* OR AB femoro-patell*	Did not add to #3
TI retro-patell* OR AB retro-patell*	Did not add to #3
TI patellofemoral OR AB patellofemoral	Did not add to #3
TI patello-femoral OR AB patello-femoral	Did not add to #3
TI peri-patell* OR AB peri-patell*	Did not add to #3
TI "lateral compression syndrome*" OR AB "lateral compression syndrome*" OR TI "lateral facet syndrome*" OR AB "lateral facet syndrome*" OR TI "lateral pressure syndrome*" OR AB "lateral pressure syndrome*" OR TI "lateral hyperpressure syndrome*" OR AB "lateral hyperpressure syndrome*" OR TI "odd facet syndrome*" OR AB "odd facet syndrome*"	Did not add to #3

Nb. "patellofemoral pain syndrome" is mapped under "plica syndrome" in SPORTDiscus.

Grey literature resources

OpenGrey:

1. ("Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain")
2. ((patell* OR femoropatell* OR femoro-patell* OR retropatell* OR retro-patell* OR "anterior knee*" OR peripatell* or peri-patell* OR "knee cap" OR patellofemoral OR patello-femoral OR "lateral compression syndrome" OR "lateral facet syndrome" OR "lateral pressure syndrome" OR "lateral hyperpressure syndrome" OR "odd facet syndrome") AND (pain* OR sore* OR discomfort* OR arthralgia* OR dysfunction* OR injur* OR syndr* OR chondromalac* OR chondropath* OR disorder*))
3. #1 OR #2

Nb. We did not limit this search with design names as there is a a low number of hits expected wih these initial steps.

Worldcat.org

(kw:(patellofemoral pain) OR kw:("anterior knee pain") OR kw:(chondromalacia patellae))
AND ti:(rct OR randomized OR randomised)
nb. A comprehensive search in this search engine yields 100.000s hits. Therefore, we restricted the search to the most important terms and restricted the search by using design terms.

TRIAL REGISTRERS

ClinicalTrials.gov

"Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain" OR patellofemoral

Excluded terms in final search	Reasons for exclusion
Patell†	No hits in addition to "patellofemoral pain syndrome"
Femoropatell†	No hits in addition to "patellofemoral pain syndrome"
femoro-patell†	No hits in addition to "patellofemoral pain syndrome"
Retropatell†	No hits relevant to the topic - not already identified by "patellofemoral pain syndrome"
retro-patell†	No hits relevant to the topic - not already identified by "patellofemoral pain syndrome"
"anterior knee"	No hits in addition to ("patellofemoral pain syndrome" OR "anterior knee pain")
peripatell†	No hits relevant to the topic - not already identified by "patellofemoral pain syndrome"
peri-patell†	One irrelevant hit
"kneecap"	17 hits - all on instability, dislocation etc.
patello-femoral	Did not add hits to patellofemoral
"lateral compression syndrome†"	No hits
"lateral facet syndrome†"	No hits
"lateral pressure syndrome†"	No hits
"lateral hyperpressure syndrome†"	No hits
"odd facet syndrome†"	No hits

N.b. There is only a limited search space in Clinicaltrials.gov. Therefore, we aimed to minimize the search in length as much as possible. **† =** The *, as used in conventional databases, is not an explode function in Clinicaltrials.gov. To the best of our knowledge no explode function exists in this trial register. We therefore trialled all endings to these words separately. E.g. patell* we tried -o/-a and -ar and =s for syndromes. Then we observed if these would yield relevant hits. If not, the term was deleted from the search strategy.

We refrained from using the symptom terms(e.g. pain, discomfort) as we only had one free text term (i.e. patellofemoral) that had 52 hits on top of the "Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain" search. We also left out the study design restriction as most of the studies registered in this register are controlled trials.

The European Union Clinical Trial Register

1. patella OR patellar

Excluded terms in final search	Reasons for exclusion
"Patellofemoral Pain Syndrome"	No hits
"Chondromalacia Patellae"	No hits
"anterior knee pain"	No hits
patellofemoral	No hits
Femoropatell†	No hits
femoro-patell†	No hits
Retropatell†	No hits
retro-patell†	No hits
"anterior knee"	No hits
peripatell†	No hits
peri-patell†	No hits
"kneecap"	No hits
patello-femoral	No hits
"lateral compression syndrome†"	No hits
"lateral facet syndrome†"	No hits
"lateral pressure syndrome†"	No hits
"lateral hyperpressure syndrome†"	No hits
"odd facet syndrome†"	No hits

N.b. Similarly to Clinicaltrials.gov, we checked the condition terms first individually. †= The *, as used in conventional databases, is not an explode function in this register. To the best of our knowledge no explode function exists in this trial register. We therefore trialled all endings to these words separately. E.g. patell* we tried -o/-a and -ar and =s for syndromes. Then we observed if these would yield relevant hits. If not, the term was deleted from the search strategy.

We refrained from using any restriction (with symptom terms (e.g. pain, discomfort) or design restriction (e.g. RCT) as we only expect a low number of hits after the first step of the search.

ISRCTN registry

"Patellofemoral Pain Syndrome" OR "anterior knee pain" OR patello OR patella OR patellar OR femoropatellar OR "anterior knee" OR "kneecap" OR patellofemoral

Excluded terms in final search	Reasons for exclusion
"Chondromalacia Patellae"	no hits
femoropatello	no hits
femoropatella	no hits
femoro-patell†	No hits for -a/-o/-ar
retropatell†	no hits in addition to "Patellofemoral Pain Syndrome" OR "anterior knee pain" OR patello OR patella OR patellar OR femoropatellar
retro-patell†	no hits
peripatell†	no hits
peri-patell†	no hits
patello-femoral	no hits in addition to "Patellofemoral Pain Syndrome" OR "anterior knee pain" OR patello OR patella OR patellar OR femoropatellar OR "anterior knee" OR "kneecap" OR patellofemoral
"lateral compression syndrome"	no hits
"lateral facet syndrome"	no hits
"lateral pressure syndrome"	no hits
"lateral hyperpressure syndrome"	no hits
"odd facet syndrome"	no hits

N.b. Similarly to Clinicaltrials.gov and the European Union clinical trial register, we checked the condition terms first individually.†= The *, as used in conventional databases, this is not an explode function in this register. To the best of our knowledge no explode function exists in this trial register. We therefore trialled all endings to these words separately. E.g. patell* we tried -o/-a and -ar and then observed if these would yield relevant hits. If not, the term was deleted from the search strategy. We refrained from using any restriction (with symptom terms (e.g. pain, discomfort) or design restriction (e.g. RCT) as we expect a low number of hits after the first step of the search.

WHO international Clinical Trials Registry Platform

"Patellofemoral Pain Syndrome" OR "anterior knee pain" OR "patella pain" OR "patella chondromalac*"

Excluded terms in final search	Reasons for exclusion
"Chondromalacia Patellae"	No hits
Femoropatell*	No hits in addition to patell*
Femoro-patell*	No hits in addition to patell*
Retropatell*	No hits in addition to patell*
Retropatell*	No hits in addition to patell*
Peripatell*	No hits in addition to patell* OR "anterior knee"
Peri-patell*	No hits in addition to patell* OR "anterior knee"
Kneecap*	No hits in addition to patell* OR "anterior knee"
Patellofemoral	No hits in addition to patell* OR "anterior knee"
Patello-femoral	No hits in addition to patell* OR "anterior knee"
"Lateral compression syndrome*"	No hits
"Lateral facet syndrome*"	No hits
"Lateral pressure syndrome*"	No hits
"lateral hyperpressure syndrome*"	No hits
"Odd facet syndrome*"	No hits
"patellar pain*"	No hits
"patellar sore*"	No hits
"patellar discomfort*"	No hits
"patellar arthralgia*"	No hits
"patellar dysfunction*	No hits
"patellar injur*"	No hits
"patellar syndr*"	No hits
"patellar chondromalac*"	No hits
"patellar chondropath*"	No hits
"patello pain*"	No hits
"patello sore*"	No hits
"patello discomfort*"	No hits
"patello arthralgia*"	No hits
"patello dysfunction*"	No hits
"patello injur*"	No hits
"patello syndr*"	No hits
"patello chondromalac*"	No hits
"patello chondropath*"	No hits
"patella sore*"	No hits
"patella discomfort*"	No hits

"patella arthralgia*"	No hits
"patella dysfunction*"	No hits
"patella injur*"	No hits
"patella syndr*"	No hits
"patella chondropath*"	No hits
"patellar arthralgia*"	No hits

Appendix 2: Data collection form for RCTs

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Report ID	
Report ID of other reports of this study including errata or retractions	
Notes	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised controlled trial	☐	☐	☐	
	Quasi-randomised controlled trial	☐	☐	☐	
Type of population		☐	☐	☐	
Types of intervention		☐	☐	☐	
Types of comparison		☐	☐	☐	
Types of outcome measures		☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper		Location in text or source *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*			
Design *(e.g. parallel, crossover, non-RCT)*			
Unit of allocation *(by individuals, cluster/ groups or body parts)*			
Start date			
End date			
Duration of participation *(from recruitment to last follow-up)*			
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear		
Notes:			

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source *(pg & ¶/fig/table/other)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method of making the diagnosis PFP		

Method of recruitment of participants *(e.g. phone, mail, clinic patients)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Total no. randomised *(or total pop. at start of study for non-RCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Severity of illness (pain at baseline)		
Co-morbidities/concurrent pain conditions/injuries		
Other relevant factors, specifically: • Quality of life • Social economic status (any indicator, e.g. income) • Duration of symptoms • Active/sedentary population • Uni- vs. bilateral pain		
Subgroups measured		
Subgroups reported		
Notes:		

Intervention groups

Intervention Group 1

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components, location, physical or informational materials used))**		
Delivery *(e.g. modes of delivery, mechanism, medium, intensity, fidelity, procedure)**		
Tailoring (was the intervention planned to be personalise/titrated/adapted then describe: What, why when and how)#		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Providers *(e.g. no., profession, expertise, specific training given, etc. if relevant)**		
Co-interventions		
Did any treatment modification occur during the study? If yes, describe changes in the intervention (what, why, when and how)#		
Adherence		
Notes:		

* Item added from Tidier checklist[23], # Item modified following the Tidier checklist [23]

Intervention Group 2

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components, location, physical or informational materials used))**		
Delivery *(e.g. modes of delivery, mechanism, medium, intensity, fidelity, procedure)**		
Tailoring (was the intervention planned to be personalise/titrated/adapted then describe: What, why when and how)#		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Providers *(e.g. no., profession, expertise, specific training given, etc. if relevant)**		
Co-interventions		
Did any treatment modification occur during the study? If yes, describe changes in the intervention (what, why, when and how)#		
Adherence		
Notes:		

* Item added from Tidier checklist[23], # Item modified following the Tidier checklist [23]

Outcomes

Outcome X

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Outcome name		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/ reporting		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Power *(e.g. power & sample size calculation, level of power achieved)*		
Notes:		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		

Data and analysis
Outcome X

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome					
Subgroup					
Time point *(specify from start or end of intervention)*					
No. participant	Intervention		Control		
Results List per outcome descriptor: "Completely recovered Strongly recovered Slightly recovered Unchanged Slightly worse Much worse Worse than ever"	Intervention Number	%	Control Number	%	
Overall results	Overall results (success yes/no): Succes = completely recovered + strongly recovered No success = other options Number (%) per group: Intervention: Control: Relative estimate(s), e.g. RR/Risk reduction:				
Any other results reported					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these					
Reanalysis required? *(specify)*	☐ Yes ☐ No ☐ Unclear				
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear				
Reanalysed results					

Notes:

Other information

	Description as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2/P6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	P14
Sponsor	5b	Provide name for the review funder and/or sponsor	P14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P6-7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp online material 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P9

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Pg-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	pg
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	pg-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	pg-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P11-12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P12-13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n4
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Which treatment is most effective for patients with patellofemoral pain? A protocol for a living systematic review including network meta-analysis

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Primary Subject Heading:	General practice / Family practice
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Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, SPORTS MEDICINE

Which treatment is most effective for patients with patellofemoral pain? A protocol for a living systematic review including network meta-analysis

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Word count abstract: 291

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ABSTRACT

Introduction Patellofemoral pain (PFP) affects 1 in every 14 adults. Many treatments for PFP have been evaluated, but the comparative effectiveness of all available treatments has never been examined. Network meta-analysis is the only design to study the comparative effectiveness of all available treatments in one synthesis. This protocol describes the methods for a systematic review including network meta-analysis, to assess which treatment is most likely to be effective for patients with PFP.

Methods and analysis The primary outcome measures of this network meta-analysis are the global rating of change scale at 6-12 weeks, 13 – 52 weeks and >52 weeks. The secondary outcome measures are patient-rated pain scales at 6-12 weeks, 13 – 52 weeks and >52 weeks. Completed published and unpublished randomised controlled trials with full text reports are eligible for inclusion. We will search EMbase, Pubmed (including MEDLINE), CENTRAL, Scopus, Web of Science, and CINAHL, SPORTDiscus, OpenGrey, Worldcat, Conference Proceedings and multiple trial registers for relevant reports. Two researchers will appraise the study eligibility and perform data extraction. Risk of bias will be assessed with the Cochrane Risk of Bias Tool v.2.0.

Bayesian network meta-analyses will be constructed for global rating of change scale and patient-rated pain. Consistency between direct and indirect comparisons will be assessed. Between study variability will be explored and a threshold analysis for the credibility of the network meta-analyses' conclusions will be performed.

Ethics and dissemination Ethical approval is not required, as this study will be based on published data. The study commenced at 1 February 2018 and its expected completion date is 15 January 2019. Full publication of the work will be sought in an international peer-reviewed journal, as well as translational articles to disseminate the work to clinical practitioners.

PROSPERO registration number: CRD42018079502

Keywords: Patellofemoral pain, knee cap, network meta-analysis, evidence synthesis, ranking

ARTICLE SUMMARY

Strengths and limitations of this study

- This living systematic review will include thorough search methods, searching conventional databases, grey literature resources and trial registers.
- Risk of bias in randomised controlled trials will be appraised using the new Cochrane Risk of Bias tool, v2.0, for intervention studies.
- This living systematic review and network meta-analysis enables clinicians to consult a contemporary, comprehensive overview of the comparative effectiveness of treatments for patellofemoral pain.
- The feasibility of this study is depending on the availability and the homogeneity of the trials and the consistency between direct and indirect evidence.

INTRODUCTION

Patellofemoral pain (PFP) affects 1 in every 14 adolescents and 1 in every 8 adults.[1] PFP is characterised by diffuse pain around or behind the knee cap, provoked during activities which load the knee-joint, such as stair climbing, running and jumping.[2] One in every two patients with PFP continue to suffer from knee pain, which can impact their quality of life, and physical activity.[3,4]

Similar to other chronic musculoskeletal pain conditions, there are many different treatments. Recent recommendations from an expert panel based on the available evidence are for the use of exercise of the hip and knee, foot orthoses and combinations that include patellar taping or manual therapy.[5] Patient education and gait retraining have been recently promoted as well, but with little research support.[5, 6] While there are several systematic reviews that focus on different treatments for PFP,[7-12] the comparative effectiveness of all available treatments has never been examined. This is challenging for clinicians and patients, who are faced with uncertainty when presented with so many potentially beneficial treatment options.

Traditional systematic reviews present fragmented pairwise 'head to head' comparisons, e.g. treatment A versus B, and treatment B versus C. The limitation with this approach is that multiple treatments cannot be compared simultaneously (i.e. treatment A versus B versus C). The traditional approach may lead to invalid interpretations regarding the comparative effectiveness of treatments.[13] Clinicians are left to speculate on which treatment is most effective, based on multiple, independent 'head to head' comparisons. Network meta-analyses offer the opportunity to combine both direct and indirect treatment comparisons in a single analysis, which overcomes main limitations of pairwise systematic reviews. They do this by allowing for:

- a coherent comparison of effectiveness of multiple treatments in one statistical model, while maintaining the randomised nature of the evidence, and
- comparison of treatments even if the treatments have not been investigated directly in a randomised controlled trial.[14-16]

Based on the network meta-analysis, a ranking from "most likely to be effective" to "least likely to be effective" treatment (for a given outcome) can be estimated. In this way, the results from the network meta-analysis can directly feed into shared decision-making in clinical practice.

A common critique on systematic reviews is that they are soon out-of-date.[17] Living network meta-analysis are particularly suitable to control for this issue as they are regularly updated, preferably as open access content. This enables clinicians to consult a comprehensive overview of the comparative effectiveness of treatments for a given condition, while ensuring a contemporary evidence synthesis for clinical practice (Table 1).[18, 19].

The comparative effectiveness of all studied treatments for patients with PFP has never been examined. The aim of this living systematic review with network meta-analysis is to evaluate the comparative effectiveness of all available treatments for patients with PFP, providing a comprehensive and up-to-date overview of evidence-based treatments.

	Traditional systematic review + meta-analysis	**Systematic review + NMA**	**Living systematic review + NMA**
Direct comparison between treatments	X	X	X
Indirect comparisons between treatments that have never been compared in a RCT		X	X
Research question • Which treatment is most effective, A or B? • Which of the many available treatments that have been tested in randomised trials are most effective?	X	X X	X X
Always-up-to-date best evidence synthesis to inform clinical practice			X

Table 1. The advantages of a living network meta-analysis compared to traditional systematic reviews

NMA = network meta-analysis, RCT = randomised controlled trial

METHODS

Protocol registration

The protocol for this living systematic review with network meta-analysis is registered on PROSPERO [CRD42018079502]. This protocol follows the PRISMA-P and PRISMA extension for network meta-analysis checklist for reporting systematic review protocols and network meta-analysis.[20-22]

Patient involvement & prioritising outcomes

Patients with PFP (N=7) from a patient reference group have been involved in setting a hierarchy of outcomes (global rating of change scale and pain scales) for this network meta-analysis. One researcher, otherwise not involved in the study (see acknowledgements), contacted the patient panel members by phone. He explained the various outcomes. All participants were subsequently sent a list and asked to indicate the most relevant instrument to judge their knee pain. Six out of seven (86%) indicated a preference for the global rating of change scale over pain outcomes. Consequently, the outcomes selected are as follows:

Primary outcome measure:

- Global rating of change scale (GROC). This scale usually has 7 descriptors for perceived change: completely recovered, strongly recovered, slightly recovered, unchanged, slightly worse, strongly worse and worse than ever. The reliability of the GROC is excellent with intraclass correlation coefficient (ICC) from 0.90-0.99.[23, 24]

Secondary outcome measures:

- Pain intensity, measured by 'worst pain in the previous week' on a visual analogue scale (0-10/0-100) or numerical rating pain scale (0-10/0-100). The reliability is excellent, ICC = 0.76.[24, 25]
- Patient-rated pain during specific activities of daily life (ADL) and during sporting activities. We will synthesize one pain outcome for ADL, and one for sporting activities. The choice for these outcomes will be made based on availability; an outcome that allows for inclusion of the highest number of comparisons. Pain will be expressed a visual analogue scale (0-10/0-100) or numerical rating pain scale (0-10/0-100). Reliability for pain during activity is excellent, ICC = 0.83.[24, 25]

Research questions

1. Which treatment(s) is most likely to be effective for patients with PFP on global rating of change and patient-rated pain?
2. Which treatment class(es) is most likely to be effective for patients with PFP on global rating of change and patient-rated pain? The study of treatment classes is relevant when more than one subtype for a treatment is available, e.g. multiple types of exercise regimes, which can be grouped together to answer this question.

Eligibility criteria

Type of studies

Published or unpublished RCT's (including randomisation through minimisation, or clustering), for which a full-text report or full text protocol of a completed trial is available, are eligible for inclusion.

Type of population

All patients with a clinical diagnosis of PFP are included. Studies will be included if they use synonyms for PFP, but as minimum criterion, should describe patients with retropatellar or peri-patellar pain, of at least 6 weeks duration, and a non-traumatic onset. The diagnostic criteria used in the original studies, will be followed, given that the aforementioned minimal diagnostic criteria are met. Studies examining other conditions are excluded (e.g. patellar dislocations, patellofemoral osteoarthrosis, patellar tendinopathy, Osgood-Schlatter, iliotibial band syndrome, Sinding-Larsen-Johansson syndrome). Trials that include participants diagnosed with PFP, but with concomitant pain around the patella caused by other conditions (e.g. patellar tendinopathy) will be considered eligible for inclusion. No age restrictions will be imposed.

Type of treatments and control treatments

Any treatment, control treatment, placebo, wait-and-see, or no treatment group studied in a RCT is eligible for inclusion. Examples of treatment classes are exercise therapy, orthoses, braces, patient education, pain medicine or surgery.

Type of outcomes

Studies assessing the treatment effect after a minimum of 6 weeks will be included. Studies assessing the following outcomes will be included:

- Global rating of change scale
- Worst pain in the previous week, measured with a VAS (0-10) or NRPS (0-100).
- Patient-rated pain during activities of daily living and sporting activities, measured with a VAS (0-10) or NRPS (0-100).

Search strategy

A sensitive search strategy has been developed for each of the data sources by a research librarian and one investigator (MW). We used the Cochrane sensitive search strategy for RCTs and modified this for the purpose of our study.[26] The search strategy includes a mix of indexed and free text terms, where applicable (supplementary file, appendix 1). No restrictions (e.g. language or full-text availability) were applied to the search.

One investigator (MW) will search conventional databases, grey literature databases and trial registers from their date of inception. Supplementary file, appendix 1 provides a detailed explanation of how the search is built, and with source-specific search strategies for each database, grey literature sources and trial registers.

Conventional databases

Conventional electronic databases EMbase, Pubmed (including MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science, and CINAHL and SPORTDiscus (both via Ebsco) will be searched for relevant reports.

Identifying grey literature and ongoing studies

Databases

OpenGrey.eu and WorldCat.org will be searched for studies that have remained unpublished.

Conference proceedings

We will search the conference proceedings from all Patellofemoral Research Retreats (2009, 2011, 2013, 2015 and 2017) for relevant reports and request authors to make available their full reports or protocols for unpublished studies.

Trial registers

We will search the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) Clinical Trials.gov, The European Union Clinical Trials Register and the ISRCTN registry for unpublished or ongoing studies.

Hand searching

We will screen reference lists of all Cochrane Reviews (N=6) on PFP for possible relevant studies that were not identified by our search. We will also screen reference lists of all the reports included in our systematic review.

Study selection

Two researchers will screen titles and abstracts independently, after duplicate removal by one of the investigators. Consensus will be sought in case of initial disagreement. If consensus cannot be reached, the report will be included for full text evaluation.

Both investigators will independently apply inclusion and exclusion criteria to the full text reports. In case of disagreement, consensus will be sought, however, if disagreement persists a third author (AW) will take the decision.

Data extraction

Data will be independently extracted by two researchers using standardised extraction forms adopted from the Cochrane Collaboration (see supplementary file, appendix 2).[27] Disagreements will be resolved by seeking consensus, and by a third reviewer (AW) in case of persistent disagreement. The following data will be extracted:

- Publication and study details: E.g. authors, year of publication, funding source, possible conflicts of interest, aim study, design, unit of allocation
- Population: Number of included patients, population characteristics for age, sex, body mass index, activity level, setting where population was recruited, baseline scores for outcome measures

(mean, standard deviations (SDs), standard errors extracted for continuous outcomes, and number and percentage for categorical outcomes)

- Eligibility criteria and diagnostic criteria used for PFP
- Treatments: E.g. number randomised to group, detailed description of e.g. application, dose, intensity, frequency, number of sessions, delivery, tailoring (individual/group), duration of treatment, providers, co-treatments, modification (change to treatment), adherence. We used items from the Template for Intervention Description and Replication (TIDierR) checklist to assure comprehensive data extraction in this section of the extraction form.[28]
- Outcomes: time points measured, and the time points reported upon, outcome definition, person measuring, unit of measurement, scales (upper and lower limits), imputation of missing data, primary and secondary outcomes used in the original trials, unintentional outcomes (e.g. adverse events, adverse effects, side effects etc.).
- Data and analysis: comparisons, outcomes, subgroups, time points, results (central estimates and measures of dispersion; e.g. mean for both groups, mean difference, SD's/95 confidence intervals/standard errors), number of missing patients, statistical methods used and appropriateness of these.
- Other information: key conclusions of study authors

Risk of bias assessment

The Cochrane Risk of Bias Tool 2.0 will be used to assess the risk of bias for each outcome per study, and for outcomes across a (direct) comparison. In this tool risk of bias can be assessed following the "intention-to-treat" principle (i.e. assignment to intervention) or "per protocol" (i.e. adherence to intervention). We will assess risk of bias on the basis of "assignment to intervention". This new tool has a fixed set of items to use for the risk of bias appraisal, i.e. 'bias arising from the randomization process', 'bias due to deviations from intended interventions', 'bias due to missing outcome data', 'bias in measurement of the outcome', 'bias in selection of the reported result', and overall risk of bias judgement for each outcome.[29, 30]

Two experienced reviewers will independently assess the risk of bias for each outcome within the study, for each follow-up. They will trial the approach by assessing 20 RCT's in other musculoskeletal conditions, before the study starts. Each major domain of bias will be appraised in light of each

outcome. The tool's signalling questions and criteria will be followed to inform a domain-based appraisal of the risk of bias.[29, 30] The risk of distortion of the outcome estimate by the methodology will be appraised as at 'low', 'some' or 'high' risk of bias. Judgements will be made regarding the direction of distortion 'favours experimental', 'favours comparator', 'towards null', 'away from null', or 'unpredictable'. Each outcome within a study will receive an overall risk of bias judgement based on the individual domains; 'low', 'some' or 'high' risk of bias.[29, 30]

In case of disagreements between reviewers, consensus will be sought through discussions. If consensus is not met, a third reviewer (AW) will take the decision.

Data synthesis and statistical methods

We plan a network meta-analysis to assess which treatment for PFP is most effective. Networks of treatment comparisons will be constructed for the primary and (each) secondary outcome separately. Three authors (MW, SH, MSR) will appraise the clinical homogeneity before any analysis is commenced, by tabulating study and population characteristics and inspecting them for differences in potential effect modifiers. This is to assess the assumption of exchangeability required for network meta-analysis. In addition, treatments will be assigned to a class, e.g. exercise therapy, surgery, drug therapy.

Bayesian network meta-analysis

We will model networks following the Bayesian approach, using Markov chain Monte Carlo simulations in WinBUGS (v1.4, Medical Research Council, United Kingdom, and Imperial College of Science, Technology and Medicine, University of Cambridge, United Kingdom). Direct, pair-wise comparisons will be estimated first. For treatments that are connected in a network of comparisons from our included studies, we will estimate relative treatment effects using network meta-analysis, and hierarchical network meta-analysis using classes if possible.[31, 32]

Our primary outcome measure, the GROC, will be synthesized using a proportional odds model and expressed with an odds ratio (OR) and their 95% credible interval, if GROCs across studies are similar. Otherwise, GROCs will be dichotomized at a common cut-off point where all scales coincide, e.g. improved/not improved, recovered/not-recovered. In the latter case a logistic regression model will be run.

For our secondary outcome measures, continuous outcomes will be presented as mean difference (MD), with their 95% credible intervals when outcomes are measured with the same instrument. We will present standardised MDs if different continuous measures are used to evaluate the same construct.

For all analyses, we will fit both fixed and random effects models and compare model fit using the deviance information criterion and posterior mean residual deviance. A lower deviance depicts a better model fit. We will group outcome follow-ups based on the available data, seeking the following approximate timeframes; 6-12 weeks, 13 – 52 weeks and >52 weeks. If there are multiple time points available for an outcome, and these are equally close to the time point to be synthesised across studies, the last follow-up in this timeframe will be used. For >52 weeks, a slightly different approach will be followed, where multiple time points will be synthesized following available data. We will make attempts to model a time-course function for pain scales instead of analysis for multiple timeframes, if possible.

Surface under the cumulative ranking curves (SUCRAs) and probability ranks will be used to estimate the likelihood of individual treatments being superior than the other treatments for the individual with PFP.

Assessing statistical heterogeneity and exploring it with individual patient data

Statistical heterogeneity will be assessed by inspecting the between study standard deviation, comparing fit of the fixed and random effect models. Depending on resources and data availability, individual patient data from a previous randomised controlled trial by our group, will be used together with study level data to explore statistical heterogeneity.[33] Otherwise, only study level data will be used. The following factors are considered for exploration when sufficient data are available (>10 studies/events per variable), in the following order: diagnostic approach used (clinical vs imaging), pain intensity, symptom duration, active or sedentary population, age, sex (male/female), quality of life, uni- versus bilateral pain and publication status (published/unpublished).[34, 35]

Exploring inconsistency in the network

The consistency assumption will be tested for each network. We will compare results from a model that assumes consistency with a model that relaxes the consistency assumption, to assess whether

there is evidence of inconsistency. For this purpose, we will compare the models' residual deviance and deviance information criterion to examine model fit. If we identify evidence of inconsistency, we will use the node-split method to identify where in the network the inconsistency is.[36] We will use a Bonferroni correction for interpreting multiple P-values.

Assessing small study bias

Where possible, we will use comparison-adjusted funnel plots to examine small study bias. In this case, we assume that small study bias is consistent across comparisons, and experimental treatments are more likely to be favoured in small studies compared to control treatments/groups. The funnel plot will be evaluated for its distribution, where missing small studies are expected favouring the control treatment in the presence of small study bias. Funnel plots will be generated for each outcome, but only when ≥10 studies are available. [37] Conventional funnel plots for pairwise comparisons are constructed if comparison-adjusted funnel plots cannot be constructed. [26]

Threshold analysis for credibility of the network meta-analysis' conclusions

Risk of bias in the pair-wise estimates may distort the reliability of the network's estimate, and can, therefore, affect the credibility of the network meta-analysis' conclusion. We will investigate if bias in the estimate for global rating of change and pain would change the posterior mean treatment effect, and hence, the recommended treatment based on the probability ranks.[38] We will perform a threshold analysis where the variance around the bias estimate is assumed to be 0. We assume bias for both measures to over or underestimate treatment effects by maximally 20%, following empirical estimations of bias by Page et al., Wood et al., and Armijo-Olivo et al. [39-41] The threshold analysis will be run with steps of 5%, to detect the level at which bias may attenuate rankings.

Potential limitations of the planned work

Network meta-analysis allows multiple interventions to be compared simultaneously, and can form a coherent basis for intervention recommendations. Notwithstanding this, with any evidence synthesis, the quality of the planned work is dependent on the availability of study data and the comparisons investigated to allow the construction of a network. Network meta-analysis relies on connected networks of evidence - it is not possible to make comparisons between interventions that are

unconnected. The method assumes that the evidence is consistent, so that the intervention effects observed directly in head-to-head studies are in agreement with those obtained indirectly via the network of comparisons. It is therefore essential to check the consistency assumption when possible (i.e. both direct and indirect evidence are available). As with all evidence syntheses, the NMA estimates reflect the evidence available including the limitations in that evidence. Assessment of risk of bias of the included studies is therefore essential. Exploration of heterogeneity through sub-group analysis is limited by the evidence available with limited power to detect effects, and may suffer from aggregation bias. There are also limitations to the living nature of the proposed research. Living reviews are labour intensive and rely on regular updates. Moreover, the chance of type 1 errors, i.e. incorrectly concluding there is a significant effect in the meta-analysis, increases with the growing number of updates.

Administration, dissemination and updating the living systematic review

The living systematic review will be administered at the Research Unit for General Practice in Aalborg, and we plan to update the network meta-analysis for at least 5 years. The study started at 1 February 2018 and the expected completion date for its first version is 15 January 2019. The search and review process will be updated every 12 months, if needed. When new data has become available, we will update the analysis and present the updated findings at the website of Aalborg University. Here, we will also provide a plain-language summary for patients and clinicians dealing with PFP. If there is a change in conclusions, re-publication will be sought in an international peer-reviewed journal. We will seek presentation of the study results on national and international conferences, and we will submit the full text report for “open access” publication in an international peer-reviewed journal.

PERSPECTIVES

Systematic reviews should inform clinical practice and treatment decisions. When multiple treatments exist, traditional systematic reviews come shorthanded. Network meta-analysis is the only design that can study the comparative effectiveness of *all* available treatments for a condition. Patients and clinicians dealing with PFP are in urgent need of evidence rather than expert opinion-based guidance for the treatment of this often long-living condition. Network meta-analysis will rank treatments according to their probability of being the most effective treatment. In this way, it directly informs the clinician and patient when making a shared decision-making on how to treat PFP. The ‘living’ nature of

this network meta-analysis facilitates to make an informed shared decision in clinical practice based on the latest Level 1 evidence.

ETHICS AND DISSEMINATION

Ethical approval is not required, as this study will be based on published data. The study commenced at 1 February 2018 and its expected completion date is 15 January 2019. Full publication of the work will be sought in an international peer-reviewed journal, as well as translational articles to disseminate the work to clinical practitioners.

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AUTHOR STATEMENT

MW, AW and MSR came up with the study idea. MW, SH, BV, AW and MSR designed the study. MW and CBL designed the risk of bias approach, MW, SH, NJW, DMC and MSR designed the statistical analysis plan. MW, SH and MSR drafted the manuscript. All authors provided feedback and gave important intellectual input. All authors read and consented to the content of the article.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICTS OF INTEREST

MW receives funding outside this project from Trygfonden, a non-profit organization in Denmark. The funding body has no influence in the planning, execution or reporting of this study. NJW leads a research project in collaboration with Pfizer plc. Pfizer part-funds a junior researcher. The projects is

purely methodological, using historical data on treatments for pain relief. NJW has no other conflicts.

All other authors report to have no conflicts of interest.

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Supplementary file

Appendix 1: Sensitive search strategy in conventional and grey literature resources, and trial registers.

We used a mix of indexed and title & abstract terms to construct a sensitive search strategy for all databases, grey literature resources and trial registers and registries. Three team members (a clinical epidemiologist(MW), a physiotherapist(MSR) and a health & performance scientist(SH)) with extended experience in the field of PFP generated terms for PFP. We also consulted previous systematic reviews published in this field to find any relevant terms not identified by our team.[#1, 2]

We built up our search strategy in four steps:

1. Indexed terms for the condition
2. Free text terms for the anatomical region
3. Free text terms for symptoms (e.g. pain/dysfunction/injury/syndrome)
4. Indexed terms for the design (e.g. randomised controlled trials, cohort studies etc)
5. Free text terms for the design.

We used multiple synonyms to identify indexed terms for the condition, for each database if applicable. We scanned the term trees upwards to determine any term that was relevant and overlapping the field more broadly - and more appropriately. The indexed terms for the condition were then used as a first step in the search. The second step was the use of free text term for the condition. An extensive list of possible terms to describe the condition was used. First only the anatomical terms were used (step 2 of the search) which were then combined with synonyms for pain, and syndrome.

Free text terms were individually trialled in each database, to determine if these were actually yielding any hits, and if it yielded any hits, if they were covering patellofemoral pain. After this step we went down the list of conditions terms and built the search strategy.

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Terms were removed when they did not yield additional hits to the existing search. The free text terms for the anatomical location were then combined by AND, with the free text terms for pain, syndrome etc.

Finally, we chose to restrict our search by the study design of interest (i.e. (synonyms for); RCT's. We searched for indexed terms for designs in each database. Relevant indexed terms for designs were then combined (with OR) with free text terms for design names. Lastly, this search was then combined with the initial steps of the search for each database.

During the search building process, OR and NOT were used to determine if an indexed or free text term added to the existing search strategy. The number of hits for each search was used to observe if the particular term yielded hits in addition to what was already found with the existing terms. As we aimed to search as sensitive as possible, we used all known terminology for the condition to find relevant papers. We listed our final search strategy for each database and briefly state which terms were left out of the search strategy along with the reasons for doing so.

EMBASE:

1. "patellofemoral pain syndrome"/exp
2. "anterior knee pain"/exp
3. patell*:ab,ti OR femoropatell*:ab,ti OR femoro-patell*:ab,ti OR retropatell*:ab,ti OR retro-patell*:ab,ti OR "anterior knee*":ab,ti OR peripatell*:ab,ti OR peri-patell*:ab,ti OR kneecap*:ab,ti
4. pain*:ab,ti OR sore*:ab,ti OR discomfort*:ab,ti OR arthralgia*:ab,ti OR dysfunction*:ab,ti OR injur*:ab,ti OR syndr*:ab,ti OR chondromalac*:ab,ti OR chondropath*:ab,ti OR disorder*:ab,ti
5. 'clinical trial'/de
6. randomised:ab,ti OR randomized:ab,ti OR randomly:ab,ti OR trial:ab,ti OR groups:ab,ti
7. # 1 OR #2
8. #3 AND #4
9. #5 OR #6
10. #7 OR #8
11. #9 AND #10

Excluded term(s) EMBASE	**Reason for exclusion**
'lateral compression syndrome*':ab,ti OR 'lateral facet syndrome*':ab,ti OR 'lateral pressure syndrome*':ab,ti OR 'lateral hyperpressure syndrome*':ab,ti OR 'odd facet syndrome*':ab,ti	1 irrelevant hit in addition to #1 OR #2 OR (#3 AND #4)
Patellofemoral OR patello-femoral	No relevant hits in additon to #3 - based on title and abstract screening
'knee malalignment'	No relevant hits in additon to #3 - based on title and abstract screening
'randomized controlled trial/de	Included in 'clinical trial'/de

Pubmed (including MEDLINE)

1. "Patellofemoral Pain Syndrome"[Mesh]
2. "Chondromalacia Patellae"[Mesh]
3. patell*[tiab] OR femoropatell*[tiab] OR retropatell*[tiab] OR "anterior knee*"[tiab] OR peripatell*[tiab] OR "kneecap"[tiab] OR patellofemoral[tiab] OR patello-femoral[tiab]
4. pain*[tiab] OR sore*[tiab] OR discomfort*[tiab] OR arthralgia*[tiab] OR dysfunction*[tiab] OR injur*[tiab] OR syndr*[tiab] OR chondromalac*[tiab] OR chondropath*[tiab] OR disorder*[tiab]
5. "controlled clinical trial"[Publication Type]
6. randomised[tiab] OR randomized[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]
7. #1 OR #2
8. #3 AND #4
9. #5 OR #6
10. #7 OR #8
11. #9 AND #10

Excluded term(s) Pubmed	Reason for exclusion
femoro-patell*[tiab]	Does not add to "patell*[tiab] OR femoropatell*[tiab]"
retro-patell*[tiab]	Does not add to "patell*[tiab] OR femoropatell*[tiab]" OR retropatell*[tiab]
peri-patell*[tiab]	Does not add to "patell*[tiab] OR femoropatell*[tiab]" OR retropatell*[tiab] OR "anterior knee*"[tiab] OR peripatell*[tiab]
"knee malalignment"[tiab]	No relevant hits in additon to #3 - based on title and abstract screening
"lateral compression syndrome*"[tiab] OR "lateral facet syndrome*"[tiab] OR "lateral pressure syndrome*"[tiab] OR "lateral hyperpressure syndrome*"[tiab] OR "odd facet syndrome*"[tiab]	1 irrelevant hit in addition to #3

CENTRAL

1. MeSH descriptor: [Patellofemoral Pain Syndrome] explode all trees
2. MeSH descriptor: [Chondromalacia Patellae] explode all trees
3. patell*:ti,ab OR femoropatell*:ti,ab OR retropatell*:ti,ab OR "anterior knee*":ti,ab OR peripatell*:ti,ab OR "kneecap*":ti,ab
4. pain*:ti,ab OR sore*:ti,ab OR discomfort*:ti,ab OR arthralgia*:ti,ab OR dysfunction*:ti,ab OR injur*:ti,ab OR syndr*:ti,ab OR chondromalac*:ti,ab OR chondropath*:ti,ab OR disorder*:ti,ab
5. MeSH descriptor: [Controlled Clinical Trial] explode all trees
6. randomised:ti,ab OR randomized:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab
7. # 1 OR #2
8. #3 AND #4
9. #5 OR #6
10. #7 OR #8
11. #9 AND #10

Excluded term(s) CENTRAL	**Reason for exclusion**
femoro-patell*:ti,ab	Did not add to #3
retro-patell*:ti,ab	Did not add to #3
peri-patell*: ti,ab	Did not add to #3
patellofemoral:ti,ab	Did not add to #3
patello-femoral:ti,ab	Did not add to #3
"lateral compression syndrome*":ti,ab or "lateral facet syndrome*":ti,ab or "lateral pressure syndrome*":ti,ab or "lateral hyperpressure syndrome*":ti,ab or "odd facet syndrome*":ti,ab	Did not add to #1, #2 and #5
knee malalignment":ti,ab	No relevant hits (n= 7) in addition to #3

SCOPUS

1. (TITLE-ABS-KEY (patella*)) OR (TITLE-ABS-KEY (patellofemoral)) OR (TITLE-ABS-KEY (patello-femoral)) OR (TITLE-ABS-KEY (femoropatell*)) OR (TITLE-ABS-KEY (femoro-patell*)) OR (TITLE-ABS-KEY (retropatell*)) OR (TITLE-ABS-KEY (kneecap*)) OR (TITLE-ABS-KEY (retro-patell*)) OR (TITLE-ABS-KEY ("anterior knee*")) OR (TITLE-ABS-KEY (peripatell*)) OR (TITLE-ABS-KEY (peri-patell*)) OR (TITLE-ABS-KEY (peri-patell*)) OR (TITLE-ABS-KEY ("lateral compression syndrome*")) OR (TITLE-ABS-KEY ("lateral facet syndrome*")) OR (TITLE-ABS-KEY ("lateral pressure syndrome*")) OR (TITLE-ABS-KEY ("lateral hyperpressure syndrome*")) OR (TITLE-ABS-KEY ("odd facet syndrome*"))
2. (TITLE-ABS-KEY (pain*)) OR (TITLE-ABS-KEY (sore*)) OR (TITLE-ABS-KEY (discomfort*)) OR (TITLE-ABS-KEY (arthralgia*)) OR (TITLE-ABS-KEY (dysfunction*)) OR (TITLE-ABS-KEY (injur*)) OR (TITLE-ABS-KEY (syndr*)) OR (TITLE-ABS-KEY (chondromalac*)) OR (TITLE-ABS-KEY (chondropath*)) OR (TITLE-ABS-KEY (disorder*))
3. (TITLE-ABS-KEY (randomised)) OR (TITLE-ABS-KEY (randomized)) OR (TITLE-ABS-KEY (randomly) OR (TITLE-ABS-KEY (trial)) OR (TITLE-ABS-KEY (groups))
4. #1 AND #2
5. #4 AND #3

Excluded term Scopus	**Reasons for exclusion**
TITLE-ABS-KEY ("chondromalacia patellae")	Did not add hits to #1
TITLE-ABS-KEY ("patellofemoral pain syndrome")	Did not add hits to #1
TITLE-ABS-KEY ("anterior knee pain")	Did not add hits to #1

Web of Science

1. TS=(patell* OR femoropatell* OR femoro-patell* OR retropatell* OR retro-patell* OR "anterior knee*" OR peripatell* or peri-patell* OR "kneecap" OR patellofemoral OR patello-femoral OR "lateral compression syndrome*" OR "lateral facet syndrome*" OR "lateral pressure syndrome*" OR "lateral hyperpressure syndrome*" OR "odd facet syndrome*")

2. TS=(pain* OR sore* OR discomfort* OR arthralgia* OR dysfunction* OR injur* OR syndr* OR chondromalac* OR chondropath* OR disorder*)

3. TS=(randomised OR randomized OR randomly OR trial OR groups)
4. #1 AND #2
5. #3 AND #4

Excluded term(s) Web of Science	**Reason for exclusion**
TS=("Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain") OR	Did not add hits to #4

CINAHL (via EBSCOhost)

1. (MH "Patellofemoral Pain Syndrome")
2. (MH "Chondromalacia Patella")
3. TI patell* OR AB patell* OR TI "anterior knee*" OR AB "anterior knee*" OR TI femoropatell* OR AB femoropatell* OR TI retropatell* OR AB retropatell* OR TI peripatell* OR AB peripatell* OR TI "kneecap" OR AB "kneecap"
4. TI pain* OR AB pain* OR TI sore* OR AB sore* OR TI discomfort* OR AB discomfort* OR TI arthralgia* OR AB arthralgia* OR TI dysfunction* OR AB dysfunction* OR TI injur* OR AB injur* OR TI syndr* OR AB syndr* OR TI chondromalac* OR AB chondromalac* OR TI chondropath* OR AB chondropath* OR TI disorder* OR AB disorder*
5. MH "Clinical Trials"
6. TI “randomised" OR AB "randomised" OR TI "randomized" OR AB "randomized" OR TI "randomly" OR AB "randomly" OR TI "trial" OR AB "trial" OR TI "groups" OR AB "groups"
7. S1 OR S2
8. S3 AND S4
9. S5 OR S6
10. S7 OR S8
11. S9 AND S10

Excluded term(s) CINAHL	Reason for exclusion
TI femoro-patell* OR AB femoro-patell*	Did not add to #3
TI retro-patell* OR AB retro-patell*	Did not add to #3
TI patellofemoral OR AB patellofemoral	Did not add to #3
TI patello-femoral OR AB patello-femoral	Did not add to #3
TI peri-patell* OR AB peri-patell*	Did not add to #3
TI "lateral compression syndrome*" OR AB "lateral compression syndrome*" OR TI "lateral facet syndrome*" OR AB "lateral facet syndrome*" OR TI "lateral pressure syndrome*" OR AB "lateral pressure syndrome*" OR TI "lateral hyperpressure syndrome*" OR AB "lateral hyperpressure syndrome*" OR TI "odd facet syndrome*" OR AB "odd facet syndrome*	Did not add to #3

SPORTDiscus (via EBSCOhost)

1. DE "PLICA syndrome"
2. DE "CHONDROMALACIA patellae"
3. DE "PATELLA -- Diseases"
4. TI patell* OR AB patell* OR TI "anterior knee*" OR AB "anterior knee*" OR TI femoropatell* OR AB femoropatell* OR TI retropatell* OR AB retropatell* OR TI peripatell* OR AB peripatell* OR TI "kneecap" OR AB "kneecap"
5. TI pain* OR AB pain* OR TI sore* OR AB sore* OR TI discomfort* OR AB discomfort* OR TI arthralgia* OR AB arthralgia* OR TI dysfunction* OR AB dysfunction* OR TI injur* OR AB injur* OR TI syndr* OR AB syndr* OR TI chondromalac* OR AB chondromalac* OR TI chondropath* OR AB chondropath* OR TI disorder* OR AB disorder*
6. TI "randomised" OR AB "randomised*" OR TI "randomized" OR AB "randomized" OR TI "randomly" OR AB "randomly" OR TI "trial" OR AB "trial" OR TI "groups" OR AB "groups"
7. #1 OR #2 OR #3
8. #4 AND #5
9. #7 OR #8
10. #6 AND #9

Excluded term(s)	Reason for exclusion
TI femoro-patell* OR AB femoro-patell*	Did not add to #3
TI retro-patell* OR AB retro-patell*	Did not add to #3
TI patellofemoral OR AB patellofemoral	Did not add to #3
TI patello-femoral OR AB patello-femoral	Did not add to #3
TI peri-patell* OR AB peri-patell*	Did not add to #3
TI "lateral compression syndrome*" OR AB "lateral compression syndrome*" OR TI "lateral facet syndrome*" OR AB "lateral facet syndrome*" OR TI "lateral pressure syndrome*" OR AB "lateral pressure syndrome*" OR TI "lateral hyperpressure syndrome*" OR AB "lateral hyperpressure syndrome*" OR TI "odd facet syndrome*" OR AB "odd facet syndrome*"	Did not add to #3

Nb. "patellofemoral pain syndrome" is mapped under "plica syndrome" in SPORTDiscus.

Grey literature resources

OpenGrey:

1. ("Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain")
2. ((patell* OR femoropatell* OR femoro-patell* OR retropatell* OR retro-patell* OR "anterior knee*" OR peripatell* or peri-patell* OR "knee cap" OR patellofemoral OR patello-femoral OR "lateral compression syndrome" OR "lateral facet syndrome" OR "lateral pressure syndrome" OR "lateral hyperpressure syndrome" OR "odd facet syndrome") AND (pain* OR sore* OR discomfort* OR arthralgia* OR dysfunction* OR injur* OR syndr* OR chondromalac* OR chondropath* OR disorder*))
3. #1 OR #2

Nb. We did not limit this search with design names as there is a a low number of hits expected wih these initial steps.

Worldcat.org

(kw:(patellofemoral pain) OR kw:(“anterior knee pain”) OR kw:(chondromalacia patellae))

AND ti:(rct OR randomized OR randomised)

nb. A comprehensive search in this search engine yields 100.000s hits. Therefore, we restricted the search to the most important terms and restricted the search by using design terms.

TRIAL REGISTRERS

ClinicalTrials.gov

"Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain" OR patellofemoral

Excluded terms in final search	**Reasons for exclusion**
Patell†	No hits in addition to "patellofemoral pain syndrome"
Femoropatell†	No hits in addition to "patellofemoral pain syndrome"
femoro-patell†	No hits in addition to "patellofemoral pain syndrome"
Retropatell†	No hits relevant to the topic - not already identified by "patellofemoral pain syndrome"
retro-patell†	No hits relevant to the topic - not already identified by "patellofemoral pain syndrome"
"anterior knee"	No hits in addition to ("patellofemoral pain syndrome" OR "anterior knee pain")
peripatell†	No hits relevant to the topic - not already identified by "patellofemoral pain syndrome"
peri-patell†	One irrelevant hit
"kneecap"	17 hits - all on instability, dislocation etc.
patello-femoral	Did not add hits to patellofemoral
"lateral compression syndrome†"	No hits
"lateral facet syndrome†"	No hits
"lateral pressure syndrome†"	No hits
"lateral hyperpressure syndrome†"	No hits
"odd facet syndrome†"	No hits

N.b. There is only a limited search space in Clinicaltrials.gov. Therefore, we aimed to minimize the search in length as much as possible. **† =** The *, as used in conventional databases, is not an explode function in Clinicaltrials.gov. To the best of our knowledge no explode function exists in this trial register. We therefore trialled all endings to these words separately. E.g. patell* we tried -o/-a and -ar and =s for syndromes. Then we observed if these would yield relevant hits. If not, the term was deleted from the search strategy.

We refrained from using the symptom terms(e.g. pain, discomfort) as we only had one free text term (i.e. patellofemoral) that had 52 hits on top of the "Patellofemoral Pain Syndrome" OR "Chondromalacia Patellae" OR "anterior knee pain" search. We also left out the study design restriction as most of the studies registered in this register are controlled trials.

The European Union Clinical Trial Register

1. patella OR patellar

Excluded terms in final search	Reasons for exclusion
"Patellofemoral Pain Syndrome"	No hits
"Chondromalacia Patellae"	No hits
"anterior knee pain"	No hits
patellofemoral	No hits
Femoropatell†	No hits
femoro-patell†	No hits
Retropatell†	No hits
retro-patell†	No hits
"anterior knee"	No hits
peripatell†	No hits
peri-patell†	No hits
"kneecap"	No hits
patello-femoral	No hits
"lateral compression syndrome†"	No hits
"lateral facet syndrome†"	No hits
"lateral pressure syndrome†"	No hits
"lateral hyperpressure syndrome†"	No hits
"odd facet syndrome†"	No hits

N.b. Similarly to Clinicaltrials.gov, we checked the condition terms first individually. †= The *, as used in conventional databases, is not an explode function in this register. To the best of our knowledge no explode function exists in this trial register. We therefore trialled all endings to these words separately. E.g. patell* we tried -o/-a and -ar and =s for syndromes. Then we observed if these would yield relevant hits. If not, the term was deleted from the search strategy.

We refrained from using any restriction (with symptom terms (e.g. pain, discomfort) or design restriction (e.g. RCT) as we only expect a low number of hits after the first step of the search.

ISRCTN registry

"Patellofemoral Pain Syndrome" OR "anterior knee pain" OR patello OR patella OR patellar OR femoropatellar OR "anterior knee" OR "kneecap" OR patellofemoral

Excluded terms in final search	Reasons for exclusion
"Chondromalacia Patellae"	no hits
femoropatello	no hits
femoropatella	no hits
femoro-patell†	No hits for -a/-o/-ar
retropatell†	no hits in addition to "Patellofemoral Pain Syndrome" OR "anterior knee pain" OR patello OR patella OR patellar OR femoropatellar
retro-patell†	no hits
peripatell†	no hits
peri-patell†	no hits
patello-femoral	no hits in addition to "Patellofemoral Pain Syndrome" OR "anterior knee pain" OR patello OR patella OR patellar OR femoropatellar OR "anterior knee" OR "kneecap" OR patellofemoral
"lateral compression syndrome"	no hits
"lateral facet syndrome"	no hits
"lateral pressure syndrome"	no hits
"lateral hyperpressure syndrome"	no hits
"odd facet syndrome"	no hits

N.b. Similarly to Clinicaltrials.gov and the European Union clinical trial register, we checked the condition terms first individually.†= The *, as used in conventional databases, this is not an explode function in this register. To the best of our knowledge no explode function exists in this trial register. We therefore trialled all endings to these words separately. E.g. patell* we tried -o/-a and -ar and then observed if these would yield relevant hits. If not, the term was deleted from the search strategy. We refrained from using any restriction (with symptom terms (e.g. pain, discomfort) or design restriction (e.g. RCT) as we expect a low number of hits after the first step of the search.

WHO international Clinical Trials Registry Platform

"Patellofemoral Pain Syndrome" OR "anterior knee pain" OR "patella pain" OR "patella chondromalac*"

Excluded terms in final search	Reasons for exclusion
"Chondromalacia Patellae"	No hits
Femoropatell*	No hits in addition to patell*
Femoro-patell*	No hits in addition to patell*
Retropatell*	No hits in addition to patell*
Retropatell*	No hits in addition to patell*
Peripatell*	No hits in addition to patell* OR "anterior knee"
Peri-patell*	No hits in addition to patell* OR "anterior knee"
Kneecap*	No hits in addition to patell* OR "anterior knee"
Patellofemoral	No hits in addition to patell* OR "anterior knee"
Patello-femoral	No hits in addition to patell* OR "anterior knee"
"Lateral compression syndrome*"	No hits
"Lateral facet syndrome*"	No hits
"Lateral pressure syndrome*"	No hits
"lateral hyperpressure syndrome*"	No hits
"Odd facet syndrome*"	No hits
"patellar pain*"	No hits
"patellar sore*"	No hits
"patellar discomfort*"	No hits
"patellar arthralgia*"	No hits
"patellar dysfunction*	No hits
"patellar injur*"	No hits
"patellar syndr*"	No hits
"patellar chondromalac*"	No hits
"patellar chondropath*"	No hits
"patello pain*"	No hits
"patello sore*"	No hits
"patello discomfort*"	No hits
"patello arthralgia*"	No hits
"patello dysfunction*"	No hits
"patello injur*"	No hits
"patello syndr*"	No hits
"patello chondromalac*"	No hits
"patello chondropath*"	No hits
"patella sore*"	No hits
"patella discomfort*"	No hits

"patella arthralgia*"	No hits
"patella dysfunction*"	No hits
"patella injur*"	No hits
"patella syndr*"	No hits
"patella chondropath*"	No hits
"patellar arthralgia*"	No hits

Appendix 2: Data collection form for RCTs

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Report ID	
Report ID of other reports of this study including errata or retractions	
Notes	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised controlled trial	☐	☐	☐	
	Quasi-randomised controlled trial	☐	☐	☐	
Type of population		☐	☐	☐	
Types of intervention		☐	☐	☐	
Types of comparison		☐	☐	☐	
Types of outcome measures		☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper		**Location in text or source** *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*			
Design *(e.g. parallel, crossover, non-RCT)*			
Unit of allocation *(by individuals, cluster/ groups or body parts)*			
Start date			
End date			
Duration of participation *(from recruitment to last follow-up)*			
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear		
Notes:			

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source *(pg & ¶/fig/table/other)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method of making the diagnosis PFP		

Method of recruitment of participants *(e.g. phone, mail, clinic patients)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Total no. randomised *(or total pop. at start of study for non-RCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Severity of illness (pain at baseline)		
Co-morbidities/concurrent pain conditions/injuries		
Other relevant factors, specifically: • Quality of life • Social economic status (any indicator, e.g. income) • Duration of symptoms • Active/sedentary population • Uni- vs. bilateral pain		
Subgroups measured		
Subgroups reported		
Notes:		

Intervention groups

Intervention Group 1

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components, location, physical or informational materials used))**		
Delivery *(e.g. modes of delivery, mechanism, medium, intensity, fidelity, procedure)**		
Tailoring (was the intervention planned to be personalise/titrated/adapted then describe: What, why when and how)#		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Providers *(e.g. no., profession, expertise, specific training given, etc. if relevant)**		
Co-interventions		
Did any treatment modification occur during the study? If yes, describe changes in the intervention (what, why, when and how)#		
Adherence		
Notes:		

* Item added from Tidier checklist[23], # Item modified following the Tidier checklist [23]

Intervention Group 2

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components, location, physical or informational materials used))**		
Delivery *(e.g. modes of delivery, mechanism, medium, intensity, fidelity, procedure)**		
Tailoring (was the intervention planned to be personalise/titrated/adapted then describe: What, why when and how)#		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Providers *(e.g. no., profession, expertise, specific training given, etc. if relevant)**		
Co-interventions		
Did any treatment modification occur during the study? If yes, describe changes in the intervention (what, why, when and how)#		
Adherence		
Notes:		

* Item added from Tidier checklist[23], # Item modified following the Tidier checklist [23]

Outcomes

Outcome X

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Outcome name		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/ reporting		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Power *(e.g. power & sample size calculation, level of power achieved)*		
Notes:		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		

Data and analysis

Outcome X

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome					
Subgroup					
Time point *(specify from start or end of intervention)*					
No. participant	Intervention		Control		
Results List per outcome descriptor: "Completely recovered Strongly recovered Slightly recovered Unchanged Slightly worse Much worse Worse than ever"	Intervention Number	%	Control Number	%	
Overall results	Overall results (success yes/no): Succes = completely recovered + strongly recovered No success = other options Number (%) per group: Intervention: Control: Relative estimate(s), e.g. RR/Risk reduction:				
Any other results reported					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these					
Reanalysis required? *(specify)*	☐ Yes ☐ No ☐ Unclear				
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear				
Reanalysed results					
Notes:					

Other information

	Description as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2/P6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	P14
Sponsor	5b	Provide name for the review funder and/or sponsor	P14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P6-7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp online material 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P9

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Pg-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	pg
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	pg-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	pg-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P11-12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P12-13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n4
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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