BMJ Open

Relative effectiveness of non-surgical interventions for pain management in knee osteoarthritis: a protocol for a component network meta-analysis of randomised controlled trials

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To cite: Thompson T, Ahmed B, Weldon SM, *et al*. Relative effectiveness of non-surgical interventions for pain management in knee osteoarthritis: a protocol for a component network meta-analysis of randomised controlled trials. *BMJ Open* 2021;**11**:e048298. doi:10.1136/bmjopen-2020-048298

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-048298).

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Received 22 December 2020
Accepted 17 September 2021

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ABSTRACT

Introduction Knee osteoarthritis is a chronic degenerative disease associated with significant chronic pain, disability and impaired quality of life and is the most common form of osteoarthritis. There is no cure for knee osteoarthritis, and the main therapeutic goals are pain management and improving quality of life. The objective of this study is to evaluate the relative efficacy and acceptability of available interventions using network meta-analysis (NMA) to provide a comprehensive evidence base to inform future treatment guidelines.

Methods and analysis A comprehensive literature search of major electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials) and clinical trial registries will identify randomised control trials (RCTs) of interventions listed in NICE guidelines for the treatment of knee osteoarthritis in adults. We will perform an NMA to estimate relative intervention effects across the whole treatment network. If any studies use multicomponent intervention packages, we will employ a component NMA model to estimate the contribution of individual components. The quality of evidence will be assessed using the Confidence in Network Meta-Analysis approach, which is based on the traditional GRADE framework adapted for NMA. Risk of bias (RoB) will be assessed using the revised Cochrane RoB 2.0 tool for RCTs.

Ethics and dissemination This study does not require ethical approval. Findings will be submitted to a peer-reviewed journal.

PROSPERO registration number CRD42020184192.

Strengths and limitations of this study

- Network meta-analysis (NMA) will estimate the relative effects of two treatments even when no primary studies have directly compared them.
- Component NMA will assess the relative contributions of individual components in a treatment package.
- Confidence in Network Meta-Analysis methodology will providence confidence ratings of evidence quality.
- Individual treatment component effects may not be estimable if there are insufficient combined intervention studies.
- Treatments that violate the consistency assumption cannot be reliably assessed with NMA.

BACKGROUND

Osteoarthritis (OA) is a chronic degenerative musculoskeletal disorder of the joints, which most commonly affects the knee, hip and hand.[1] OA is characterised by microscopic and macroscopic anatomical changes of the joint with a complex pathophysiological change of articular cartilage and subchondral bone.[2] This complex pathophysiology leads to cartilage degradation, bone remodelling, osteophyte formation and synovial inflammation, causing pain, disability and loss of normal biomechanical joint function.[3] OA resulting from 'wear and tear' is by far the most common and typically develops at around 55–60 years; although secondary OA resulting from injury, congenital abnormality or inflammation can also occur.[1]

OA is the most common form of arthritis and affects more than 300 million people worldwide.[3] Since OA is associated with major structural changes of the joints leading to pain and functional disability, its epidemiological and economic burden on healthcare providers and society are substantial.[4] OA was estimated to be the fourth-leading cause of disability by the year 2020.[5] In the UK alone, it is estimated that around 34% of people aged 45 years and older, approximately 8.75 million people, have sought treatment for OA.[6] The economic burden can be direct (eg, treatments) or indirect (eg, working days lost). A study in 2013 estimated that the negative economic impact of OA on UK economy

was the equivalent of 1% Gross National Product.[7] The most common form of OA affects the knee joint and accounts for almost 83% of OA burden.[8 9] Furthermore, because of the knee joint's anatomical location its impact on disability is substantial.[10]

Currently, there is no cure for OA. As pain is the most common symptom associated with OA, with more than 66% of patients with OA in constant pain,[11] interventions are primarily focused on pain management using a range of non-pharmacological and pharmacological approaches.[3] While there is an abundance of research evaluating the effectiveness of different interventions compared with placebo, the question of which treatment is optimal is inhibited by a lack of data on the relative efficacies of competing interventions. Similarly, a better understanding of the relative adverse effects of different treatments is needed, with the risk-to-benefit ratio a critical aspect of decision making. This is particularly true in the geriatric population where OA is most prevalent and for whom treatment selection is often determined by adverse events, patient compliance and polypharmacy considerations.[12]

Network meta-analysis (NMA) provides a powerful means of providing relative estimates of the effects of different interventions for a particular indication.[13] NMA allows the synthesis of data from both head-to-head trials and placebo-controlled trials and can provide estimates of relative treatment effects among any two treatments in the network, even in the absence of any existing head-to-head trials. Furthermore, component NMA (CNMA) allows the estimation of the effects of individual components of combined treatments and can be especially useful for indications commonly treated by intervention packages.[14]

The objective of this NMA is to assess the relative effectiveness and acceptability of treatments for the management of pain from knee OA. As surgical interventions are generally used as a last resort, we will focus on non-surgical treatments and examine interventions listed in the NICE 2014 guidelines CG177[15] or the NICE 2017 surveillance guideline update report.[16] The project is called Relative Effectiveness of Interventions for Knee Osteoarthritis.

METHODS

The protocol conforms to Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines[17] for the reporting of systematic review and meta-analysis protocols (see online supplemental file 1) and also incorporates additional considerations specific to NMA (online supplemental file 2). Eligibility criteria were developed using the Population, Intervention, Comparison, Outcome, Study framework, which are summarised in table 1 and described in detail in the sections below. The planned start date for the initial searches is September 2021 and we aim to complete the study by September 2022.

Table 1 Summary of PICOS eligibility criteria (detailed descriptions in manuscript text)

	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with knee osteoarthritis based on a clinical or radiographic diagnosis	
Intervention	Non-surgical primary care interventions for pain management of knee OA based on National Institute for Health and Care Excellence (NICE) guidelines	Invasive interventional or surgical procedures
Comparison	Another active intervention or control (placebo/sham, treatment as usual, no treatment)	
Outcome	Pain rating, tolerance and acceptability (discontinuation or withdraw)	
Study type	Randomised control trials	

OA, osteoarthritis.

Population

We will include studies of adults (≥18 years) with knee OA based on a clinical or radiographic diagnosis. Where a mixed arthritis sample has been used, we will only include the study if (A) data for participants with knee OA can be extracted separately, or (B) at least 75% of the sample has knee OA.

Interventions

We will include interventions for pain management in knee OA with any of the treatment components listed below. These interventions were chosen for inclusion as they are either recommended in NICE (2014) guidelines (CG177) for the management of knee OA pain or listed in the NICE (2017) interim review as potential candidates for inclusion in future guidelines. The rationale for focusing on internationally recognised clinical guidelines is that these interventions more likely to be prescribed or recommended for patients.

Pharmacological: Paracetamol, topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), NSAIDs (non-selective) with or without a proton pump inhibitor, COX-2 inhibitors, opioids, topical capsaicin, duloxetine, intra-articular hyaluronan injections, intra-articular corticosteroid injection. Non-pharmacological: aerobic exercise, local muscle strengthening, education, local thermotherapy, TENS (transcutaneous electrical nerve stimulation), electromagnetic field therapy, ultrasound.

Medications may be fixed or flexibly dosed. For medications approved for pain, we will only include study arms where dosages are within the licensed range. Where a drug is used off-label, we will include all trials but perform sensitivity analysis removing study arms using dosages outside the approved range for that drug's indication. If different dosages have been used across multiple arms within a study, we will combine data and treat as a single node; unless multiple studies are available with similar dosing levels for that medication, in which case we will consider treating these as separate nodes.

Comparator(s)

A different eligible individual treatment or a control group (including placebo/sham, treatment as usual, no treatment).

Outcomes

Primary outcome

Self-reported pain assessed with the following measures in order of prioritisation as recommended by Juhl *et al*[18]: (1) the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale, (2) a Visual Analogue Scale (VAS)/Numerical Rating Scale (NRS) pain rating measure and (3) any other acceptable instrument for pain listed in Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of OA.[19]

Assessment will be at the following distinct time periods following allocation to treatment: immediate (up to 2 weeks), short-term (closest to 3 months), medium-term (closest to 6 months) and long-term follow-up (closest to 12 months). If these divisions fail to sensitively reflect the pattern of assessment timings used across studies, we may reclassify these windows prior to analysis to reflect trial practices.

As many pharmacological interventions are often trialled for immediate-term and short-term outcomes, and non-pharmacological treatment (eg, exercise) trials may more frequently include long-term outcomes, separate analyses in each time window ensures that treatments are compared in time windows appropriate for how those interventions are used.[20]

When pain ratings have been collected at multiple time points within a time window, we will use the time point closest to the median value across studies for the immediate and short-term windows and the longest follow-up for the long-term follow-up window. If data were collected across multiple time points but only reported for a subset of these, we will make every possible attempt to retrieve all data to reduce the possibility of exaggerated treatment effects from selective reporting.[21] If we are unable to retrieve the preferred data, we will use outcomes at the next closest time point but conduct sensitivity analysis excluding these studies.

Secondary outcomes

1. Acceptability—the proportion of patients in each group who withdraw before the end of the treatment for (A) any reason and (B) due to adverse effects.
2. Physical function—any valid patient reported outcome of physical functioning, with prioritisation of the WOMAC function subscale.
3. Stiffness—any valid patient reported outcome of stiffness prioritising the WOMAC stiffness subscale.

Study designs

Only randomised controlled trials (RCTs) comparing an active intervention with another eligible intervention or control will be included. Randomisation can be at the individual or group level. SEs from cluster RCTs will be adjusted to account for design effects using a standard formula.[22] Both parallel group and crossover designs will be included, although for cross-over designs we will extract data from the first trial period only to eliminate the possibility of carryover effects.

Measures of effect size

For continuous scores (pain, physical function, stiffness), we will compute the mean difference (MD) as the effect size, based on differences in post-treatment scores but using group differences in change scores if these are unavailable (which for randomised designs should give the same expected effect sizes as postscore differences, but often with larger variance).

As the WOMAC scale is available with three different response formats (0–4, 0–10 and 0–100)[23] we will normalise all WOMAC scores to the metric of the most commonly used format.[24] If a non-WOMAC measure has been used, we will attempt to normalise scores to the WOMAC metric using any conversion algorithm that may exist. If a study assesses pain both under load (eg, while walking) and at rest we will take the average of these measures (consistent with the WOMAC scoring), otherwise we will use whichever of the two is reported and examine the impact of this decision in sensitivity analysis. If a substantial number of scale conversions are necessary, we will use the standardised MDs as the effect size.

For the binary outcomes of acceptability, we will compute the OR comparing the odds of discontinuation in one intervention with the odds of discontinuation in another intervention/control arm.

Information sources

The following bibliographic sources will be searched for studies indexed from database inception to the date of the search: MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Central Register of Controlled Trials. We will also search for unpublished and ongoing trials using the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov. It is important to include unpublished data, since the well-known bias towards publication of significant findings can, when relying on published

literature alone, lead to an overestimation of treatment effects and an underestimation of adverse effects.[25]

Where complete data for a relevant outcome are not available from a report of an eligible trial, we will contact authors to request data. In addition, we will conduct a manual search of relevant reviews and reference lists of eligible studies.

Search strategy

A broad search strategy will be used to identify eligible trials using controlled vocabulary terms and free-text keywords of titles and abstracts relating to randomised trials, OA and pain. For identifying randomised trials, we will use RCT filters provided by the Cochrane group for MEDLINE and by Wong *et al*[26] for Embase. No publication date or language restrictions will be implemented, although studies for which a translation cannot be obtained will be listed as potentially eligible but not considered for full review. Searches will be rerun just before submission of the review and updated to account for any additional data. The search strategy for Medline (OVID) is provided in online supplemental file 3.

Study selection

Titles and abstracts of each record returned by initial searches will be independently screened by BA and one other member of the review team, who will exclude studies not meeting eligibility criteria. BA and one other reviewer will then independently screen the full text of remaining articles, retaining only eligible studies for inclusion in the NMA. Disagreements at any stage will be resolved through discussion or with a third member of the review team if necessary.

Statistical analysis plan

Data extraction

One reviewer (BA) will perform data extraction and coding, with extracted data checked for accuracy by an experienced data analyst from the review team. We will use a standardised coding form based on our previous studies accompanied by an explanatory codebook. Information extracted will include: study characteristics (such as trial design, source of financial support, trial size, study location), participant and disease characteristics (such as mean age, male/female ratio, disease duration, disease severity and baseline pain severity), intervention and control details, outcome data (including timing of assessments and any information provided on missing data).

When available study data do not allow computation of effect sizes using standard formula we will: (A) extract inferential statistics (eg, F, p, t) that allow effect sizes to be computed,[27] (B) contact study authors for data and (C) for missing SDs, used the pooled SD from other similar studies.[28] In the event of the same data published in multiple sources, we will extract data from the source which reports data with the most clarity. In the case of both published and unpublished data being available, we will prioritise published data which would have been subject to peer review, but we will conduct sensitivity analysis to examine the impact of this decision.

When a study reports participant drop-out, we will note whether effect sizes were computed from the reduced sample (ie, per protocol) or the entire sample (ie, intention to treat, eg, using last observation carried forward) and prioritise intention to treat. When data are missing or ambiguously presented, we will contact study authors up to three times over 6 weeks for clarification.

Study characteristics and treatment network

We will provide a descriptive table summarising the key characteristics of each eligible study including interventions used, patient populations and trial characteristics. A network diagram will show which interventions were compared, with larger network nodes indicating a greater number of patients and thicker connecting lines between nodes indicating a greater number of trials.

Network meta-analysis

Relative treatment effects across the whole network will be estimated with NMA. This method makes use of a wide pool of evidence by aggregating data from both direct head-to-head trials and indirect evidence (where two treatments can be compared indirectly via a common comparator such as placebo). The results of each treatment comparison will be provided in a tabular form, which will present results based on NMA estimates and those from head-to-head trials only. The effectiveness of each treatment relative to a control reference will be presented in a forest plot. Mean ranks with their 95% credible intervals and a simple transformation of the mean rank will be used to provide a hierarchy of the best treatments.

If combined intervention data are available, we will use CNMA to estimate the relative effects of different treatment components. CNMA[14] can estimate the effects of individual treatment components based on single component interventions (eg, exercise only) and combined interventions (eg, exercise+education) after disaggregation of the individual intervention components, and thus can provide greater statistical power than NMA with conventional parametrisation. Similarly, individual treatment component effects can be added to provide a more robust estimate of combined treatment effects compared with relying on direct combination studies only, and combinations can be modelled as additive or interactive (synergistic or antagonistic) effects.[29] This may be of particular benefit for OA intervention research given that combination treatments can be a particularly effective way for older adults to manage their greater adverse safety profile from pharmacological agents[30] and that empirical data on combination treatments are relatively sparse.[15]

Estimation will be based on a random-effects model using the netmeta package in R,[31] with any additional analysis that cannot be performed in netmeta carried out in an alternative package (eg, mvmeta in Stata 15.0).

Transitivity and inconsistency in NMA

A fundamental assumption of NMA in general is that studies of different treatment comparisons should be similar in effect modifiers (participant and study characteristics that modify the relative efficacy of the treatments). To help assess this assumption, we will create and visually inspect a table summary of the distribution of potential effect modifiers (eg, baseline pain severity, OA severity, age, gender) across different treatment comparisons. We will also compare direct and indirect estimates for consistency, both globally across the whole network using a design by treatment interaction approach[32] and locally for each comparison using the 'back-calculation' method.[33] Using the latter method, we will highlight any substantive difference between direct and indirect estimates and advise caution in the interpretation of the corresponding NMA estimates.

We will proceed with NMA in the case of minor dissimilarities, and if there are sufficient data, we will explore the influence of effect modifiers on inconsistency using network meta-regression. In the event of considerable dissimilarity, we will consider excluding network nodes or not proceeding with NMA if substantive inconsistency across nodes is still present.

If there is evidence of sequestration of pharmacological and non-pharmacological treatments, such that there are no or very limited head-to-head pharmacological versus non-pharmacological comparisons, we will split the network and conduct separate analyses on pharmacological and non-pharmacological treatment networks separately and we will assume a common heterogeneity variance τ^2 for each network. If splitting the network is not required, we will use one common heterogeneity variance for each of medication interventions vs control, non-pharmaceutical interventions vs control and medication vs non-pharmaceutical comparisons if data suggests τ^2 is notably different for these three networks.[34 35]

Additivity assumption in CNMA

An assumption of CNMA is that summing individual treatment component effects to estimate the effect of a combined treatment reliably reflects the effect of this combination administered in practice.[29] To help determine the plausibility of this assumption, we will check for consistency between effects estimated for combination interventions based on the additive model with those from any direct combination studies.[36] We will also carry out a test of additivity,[29] based on a comparison of treatment estimates from the standard NMA model and the additive CNMA model. We will use clinical judgement to assess whether it is plausible that the components involved in a treatment combination are likely to operate through different pathways[36] and, therefore, whether considering effects to be additive is appropriate. We will also compare the fit of additive and interaction models with the Deviance Information Criteria statistic, and favour the additive model unless the interaction model is a significantly better fit. If any of these checks suggests intractable problems, we will conduct only a standard NMA where combination treatments are entered as distinct nodes in the network rather than estimating these based on a CNMA model.

Meta-regression and sensitivity analysis

If there are sufficient data, we will conduct network meta-regression to identify possible sources of notable heterogeneity adding the effect modifiers listed previously. We will also use meta-regression to examine whether relative treatment effects are moderated by the following: diagnostic method (clinical/radiographic), dosage (above or below the median dosage) and industry sponsorship (yes/no).

We will also assess the robustness of the findings to various decisions by performing sensitivity analyses removing studies with high risk of bias (RoB), samples with secondary OA and where scale conversions have been performed.

Publication bias

We will visually examine contour enhanced treatment-control comparison adjusted funnel plots when 10 or more studies are available, and further explore small study effects with Egger's test for continuous outcomes and Peters' test for binary outcomes.[37 38] If bias is suspected we will explore this by including sample size as a covariate.

Evidence grading

The quality of the study evidence for the primary outcome of pain will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) and presented in a Summary of Findings table. This approach was developed by Salanti *et al*[39] and recently refined by Papakonstantinou *et al*.[40] CINeMA is based on the traditional GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework adapted for NMA, and provides a single overall confidence rating ('high', 'moderate', 'low', 'very low') for each pairwise comparison based on the six domains: (1) within-study bias, (2) reporting bias, (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence. The overall confidence rating for each comparison is based on individual study ratings applying weights that mimic the study's contribution to the treatment effect size.

Within-study bias will be assessed with the revised Cochrane RoB 2.0 tool for RCTs,[41] which rates potential for study bias arising from the randomisation process, deviations from the intended intervention, missing outcome data, measurement of outcomes and selective reporting. RoB and evidence appraisal will be conducted independently by two reviewers, with any disagreement resolved by discussion or arbitration by a third reviewer if required. We will present network plots[40] to illustrate the level of bias in each comparison.

Patient and public involvement

This study is a synthesis of secondary data and will not require patient or public involvement.

Ethics and dissemination

This study does not require ethical approval. We will disseminate our findings by publishing results in a peer-reviewed journal.

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Contributors TT conceived and designed the study and wrote the statistical analysis plan. BA wrote the majority of the protocol and contributed substantially to the design. SMW, OE and BS evaluated the study protocol for important intellectual content and contributed to critical revisions. All authors gave their approval to the final protocol.

Funding This work was supported by a Vice-Chancellor Scholarship fund (vcs-eh-03-19) from the University of Greenwich. OE was supported by the Swiss National Science Foundation (grant number 180083).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary File 1

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	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
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	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
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	18
Sponsor	5b	Provide name for the review funder and/or sponsor	18
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-9
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	11
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	

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
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)	12
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	12-13
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	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
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	17-18
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15-16
	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).	13,16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16-19
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17-18

*** 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.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary File 2

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results**: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	6-9

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	12
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12-13
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	12-13
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	13
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	17-18
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	10, 13
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	12-16
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	14-15
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	17-18
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and*	13-16

		• *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	NA
DISCUSSION			

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	18

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary File 3

Medline (OVID) search string

1 Randomized controlled trial.pt.
2 Controlled clinical trial.pt.
3 randomi?ed.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 exp osteoarthritis/
13 (osteoarthriti* or osteo-arthriti* or degenerative joint disease or arthroses or arthrosis or osteoarthros* or coxarthrosis).tw.
14 (degenerative adj2 arthritis).tw.
15 (knee adj4 OA).tw.
16 or/12-15
17 exp pain management/
18 exp mind-body therapies/
19 exp exercise/
20 exp exercise therapy/
21 exp sports/
22 ((strength$ or isometric$ or isotonic$ or isokinetic$ or aerobic$ or endurance or weight$) adj2 (exercis$ or train$)).ti,ab.
23 (resistance training or weight training or physiotherapy or mind?body or tai?ji or tai?chi or taiji or yoga or mind?body or exercise or sport or running or jogging or treadmill or swimming or walking or cycling or rowing or physical activity or physical conditioning or aquarobics or pilates or physical fitness).ti,ab.
24 or/18-23
25 exp patient education as topic/
26 exp *health education/
27 self care/ or (self?care or self?help or self?manage*).ti,ab.
28 ((health or patient$) adj2 (educat$ or information)).tw.
29 or/25-28
30 exp Transcutaneous Electric Nerve Stimulation/
31 Transcutaneous adj4 Stimulation or TENS
32 (electric$ adj (nerve or therapy)).tw.

33 Electromagnetic Fields/
34 electromagnetic$.ti,ab.
35 exp Electric Stimulation Therapy/
36 (electric$ adj3 stimulat$).tw.
37 (alternat$ adj3 electric$).tw.
38 exp ultrasonography/
39 exp Ultrasonic Therapy/
40 us.fs.
41 (ultrasound$ or ultrasonic$).tw.
42 short wave therapy.tw.
43 ultrasonograph$.tw.
44 heat/tu
45 (heat or hot or ice).tw.
46 cryotherapy.sh,tw.
47 (vapocoolant or phonophoresis).tw.
48 exp hyperthermia, induced/
49 (hypertherm$ or thermotherapy).tw.
50 (fluidotherapy or compression).tw.
51 or/30-50
52 24 or 29 or 51
53 exp analgesics/
54 exp acetaminophen/
55 (acetaminophen or acamol or acephen or acetaco or acetamidophenol or acetaminophen or acetominophen or algotropyl or anacin 3 or anacin-3 or anacin3 or datril or hydroxyacetanilide or "n-(4-hydroxyphenyl)acetanilide" or n-acetyl-p-aminophenol or panadol or paracetamol or tylenol or p-acetamidophenol or p-hydroxyacetanilide).ti,ab.
56 or/53-55
57 exp Anti-Inflammatory Agents, Non-Steroidal/
58 aspirin.mp. or exp Aspirin/
59 etodolac.mp. or exp Etodolac/
60 diclofenac.mp. or exp Diclofenac/
61 sulindac.mp. or exp Sulindac/
62 (indometacin or indomethacin).mp. or exp Indomethacin/
63 piroxicam.mp. or exp Piroxicam/
64 fenoprofen.mp. or exp Fenoprofen/
65 flurbiprofen.mp. or exp Flurbiprofen/
66 ibuprofen.mp. or exp Ibuprofen/
67 ketoprofen.mp. or exp Ketoprofen/
68 naproxen.mp. or exp Naproxen/
69 diflunisal.mp. or exp Diflunisal/

70 metamizol.mp. or exp Dipyrone/

71 phenylbutazone.mp. or exp Phenylbutazone/

72 phenazone.mp. or exp Antipyrine/

73 exp cyclooxygenase inhibitors/ or exp cyclooxygenase 2 inhibitors/

74 exp Meclofenamic Acid/

75 tolmetin.mp. or exp Tolmetin/

76 (nsaids or non?steroidal anti?inflammat$ or acetylsalicyl$ or carbasalate calcium or aceclofenac or alclofenac or meloxicam or dexibuprofen or dexketoprofen or tiapro$ or propyphenazone or celecoxib or etoricoxib or nabumeton or parecoxib or ((cyclooxygenase or cyclo-oxygenase) adj3 inhibitor*) or rofecoxib or valdecoxib or lumiracoxib or vioxx or celebrex or bextra or prexige or arcoxia or floctafenine or meclofenamate or oxaprozin or tenoxicam).mp.

77 or/57-76

78 (bufexamac OR bufexine OR calmaderm OR ekzemase OR diclofenac OR solaraze OR pennsaid OR voltarol OR emugel OR voltarene OR voltarol OR optha OR voltaren OR etofenamate OR afrolate OR algesalona OR bayro OR deiron OR etofen OR flexium OR flogoprofen OR rheuma-gel OR rheumon OR traumalix OR traumon OR zenavan OR felbinac OR dolinac OR flexfree OR napageln OR target OR traxam OR fentiazac OR domureuma OR fentiazaco OR norvedan OR riscalon OR fepradinol OR dalgen OR flexidol OR cocresol OR rangozona OR reuflodol OR pinazone OR zepelin OR flufenamic OR dignodolin OR rheuma OR lindofluid OR sastridex OR lunoxaprofen OR priaxim OR flubiprofen OR fenomel OR ocufen OR ocuflur OR tulip OR ibuprofen OR cuprofen OR "deep relief" OR fenbid OR ibu?cream OR ibugel OR ibuleve OR ibumousse OR ibuspray OR "nurofen gel" OR proflex OR motrin OR advil OR radian OR ralgex OR ibutop OR indomethacin OR indocin OR indospray OR isonixin OR nixyn OR ketoprofen OR tiloket OR oruvail OR powergel OR solpaflex OR ketorolac OR acular OR trometamol OR meclofenamic OR naproxen OR naprosyn OR niflumic OR actol OR flunir OR niflactol topico OR niflugel OR nifluril OR oxyphenbutazone OR californit OR diflamil OR otone OR tanderil OR piketoprofen OR calmatel OR triparsean OR piroxicam OR feldene OR pranoprofen OR oftalar OR pranox OR suxibuzone OR danilon OR flamilon OR ufenamate OR fenazol OR flector OR benzydamine).mp.

79 or/77-78

80 exp Administration, Topical/ or (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR creme OR lotion OR mouse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster).mp.

81 79 AND 80

82 capsaicin.mp. AND 80

83 exp analgesics, opioid/ or (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or

ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opiate alkaloids or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or remifentanil or sufentanil or tapentadol or tilidine or tramadol).mp.

84 (cymbalta or duloxetine).mp.

85 exp hyaluronic acid/ or viscosupplement/ or viscosupplementation/ or (hyaluronic or hyaluronate* or hyaluronan*).mp.

86 (adant or arthrease or arthrum h or artz or artzal or biohy or durolane or etapharm or euflexxa or fermathron or go-on or healon or healonid or hyalflex or hyalgan or hyalurons or hylan* or hylartil or hylectin or hyruan or nasha or neovisc or nrd-101 or nuflexxa or orthovisc or ostenil or polireumin or polyreumin or replasyn or slm-10 or supartz or suplasyn or suvenyl or synject or synocrom or synvisc).mp.

87 or/85-86

88 *Adrenal Cortex Hormones/ or *17-Hydroxycorticosteroids/ or *11-Hydroxycorticosteroids/ or *Hydroxycorticosteroids/ or *Ketosteroids/ or *17-Ketosteroids/ or *Androstenedione/ or *Prednisolone/ or *Glucocorticoids/ or *Triamcinolone Acetonide/ or *Hydrocortisone/ or *cortisone/

89 (adrenal cortex hormone* or adrenal cortical hormone* or adrenal steroid* or adrenocortical hormone* or adrenocortical steroid* or adrenocorticalsteroid* or adrenocorticosteroid* or cortical steroid* or cortico-steroid* or corticoid* or corticosteroid* or dermocortico-steroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or steroid or triamcinolone hexacetonide or hydrocortison* or prednisolone or Prednison* or cortison* or Pregnadiene*).mp.

90 or/88-89

91 (intraartic* or intra-artic* or inject* or infiltration* or infiltrating).mp.

92 and/90,91

93 56 or 77 or 81 or 82 or 83 or 84 or 87 or 87 or 92

94 17 or 52 or 93

95 11 AND 16 AND 94