Comparative effectiveness of pharmacological interventions for hand osteoarthritis exploring the impact of contextual factors:

Protocol for a systematic review and network meta-analysis of randomised trials

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3 SUMMARY

Background

Pharmacological treatment guidelines for hand osteoarthritis (OA) are continuously updated due to emerging research. Comparative effectiveness research on a multitude of treatment options can be performed using multiple-comparison meta-analysis designs, testing the relative effects of all treatments against each other. However, since a fundamental assumption behind the validity of these so-called network meta-analyses is transitivity (i.e. the existence of comparable distributions of patient characteristics across studies in the treatment network), it is important to explore the impact of contextual factors that could act as effect modifiers.

The main objective of this study is to explore the influence of contextual factors (i.e. study characteristics) on intervention effect estimates. Secondary we wish to pragmatically explore the comparative effectiveness of pharmacological treatments of hand OA using a network meta-analysis design, to estimate the relative effects of all treatments against each other.

Methods

MEDLINE (via PubMed), EMBASE (via Ovid), and The Cochrane Central Register of Controlled Trials (CENTRAL) will be searched from inception to date. Randomised controlled trials of people with hand OA including a pharmacological intervention in at least one arm will be included. For the network meta-analyses, comparator arms include both specific active pharmacological agents, placebo or care as usual. In the standard contrast-based meta-analyses, similar comparators will be clustered into two control groups as either placebo/sham control or unmasked no-attention control. We will attempt to collect all the OMERACT Core Outcome Set domains for hand OA, while considering the primary efficacy outcome domain to be pain (extracting data on pain measures following a predefined hierarchy). Two reviewers will independently select the eligible papers, use duplicate data abstractions, and assess study characteristics (incl. risk of bias evaluation).

We will summarise contrasts between groups for continuous outcomes using standardised mean differences (SMD) and dichotomous outcomes as odds ratios (ORs) both presented with 95% confidence intervals (CIs). For all major outcomes a standard (contrast-based) inverse-variance random-effects meta-analysis will be used to combine the trials. Heterogeneity between trials will be quantified using the I^2 statistic. For the comparative effectiveness (i.e. network meta-analysis), random-effects Bayesian network meta-analyses will be performed to compare interventions.

Perspective

This meta-research project will provide important insight into the effect of contextual factors on treatment efficacy. This will aid future research and may potentially (as a downstream consequence) help individualise treatment strategies based on person specific contextual factors. The project will aid pharmacological treatment strategy used in clinical practice by providing relative effect estimates.

Systematic review registration

PROSPERO: Submitted for registration October 21, 2020. Registration approved January 14, 2021: CRD42021215393.

Keywords

Meta-research, meta-analysis, meta-networks analysis, systematic, randomised controlled trials, hand osteoarthritis, pharmacology, pain, treatment

4 ABBREVIATIONS

ACR   American College of Rheumatology

AUSCAN   Australian/Canadian hand index

AE   Adverse events

bDMARD   Biological disease modifying anti-rheumatic drugs

CENTRAL   Cochrane Central Register of Controlled Trials

CI   Confidence interval

csDMARD   Conventional synthetic disease modifying anti-rheumatic drugs

DIP   Distal interphalangeal

DMARD   Disease modifying anti-rheumatic drugs

D d/t AEs   Discontinuation due to adverse events

EULAR   European League Against Rheumatism

FIHOA   Functional index for hand osteoarthritis

GRADE   Grading of recommendations, assessment, development and evaluation

MCP   Metacarpophalangeal

NICE   National Institute for Care and Health Excellence

NRS   Numeric rating scale

NSAID   Non-Steroidal Anti-Inflammatory Drugs

OA   Osteoarthritis

OMERACT   Outcome Measures in Rheumatology

OR   Odds ratio

PIP   Proximal interphalangeal

PRPs   Patient research partners

RCT   Randomised controlled trial

RoB   Risk of bias

ROR   Ratio of odds ratio

SAE   Serious adverse event

SF-36   Short Form-36

SMD   Standardised mean difference

VAS   Visual analogue scale

5   INTRODUCTION

5.1   Description of the condition

Hand osteoarthritis (OA) is more prevalent among women than men and incidence increases with age (Van Saase, Van Romunde et al. 1989). The Framingham study found the prevalence of symptomatic hand OA to be 26.2% among women and 13.4% among men for individuals >70 years old (Zhang, Niu et al. 2002), and age-standardised prevalence for individuals 40-84 years is 15.9% among women and 8.2% among men (Haugen, Englund et al. 2011). Hand OA is characterised by pain (constant and/or intermittent), stiffness (in the morning, and after inactivity, resolves after 20-40 minutes), and swelling of the joints, with pain being the dominant symptom (Altman, Alarcon et al. 1990). Inflammatory flares with attack wise symptom presentation can occur (Bijlsma, Berenbaum et al. 2011). The most commonly affected joints are the distal interphalangeal (DIP) joints and thumb base but involvement of the proximal interphalangeal- (PIP) and to less extent the metacarpophalangeal (MCP)-joints can also occur. OA is bilateral, symmetrical, and polyarticular in most cases (Dahaghin, Bierma-Zeinstra et al. 2005). Radiographic manifestations are poorly correlated to hand OA symptoms (Dahaghin, Bierma-Zeinstra et al. 2005). Despite active inflammatory signalling pathways and cytokines there is no sign of autoimmunity as in other rheumatic diseases (Clague, Morgan et al. 1991, Wang, Rozelle et al. 2011, Robinson, Lepus et al. 2016). Late clinical manifestations include deformities (Altman, Alarcon et al. 1990) and Heberden's and Bouchard's nodules (Rees, Doherty et al. 2012) plus sequelae as weakness, instability, and impaired hand function (Zhang, Niu et al. 2002).

5.2   Description of the interventions

The European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR), and the National Institute for Care and Health Excellence (NICE) all advocate for a multifactorial management strategy in people with hand OA embracing non-pharmacological, pharmacological, and surgical approaches adapted to fit the individual (National 2014, Kloppenburg, Kroon et al. 2019, Kolasinski, Neogi et al. 2020). The aim of treatment and clinical management is symptom reduction and increase in quality of life (Kloppenburg, Kroon et al. 2019). Unfortunately, at this point no therapeutic agent has proven effective in halting disease progression.

5.2.1   Recommendations for pharmacological interventions

There is overall agreement between EULAR and ACR for recommended pharmacological interventions appropriate for hand OA, see **table 1** below. Nutraceuticals such as glucosamine and diacerhein are no longer recommended. There are no recommendations for potential combination of pharmacological therapy which may be due to limited data in this area.

Table 1: Summary of EULAR and ACR recommendations for pharmacological interventions for hand OA

Pharmacological agent	EULAR	ACR
Topical capsaicin	(light green)	(red)
Topical NSAID (incl. trolamin salicylate)	(dark green)	(light green)
Paracetamol	(light green)	(light green)
Oral NSAID	(dark green)	(dark green)
Duloxetine	Not reported	(light green)
Chondroitin sulfate	(light green)	(light green)
Intraarticular glucocorticoids	(red)[1]	(light green)
Systemic glucocorticoids	No recommendation made[2]	Not reported
Tramadol	(light green)	(light green)
Other opioids (i.e. non-tramadol opioids)	Not reported	(red)
csDMARD/bDMARD	(red)[3]	(red)[4]

Light green: Weak recommendation for use. Dark green: Recommendation for use. Red: Recommendation against use.

1: Intra-articular injections may be considered in patients with painful interphalangeal joints.

2. Evidence was summarized but no recommendation made either for or against.

3: Hydroxychloroquine, tumor necrosis factor inhibitors, interleukin-1 inhibitors.

4: Hydroxychloroquine, tumor necrosis factor inhibitors, interleukin-1 inhibitors and methotrexate.

EULAR: European League Against Rheumatism.

ACR: American College of Rheumatology.

NSAID: Non-Steroidal Anti-Inflammatory Drugs.

csDMARD: conventional synthetic disease modifying anti-rheumatic drugs.

bDMARD: biological disease modifying anti-rheumatic drugs.

Table constructed based on (Kloppenburg, Kroon et al. 2019, Kolasinski, Neogi et al. 2020).

5.3 Contextual factors in OA trials

The term contextual factor has different meanings in different research fields. In 2012, the concept of contextual factors was introduced for the first time in the Outcome Measures in Rheumatology (OMERACT) process and has been described as a "*variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers*" (Boers, Kirwan et al. 2014). Currently, work is ongoing to further operationalize the definition and develop guidance on how to address contextual factors in clinical trials (Nielsen, Tugwell et al. 2019). Contextual factors can be trial characteristics that explain differences in outcome when the same intervention is tested in different randomised controlled trials (RCTs) e.g. for individuals with OA, treatment

with topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) had greater effect in females than males (Persson, Stocks et al. 2020). **Table 2** shows the OMERACT hand OA working group's candidates for contextual factors in hand OA (Kloppenburg, Bøyesen et al. 2015) along with the top 10 generic contextual factor domains for clinical trials in rheumatology (Nielsen, Tugwell et al. 2019).

5.3.1.1   *Table 2: Contextual factors; the OMERACT hand OA working group's candidate factors specific for hand OA and the top 10 generic contextual factor domains suggested for clinical trials in rheumatology*

Contextual factor	OMERACT hand OA contextual factor candidates	Top 10 generic contextual factor domains for clinical trials in rheumatology.
Age	X	X
Sex	X	X
BMI	X	
Fulfilment ACR hand OA criteria	X	
Hand OA subset	X	
Symptom duration	X	
OA at other sites	X	
Concomitant treatment for OA	X	
Comorbidities	X	X
Healthcare system		X
Psychological wellbeing		X
Adherence to treatment at baseline		X
Previous exposure to relevant drugs		X
Patient education/health literacy		X
Disease duration		X
Race		X

Table constructed based on OMERACT publications (Kloppenburg, Bøyesen et al. 2015, Nielsen, Tugwell et al. 2019). OMERACT: Outcome measures in Rheumatology.

5.4   Rationale for this systematic review and meta-analysis

New evidence on hand OA management keeps emerging and recommendations have changed accordingly (Zhang, Doherty et al. 2007, Kloppenburg, Kroon et al. 2019). A recent review summarised interventions for hand OA (Kroon, Carmona et al. 2018), however, the current evidence for management of hand OA has not

explored the possible influence of contextual factors. Also, the relative effectiveness of OA treatments is difficult to discern from the literature in part because few head-to-head comparison studies are available and traditional pairwise (contrast-based) meta-analyses cannot integrate all the evidence from several comparators.

5.5   Aim

We will explore the influence of contextual factors (i.e. study characteristics) on interventions vs. comparators, used for pain management in hand OA trials and we will assess the comparative effectiveness of treatments of hand OA. Secondary we aim to examine the efficacy and safety of pharmacological treatments for hand OA.

6   OBJECTIVES

6.1   The primary and key secondary objective

- To examine whether contextual factors can influence the efficacy of pharmacological interventions in comparison to control in superiority trials (i.e. active treatment comparator, placebo, or care as usual) in patients with hand OA.

    The efficacy-domain for the primary objective is:

    o   Pain

- To examine the comparative effectiveness of all pharmacological interventions in the network compared against each other. The efficacy-domain examined for this key secondary objective is:

    o   Pain

6.2   Secondary objectives

- To examine the efficacy of pharmacological interventions compared to various comparators (incl. placebo control) in patients with hand OA. Efficacy-domains examined are:

    o   Pain

    o   Function

    o   Patient global assessment

    o   Quality of life

    o   Hand strength

- To examine the safety of pharmacological interventions compared to control in patients with hand OA. Safety-measures examined are:

    o   Serious adverse events (SAEs)

o Discontinuation of study
  o Discontinuation due to adverse events (D d/t AEs)

7   METHODS

The protocol follows the PRISMA-P guideline for protocol reporting (Moher, Shamseer et al. 2015) with 5 extra items added to elaborate on network meta-analysis extension (Hutton, Salanti et al. 2015).

7.1   Patient research partners

Two patient research partners (PRPs), Søren Berg and Lone Zakkour, with hand OA were involved in the designing process of this study which follows the EULAR recommendations (de Wit, Berlo et al. 2011). The PRP work is voluntary. The PRPs were identified during routine care at the Parker Institute's outpatient clinic and were invited to participate. Prior to their decision of participation, they received a written and oral task description that clarified their roles and expected contributions. Both PRPs exhibited immense interest in the research collaboration and showed good communication skills. They were invited to comment on the entire protocol and study design, and requested to focus on: Study relevance, relevance of the primary objective, and the contextual factors to be investigated.

The PRPs will prospectively be invited to participate in discussion of results and contribute to the core publication. A safe and respectful environment is highly prioritised and the PRP may contact the research group whenever needed. The PRP can be offered co-authorship in relation to publication according to the recommendations from the International Committee of Medical Journal Editors (ICMJE) criteria.

7.2   Protocol and registration

The protocol was submitted for registration at PROSPERO October 21, 2020. Registration approved January 14, 2021: CRD42021215393.

7.3   Eligibility criteria

Trials including at least one pharmacological intervention for people with hand OA will be considered eligible.

7.3.1   Inclusion criteria
- Randomised controlled trials

- All pharmacological interventions are considered eligible. Comparator can be active, placebo or care as usual.

7.3.2 Exclusion criteria

- Publications in other languages than Danish, Swedish, Norwegian, German, French, Dutch, Italian, Spanish or English will be excluded from quantitative synthesis.
- Hand OA data not reported separately in trials including patients with other diseases as well.

7.4 Information sources

A systematic search of MEDLINE (via PubMed), EMBASE (via Ovid), and The Cochrane Central Register of Controlled Trials (CENTRAL) will be searched. Reference list of systematic literature reviews or meta-analyses concerning hand OA will be manually screened for eligible studies. Reference list of included studies will also be manually screened for eligible studies. Conference abstracts of the EULAR, ACR, and OARSI conferences of the last 2 years will be screened as it must be expected that conference abstracts of older date will already be published. Unpublished data will be searched for at clinicaltrials.gov, The U.S. Food and Drug Administration database, and European Medicines Agency database (Amarilyo, Furst et al. 2016).

7.5 Search strategy

The search strategy of a systematic literature review of hand OA treatment (Kroon, Carmona et al. 2018) was critically reviewed. The search strategy, which was built by an experienced librarian, was found to be a high-quality strategy for identification of relevant trials. Authors of the systematic literature review were contacted and agreed to share a list of identified trials assessed for full text eligibility. Trials assessed for full text eligibility will be rescreened. The published search strategy will be rerun from the latest update (6th of June 2017) until present. Clinicaltrials.gov was pragmatically searched for coming/ongoing/completed hand OA trials; we identified the following possibly relevant pharmaceutical interventions which were added to the search strategy and will be searched without time restriction: Colchicine, glucosamin, estrogen, shinbaro, lutikizumab, tocilizumab, cannabidiol, apremilast, denosumab, pregabalin, duloxetine, otilimab, gevokizumab, and ampion.

The search was built around three aspects: osteoarthritis, hands and management. A list of synonyms and associated words was listed for each aspect. The search terms for each aspect was then combined by the Boolean *OR* term. The complete searches for each aspect will be summarised by the

Boolean *AND* term. We will use both MeSH/keywords and text word searches. Text will be limited to searching title and abstract. The search strategy is available in **appendix 1**.

7.6   Data management

The references found using the search strategies will be exported to Covidence (Covidence systematic review software 2020). References found through other sources than the systematic search will be imported to Covidence as well. Data will be extracted manually to a customised database where they will be stored.

7.7   Study selection

One reviewer (AD) will perform the systematic search and export references. Duplicates will be removed. The remaining references will be sorted manually by two independent reviewers (AD and IMB) using Covidence (Covidence systematic review software 2020). Both reviewers will screen the reference list of systematic literature reviews or meta-analyses concerning hand OA and conference abstracts from EULAR, ACR, and OARSI of the past two years. Disagreements will be solved by discussion, if disagreement persists a third reviewer (RC) will be consulted. All identified studies will be screened for eligibility in a hierarchical manner:

Screening of title and abstract:
1. Is the population studied hand OA?
2. Is it an RCT?

Only if one or both questions are answered no with high confidence the reference will be excluded. All other references will be assessed for full text screening.

Full text screening:
1. Is the population studied hand OA?
2. Is it an RCT?
3. Does it include at least one pharmacological intervention?
4. Is the language Danish, Swedish, Norwegian, German, French, Dutch, Italian, Spanish or English?
5. Are separate outcome data available for hand OA?
6. Is one of the OMERACT core outcomes reported?

If all questions are answered yes, the study will be selected for inclusion unless other reason for not including the study exists. These reasons will be registered for subsequent reporting in the final PRISMA flow diagram.

7.8 Data collection process

Two reviewers (AD and IMB) will independently extract data and perform risk of bias (RoB) assessment in a systematic standardised way collected using a customised data-extraction form. Disagreements will be solved by discussion. If disagreement persists a third reviewer (RC) will be consulted. The preferred time point for outcome will be the time point described by the study as the primary outcome; if no time point is pre-specified as primary endpoint, the longest possible trial period (respecting the original trial design) will be extracted. From cross-over trials we will only include data from the first period of intervention to avoid the risk of accumulating carry-over effect in pooled efficacy meta-analyses (Elbourne, Altman et al. 2002).

7.9 Data items

Following items will be collected on all identified references:

- Flowchart code: included or excluded with reason for exclusion.

Included studies will be assigned an identification number.

Data items collected for included references are specified in the following section.

7.9.1 Background

- First author
- Year of publication
- Publication status
- Journal of publication
- Study acronym if any
- Clinical trial registration no. (if any)
- Study design
- No. of patients randomized in total
- Timeframe in weeks (time to primary endpoint and longest controlled period)
- Study defined primary outcome (Efficacy/safety + pain/function/patient global assessment/quality of life/hand strength/withdrawal due to adverse event/SAE/other)
  - Instrument(s) used for assessment (VAS/AUSCAN/FIHOA/other)

7.9.2 Intervention

- No. of patients randomized to the intervention arm
- Generic name
- Dose
- Unit
- Administration
- Frequency
- Duration
- If more than one intervention is included e.g. at different doses, we will register the intervention of primary interest (as stated by the article) as intervention no. 1.

7.9.3 Comparator

- No. of patients in the comparator arm
- Generic name
- Dose
- Unit
- Administration
- Frequency
- Duration
- If more than one comparator is included data will be extracted for each comparator as comparator no. 1, comparator no. 2 etc

7.9.4 Contextual factors

All contextual factors are extracted at intervention/comparator level if possible. Factors suggested by the OMERACT hand OA working group as candidate contextual factors for hand OA trials will be extracted (Kloppenburg, Bøyesen et al. 2015).

- Age (years; preferably mean)
- Sex (percentages women)
- BMI (kg/m^2; preferably mean)
  - Weight (kg; preferably mean)
  - Height (cm; preferably mean)
- Classification criteria (ACR/other)

- Hand OA subsets:
  - Subset as defined by the study (erosive OA/inflammatory OA/other)
  - Hand OA affection (thumb/fingers/both/not specified)
- Symptom duration (years; preferably median)
- OA at other sites
  - Knee OA (percentages)
  - Hip OA (percentages)
  - Other OA (location + percentages)
- Concomitant therapy (study level)
  - Training/physiotherapy (yes/no)
  - Orthoses (yes/no)
  - Other non-pharmacological (yes/no)
  - Paracetamol (yes/no)
  - NSAID, topical (yes/no)
  - NSAID, per oral (yes/no)
  - Glucocorticoids, injections at any joint (yes/no)
  - Glucocorticoids, systemic (yes/no)
  - Other pharmacological (yes/no, if yes add generic name)
  - For any concomitant therapy specified as "yes" additional data will be collected: generic name, dose, unit, administration, frequency, and duration
- Comorbidities
  - Previous musculoskeletal surgeries (percentages)
  - Other rheumatic diseases (which [text] + percentages)
  - Musculoskeletal disease not considered rheumatic, e.g. carpal tunnel syndrome and conservatively treated fractures (percentages)
  - Cardiac diseases (percentages)
  - Kidney diseases (percentages)
  - Neurological diseases (percentages)
  - Endocrinological diseases (percentages)
  - Lung diseases (percentages)
  - Gastro-intestinal diseases(percentages)
  - Other diseases (which [text] + percentages)

Following factors was discussed in the research group and will be extracted as potential contextual factors:

- Race (percentages; black/white/asian/other)

- Disease duration (years; median)

- No. of affected hand joints (preferably mean)

- Radiographic hand OA severity (Altman or Kellgren-Lawrence; mean)

- Local inflammation (yes/no; measurement tool [text])

- Systemic inflammation:

  - CRP (mg/L; median).

  - ESR (mm/hr; median).

Following factors were suggested by a PRP and considered appropriate:

- Smoking status (percentages; smoker/previous smoker/no smoker/other)

- Exercise (median hours a week)

- Alcohol (median consumption a week)

- Employment: Manual labour involving the hands (percentages; previous/current/never/other)

Diet was also suggested by the PRP as a potential contextual factor but was left out as no simple categorical or continuous categorisation exists.

7.9.5 Risk of bias
- Key risk of bias items specified in the "Risk of bias" section.
- Funding will be extracted categorical (1/2/3/4/5) as described by Lundh et al. (Lundh, Lexchin et al. 2017): 1. 100% pharmaceutical or device company funding; 2. 100% non-industry funding; 3. Mixed funding; 4. Free provision of drug or device only; 5. Undisclosed funding.

7.9.6 Efficacy outcomes
Efficacy outcome data will be extracted separately for each intervention and comparator. For all efficacy outcomes we will collect mean value at baseline with variance, mean value at primary endpoint with variance and mean reduction/increase with variance. We will extract the OMERACT endorsed efficacy outcome domains and measurements (Kloppenburg, Bøyesen et al. 2015) prioritised as shown in **Table 3**.

7.9.6.1 Table 3: Efficacy outcomes and prioritisation of measurement tools.

Outcome domain	Prioritisation of measurement tools
Pain	VAS*
	NRS*
	AUSCAN pain
	Michigan pain

	Other
Function	AUSCAN function
	FIHOA
	Michigan overall hand function
	Other
Patient global assessment	VAS
	Other
Health-related quality of life	SF-36 mental/physical component scale
	Other
Hand strength	Grip strength will be preferred over pinch strength of both are reported

* Pain at activity will be prioritised over pain at rest, if both are reported

VAS: Visual analog scale

NRS: Numeric rating scale

AUSCAN: Australian/Canadian hand index

FIHOA: functional index for hand OA

SF-36: Short Form-36

7.9.7 Safety outcomes

Safety data will be extracted separately for each intervention and comparator.

- Discontinuation of study, i.e. withdrawals

- Discontinuation due to adverse events (D d/t AEs)

- SAE: No. of participants with and SAE. Events will only be considered serious if the trial report them as such.

7.10 Outcomes and prioritisation

Outcomes included will be the OMERACT endorsed core outcomes hand OA (Kloppenburg, Bøyesen et al. 2015). The outcomes are those most prevalently used and most have validated instruments for measuring (Visser, Bøyesen et al. 2015). Primary complaints for people with hand OA are pain and reduced function, the first being more common than the latter (Altman, Alarcon et al. 1990). Therefore, pain will be prioritised as the main outcome and physical function as the secondary outcome (Christensen, Maxwell et al. 2015, Tugwell, Maxwell et al. 2015). Patient global assessment will be prioritised thirdly, quality of life fourthly, and hand strength lastly.

7.11 Risk of bias in individual studies

Risk of bias (v. 2.0) will be assessed for the following domains (Sterne, Savović et al. 2019):

1. Bias arising from the randomisation process

2. Bias due to deviations from intended interventions

3. Bias due to missing outcome data

4. Bias in measurement of the outcome

5. Bias in selection of the reported results

Assessment will be related to pain and not the whole set of outcomes. Within each domain the assessment follows a series of signalling questions. Each question will be answered as yes, probably yes, no, probably no, or not applicable/no information. Support for the responses will be placed in free text boxes alongside the signalling questions and judgments. Quotations from the text of the study report will be used whenever possible. Risk of bias judgement for the domain will be facilitated by the suggested algorithm that maps responses to signalling questions to a proposed judgment (Sterne, Savović et al. 2019). The risk of bias judgment for each domain are low risk of bias, some concerns, or high risk of bias. Overall risk of bias will be based on score for all domains. A study will be judged as low overall risk of bias if all domains are low risk of bias. A study will be judged as overall some concerns if at least one domain is some concerns, but no domains are high risk of bias. A study will be judged as overall high risk of bias if at least one domain is high risk of bias or multiple domains are of come concern in a way that substantially lowers confidence in the result.

A Cochrane review found industry sponsored studies to have more favourable efficacy results than non-industry sponsored studies, suggesting industry bias as a separate risk of bias item (Lundh, Lexchin et al. 2017). We will therefore extract information on funding in addition to the conventional risk of bias components.

7.12 Dealing with missing data

Missing data will be sought in information sources for unpublished data as described previously. The corresponding authors of the article will be contacted if data for the primary efficacy domain (i.e. pain) is not available in these sources.

7.13 Assessment of heterogeneity

We will assess heterogeneity in the contrast-based meta-analyses using I^2 inconsistency index, with values ≥ 50% interpreted as substantial heterogeneity (Higgins, Green et al. 2011).

In the network meta-analyses, heterogeneity will be quantified using τ^2 which examines heterogeneity because of study and study*intervention (interaction). Tau-squared interpretation is not

aided by cut-off values or limited ranges but smaller values indicates a better model fit (Singh, Christensen et al. 2009, Tarp, Furst et al. 2017).

7.14 Synthesis of results

All eligible studies will be included for analysis if the available data permits it. The analyses will consist of I) meta-analyses for direct effects for all outcomes, II) network meta-analyses for pain, and III) meta-regressions for each contextual factor for pain.

For continuous outcome measures we will calculate effect size as the standardised mean difference (SMD). The SMD is calculated as the mean difference (difference in mean values at the end or change from baseline of the trial between intervention and comparator) divided by corresponding the pooled standard deviation. A negative effect size will indicate reduction in the outcome of interest, thus, a negative effect size for pain indicates a beneficial effect of the intervention. This will allow us to combine different continuous outcome measures which assess the same outcome domain (e.g. pain assessed with VAS in one trial and AUSCAN in another). For binary outcomes, such as safety, results of intervention versus control within each trial will be presented by calculating odds ratio (OR) and the corresponding 95% confidence interval (CI). OR > 1 is equal to higher incidence of outcome in the interventions group, i.e. beneficial in favour of the intervention with regards to efficacy, and harmful in favour of the intervention with regards to safety. Outcomes will be interpreted based on confidence intervals rather than the ability to achieve statistical significance (Schünemann, Vist et al. 2019).

7.14.1 Meta-analyses (direct effects: Contrast-based)

Outcomes will be pooled for each intervention across trials using random-effect meta-analyses. Random-effect meta-analyses is preferred over fixed effect analyses, as we assume patient population and trial settings to be heterogenous across trials and differences in outcome are therefore not likely to rely solely on statistical variation (Riley, Higgins et al. 2011). Fixed effect analyses will be used for sensitivity.

We will use Review Manager (RevMan [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to perform meta-analyses.

7.14.2 Network meta-analysis on pain outcome (direct and indirect effects: Arm-based)

We will perform a network meta-analysis for pain using a random-effects model within a Bayesian framework using the *gemtc* package in R, version 4.0.1 (or newer; R Foundation for Statistical Computing)(R Core Team 2020, Valkenhoef and Kuiper 2020). Since the outcome is on a continuous scale, the model will correspond to a generalized linear model with an identity link (Dias, Sutton et al. 2013). We

will use non-informative prior distributions for model parameters as the relative effectiveness of the treatments currently are uncertain. We will assess the convergence using the Gelman-Rubin statistic and by visual inspection of trace plots. Results will be presented as SMD with 95% credible intervals (CrIs). Treatment rankings will be summarized using a rankogram (rank probabilities plot) showing the estimated probability that an intervention is a specific rank (first, second, etc.) when compared to the other interventions in the network.

The geometry of the network will be evaluated with a network graph where nodes will represent individual interventions. Lines between nodes will indicate that the interventions have been directly compared in a trial. The nodes will be weighted by the number of trials that have evaluated the treatment and the lines will be weighted by the number of trials that have evaluated the treatment comparison.

Transitivity is the main assumption behind a network meta-analysis (Salanti 2012). The assumption of transitivity means that indirect comparison (A vs. B and B vs. C) validly estimates the unobserved head-to-head comparison (A vs. C). For this synthesis to be valid studies included must be sufficiently similar in important clinical and methodological characteristics (Baker and Kramer 2002). The statistical manifestation of transitivity is called consistency (or coherence) which refer to agreement between direct and indirect comparisons (Salanti 2012). Transitivity cannot be tested statistically but, plausibility can be evaluated conceptually and methodologically. Network inconsistency will be assessed using the node-splitting method (Dias, Welton et al. 2010).

7.14.3 Meta-regressions for each contextual factor on the pain effect size as dependent variable

The effect of each contextual factor will be explored using meta-regression stratified by contextual factor with the SMD as dependent variable. The statistical analyses will be performed in R version 4.0.1 (or newer)(R Core Team 2020) using the package metafor (Viechtbauer 2010).

7.15 Risk of bias across studies

Publication bias will be assessed visually by asymmetry of funnel plot. Assessment of funnel plot asymmetry will only be used if at least 10 studies are included in the meta-analysis (HPage, Higgins et al. 2008). Fixed-effect estimate to random effects estimate to assess the presence of small sample bias (more beneficial effect in smaller studies i.e. random effect estimate more beneficial than fixed-effect estimate).

7.16 Confidence in cumulative evidence

Reviewers (AD and IMB) will assess the confidence in the estimates: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to summarise on an outcome-by-outcome basis as high, moderate, low, or very low (Guyatt, Oxman et al. 2008), based on the evaluation of risk of bias, risk of publication bias, imprecision, inconsistency, and indirectness.

In order to qualify the comparative effectiveness (i.e. network meta-analysis for pain), we will further categorise interventions from most to least effective based on the effect estimates obtained from networks meta-analyses and their associated certainty of evidence as follows: superior to both placebo and alternatives, superior to placebo but inferior to alternatives, and no better than placebo.

8   ETHICS AND DISSEMINATION

The results will, regardless of findings, be disseminated as article(s) in peer-reviewed scientific journal(s) and will be communicated via scientific meetings as well as presented for public outreach to patients and the public via suitable sources. Papers will be drafted by the primary investigator (AD) and revised by the collaborators who will, according to the standards of ICMJE, be authors when they provide substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, are part of drafting the work or revising it critically for important intellectual content, and will be part of the final approval of the version to be published. Finally, all authors need to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

9   PERSPECTIVE

A literature review to assess the level of evidence for different contextual factors is part of the OMERACT research strategy (Kloppenburg, Bøyesen et al. 2015). We believe that the findings of this systematic review, meta-analysis, and networks meta-analysis will have important implications for future research strategies. Hopefully it will also assist directly in clinical practice when deciding which pharmacological treatment strategy to advise for. Findings from this study will aid individualized management strategy by assessing study contextual factors that may apply on participant level. Further, the network meta-analysis may help decide between multiple pharmacological options.

10 CONTRIBUTORS

AD and RC conceived and designed the study and contributed to the development of the protocol. AD developed the search strategy. All authors assisted in the final protocol and agreed to its final approval before submission.

11 FUNDING

12 COMPETING INTERESTS

13 APPENDIXES

13.1 Appendix 1: Search strategy

13.1.1 Pubmed search strategy

Pubmed search strategy with added relevant pharmacological interventions, searched without time restriction:

("Colchicine"[mesh] OR "colchicine"[tiab] OR "glucosamin"[tiab] OR "estrogen"[mesh] OR "estrogen"[tiab] OR "shinbaro"[tiab] OR "plant extracts"[mesh] OR "lutikizumab"[tiab] OR "ABT-981"[tiab] OR "immunoglobulins"[mesh] OR "tocilizumab"[tiab] OR "cannabidiol"[tiab] OR "cannabinoids"[mesh] OR "apremilast"[tiab] OR "thalidomide"[mesh] OR "denosumab"[tiab] OR "pregabalin"[tiab] OR "pregabalin"[mesh] OR "duloxetine"[tiab] OR "duloxetine hydrochloride"[mesh] OR "GSK3196165"[tiab] OR "otilimab"[tiab] OR "Gevokizumab"[tiab] OR "ampion"[tiab] OR "Serum Albumin, Human"[mesh]) AND (("Hand"[mesh] OR "hand"[tiab] OR "hands"[tiab] OR "Hand Joints"[mesh] OR "hand joint"[tiab] OR "hand joints"[tiab] OR "intermetacarpal joint"[tiab] OR "intermetacarpal joints"[tiab] OR "finger"[tiab] OR

"fingers"[tiab] OR "Finger Joint"[mesh] OR "Carpal Joints"[mesh] OR "Carpal Joint"[tiab] OR "Carpal Joints"[tiab] OR "Carpometacarpal Joint"[tiab] OR "Carpometacarpal Joints"[tiab] OR "Finger Joint"[tiab] OR "Finger Joints"[tiab] OR "Metacarpophalangeal Joint"[tiab] OR "Metacarpophalangeal Joints"[tiab] OR "thumb"[tiab] OR "thumbs"[tiab] OR "metacarpus"[tiab] OR "trapeziometacarpal"[tiab] OR "first metacarpal-carpal"[tiab] OR "carpometacarpal"[tiab] OR "interphalangeal"[tiab] OR "distal interphalangeal"[tiab] OR "proximal interphalangeal"[tiab] OR Intermetacarp*[tiab] OR Interphalang*[tiab] OR Intercarp*[tiab] OR Carpometacarp*[tiab] OR Metacarpophalang*[tiab] OR Metacarp*[tiab] OR scaphotrapeziotrapezoid*[tiab]) AND ("Osteoarthritis"[mesh] OR "Osteoarthritis"[tiab] OR "Osteo-arthritis"[tiab] OR osteoarthr*[tiab] OR osteo-arthr*[tiab] OR "osteoarthrosis"[tiab] OR "osteoarthroses"[tiab] OR "degenerative arthritis"[tiab] OR rhizarthros*[tiab] OR "arthrosis"[tiab] OR "arthroses"[tiab] OR Heberden[tiab] OR Bouchard[tiab]))

Pubmed search strategy from Kroon et al., searched from 2017 until present:

(("Hand"[mesh] OR "hand"[tiab] OR "hands"[tiab] OR "Hand Joints"[mesh] OR "hand joint"[tiab] OR "hand joints"[tiab] OR "intermetacarpal joint"[tiab] OR "intermetacarpal joints"[tiab] OR "finger"[tiab] OR "fingers"[tiab] OR "Finger Joint"[mesh] OR "Carpal Joints"[mesh] OR "Carpal Joint"[tiab] OR "Carpal Joints"[tiab] OR "Carpometacarpal Joint"[tiab] OR "Carpometacarpal Joints"[tiab] OR "Finger Joint"[tiab] OR "Finger Joints"[tiab] OR "Metacarpophalangeal Joint"[tiab] OR "Metacarpophalangeal Joints"[tiab] OR "thumb"[tiab] OR "thumbs"[tiab] OR "metacarpus"[tiab] OR "trapeziometacarpal"[tiab] OR "first metacarpal-carpal"[tiab] OR "carpometacarpal"[tiab] OR "interphalangeal"[tiab] OR "distal interphalangeal"[tiab] OR "proximal interphalangeal"[tiab] OR Intermetacarp*[tiab] OR Interphalang*[tiab] OR Intercarp*[tiab] OR Carpometacarp*[tiab] OR Metacarpophalang*[tiab] OR Metacarp*[tiab] OR scaphotrapeziotrapezoid*[tiab]) AND ("Osteoarthritis"[mesh] OR "Osteoarthritis"[tiab] OR "Osteo-arthritis"[tiab] OR osteoarthr*[tiab] OR osteo-arthr*[tiab] OR "osteoarthrosis"[tiab] OR "osteoarthroses"[tiab] OR "degenerative arthritis"[tiab] OR rhizarthros*[tiab] OR "arthrosis"[tiab] OR "arthroses"[tiab] OR Heberden[tiab] OR Bouchard[tiab]) AND ("Treatment Outcome"[Mesh] OR "Treatment"[tw] OR "Treatments"[tw] OR "treated"[tw] OR "Therapeutics"[Mesh] OR "Therapeutics"[tw] OR "Therapeutic"[tw] OR "Therapy"[tw] OR "Therapies"[tw] OR "therapy" [Subheading] OR "Pharmaceutical Preparations"[Mesh] OR "drug"[tw] OR "drugs"[tw] OR "Exercise Therapy"[Mesh] OR "Exercise Therapy"[tw] OR "exercise"[tw] OR "Rehabilitation"[Mesh:NoExp] OR "Rehabilitation"[tw] OR "Health Education"[Mesh] OR "education"[tw] OR "Self Care"[Mesh] OR "Behavior Therapy"[Mesh] OR "Splints"[Mesh] OR "Orthotic Devices"[Mesh] OR "Self-Help Devices"[Mesh] OR splint*[tw] OR orthos*[tw] OR "assistive device"[tw] OR "Hyperthermia, Induced"[Mesh] OR "heat application"[tw] OR

"Administration, Topical"[Mesh] OR "Balneology"[Mesh] OR "balneotherapy"[tw] OR "Acetaminophen"[Mesh] OR "acetaminophen"[tw] OR "paracetamol"[tw] OR "Glucosamine"[Mesh] OR "glucosamine"[tw] OR "Chondroitin"[Mesh] OR "chondroitin"[tw] OR "chondroitin sulfate"[tw] OR "chondroitin sulphate"[tw] OR "avocado-soyabean unsaponifiables"[tw] OR "avocado-soybean unsaponifiables"[tw] OR "ASU"[tw] OR "diacetylrhein" [Supplementary Concept] OR "diacerhein"[tw] OR "diacerein"[tw] OR "Dietary Supplements"[Mesh] OR "Salicylates"[Mesh] OR salicylate*[tw] OR "Capsaicin"[Mesh] OR "Capsaicin"[tw] OR "Antirheumatic Agents"[Mesh] OR "Antirheumatic"[tw] OR "Hydroxychloroquine"[Mesh] OR "Methotrexate"[Mesh] OR "Sulfasalazine"[Mesh] OR "Hydroxychloroquine"[tw] OR "Methotrexate"[tw] OR "Sulfasalazine"[tw] OR "Analgesics"[Mesh] OR "Analgesics" [Pharmacological Action] OR "Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid" [Pharmacological Action] OR "Tramadol"[Mesh] OR "Analgesics, Non-Narcotic"[Mesh] OR "Analgesics, Short-Acting"[Mesh] OR "Analgesics, Non-Narcotic" [Pharmacological Action] OR Analgesic*[tw] OR "Tramadol"[tw] OR "opioid"[tw] OR "opioids"[tw] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Nonsteroidal Antiinflammatory"[tw] OR "Nonsteroidal Anti-inflammatory"[tw] OR "Non-steroidal Antiinflammatory"[tw] OR "Non-steroidal Anti-inflammatory"[tw] OR NSAID*[tw] OR "Diphosphonates"[Mesh] OR "bisphosphonates"[tw] OR "bisphosphonate"[tw] OR "Intra-Articular Injection"[tw] OR "Intraarticular Injections"[tw] OR "Intraarticular Injection"[tw] OR "Injections"[mesh] OR "injection"[tw] OR "injections"[tw] OR inject*[tw] OR Intraarticular*[tw] OR Intra-articular*[tw] OR "Viscosupplementation"[Mesh] OR "viscosupplementation"[tw] OR viscosupplement*[tw] OR "Hyaluronic Acid"[Mesh] OR "Hyaluronic Acid"[tw] OR "Hyaluronic Acids"[tw] OR "Hyaluronate"[tw] OR "Hyaluronan"[tw] OR corticosteroid*[tw] OR "Adrenal Cortex Hormones"[Mesh] OR "Adrenal Cortex Hormones"[Pharmacological Action] OR "Methylprednisolone"[mesh] OR "Prednisolone"[mesh] OR "Prednisone"[mesh] OR "Glucocorticoids"[tw] OR "Glucocorticoid"[tw] OR glucocorticoid*[tw] OR "Biological Therapy"[Mesh] OR "infliximab"[tw] OR "adalimumab"[tw] OR "etanercept"[tw] OR "remicade"[tw] OR "humira"[tw] OR "enbrel"[tw] OR "infliximab"[tw] OR "antibodies, monoclonal"[Mesh] OR "Monokines"[Mesh] OR "Receptors, Interleukin-1"[Mesh] OR "anakinra"[tw] OR "kineret"[tw] OR "Arthrodesis"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthrodesis"[tw] OR "Arthroplasty"[tw] OR "surgery"[tw] OR "surgical"[tw] OR "replacement"[tw] OR trapeziectom*[tw] OR "non-pharmacological"[tw] OR "Self Care"[Mesh] OR "self-management"[tw] OR "assistive devices"[tw] OR "Ultrasonography/therapeutic use"[Mesh] OR "therapeutic ultrasound" OR "pharmacological intervention"[tw] OR "pharmacological interventions"[tw] OR "diet therapy"[tw] OR "Diet Therapy"[Mesh] OR "diet therapy"[Subheading] OR "DMARDs"[tw] OR DMARD*[tw] OR "anti-IL-1"[tw] OR "anti-IL1"[tw] OR

"anti-Interleukin-1"[tw] OR "anti-Interleukin1"[tw] OR "Osteotomy"[Mesh] OR "osteotomy"[tw] OR osteotom*[tw]) NOT ("Animals"[mesh] NOT "Humans"[mesh]))

13.1.2 EMBASE search strategy

EMBASE search strategy with added relevant pharmacological interventions, searched without time restriction:

 (exp "Hand"/ OR "hand".ti OR "hands".ti OR exp "Hand Joint"/ OR "hand joint".ti OR "hand joints".ti OR "intermetacarpal joint".ti OR "intermetacarpal joints".ti OR "finger".ti OR "fingers".ti OR exp "Finger Joint"/ OR exp Carpal Joint/ OR "Carpal Joint".ti OR "Carpal Joints".ti OR "Carpometacarpal Joint".ti OR "Carpometacarpal Joints".ti OR "Finger Joint".ti OR "Finger Joints".ti OR "Metacarpophalangeal Joint".ti OR "Metacarpophalangeal Joints".ti OR exp thumb/ OR "thumb".ti OR "thumbs".ti OR exp metacarpal bone/ OR "metacarpus".ti OR "trapeziometacarpal".ti OR "first metacarpal-carpal".ti OR "carpometacarpal".ti OR "interphalangeal".ti OR "distal interphalangeal".ti OR "proximal interphalangeal".ti OR Intermetacarp*.ti OR Interphalang*.ti OR Intercarp*.ti OR Carpometacarp*.ti OR Metacarpophalang*.ti OR Metacarp*.ti OR scaphotrapeziotrapezoid*.ti) AND (exp Osteoarthritis/ OR "Osteoarthritis".ti OR osteoarthr*.ti OR "osteoarthrosis".ti OR "osteoarthroses".ti OR "degenerative arthritis".ti OR rhizarthros*.ti OR "arthrosis".ti OR "arthroses".ti OR Heberden.ti OR Bouchard.ti) AND (exp "colchicine"/ OR "colchicine".mp OR exp "estrogen"/ OR "estrogen".mp OR exp "herbaceous agent"/ OR "shinbaro".mp OR "lutikizumab".mp OR "abt-981".mp OR "tocilizumab".mp OR exp "cannabinoids"/ OR "cannabidiol".mp OR exp "apremilast"/ OR "apremilast".mp OR exp "thalidomide"/ OR "thalidomide".mp OR exp "denosumab"/ OR "denosumab".mp OR "pregabalin".mp OR exp "serotonin noradrenalin reuptake inhibitor"/ OR "duloxetin".mp OR "otilimab".mp OR "gsk3196165".mp OR "gevokizumab".mp OR exp "human serum albumin"/ OR "ampion".mp)

EMBASE search strategy from Kroon et al., searched from 2017 until present:

 (exp "Hand"/ OR "hand".ti OR "hands".ti OR exp "Hand Joint"/ OR "hand joint".ti OR "hand joints".ti OR "intermetacarpal joint".ti OR "intermetacarpal joints".ti OR "finger".ti OR "fingers".ti OR exp "Finger Joint"/ OR exp Carpal Joint/ OR "Carpal Joint".ti OR "Carpal Joints".ti OR "Carpometacarpal Joint".ti OR "Carpometacarpal Joints".ti OR "Finger Joint".ti OR "Finger Joints".ti OR "Metacarpophalangeal Joint".ti OR "Metacarpophalangeal Joints".ti OR exp thumb/ OR "thumb".ti OR "thumbs".ti OR exp metacarpal bone/ OR "metacarpus".ti OR "trapeziometacarpal".ti OR "first metacarpal-carpal".ti OR "carpometacarpal".ti OR "interphalangeal".ti OR "distal interphalangeal".ti OR "proximal interphalangeal".ti OR Intermetacarp*.ti OR

Interphalang*.ti OR Intercarp*.ti OR Carpometacarp*.ti OR Metacarpophalang*.ti OR Metacarp*.ti OR scaphotrapeziotrapezoid*.ti) AND (exp Osteoarthritis/ OR "Osteoarthritis".ti OR osteoarthr*.ti OR "osteoarthrosis".ti OR "osteoarthroses".ti OR "degenerative arthritis".ti OR rhizarthros*.ti OR "arthrosis".ti OR "arthroses".ti OR Heberden.ti OR Bouchard.ti) AND (exp "Treatment Outcome"/ OR "Treatment".mp OR "Treatments".mp OR "treated".mp OR "Therapeutics".mp OR "Therapeutic".mp OR "Therapy".mp OR "Therapies".mp OR exp therapy/ OR "drug".mp OR "drugs".mp OR medicament*.mp OR exp kinesiotherapy/ OR kinesiotherapy.mp OR "Exercise Therapy".mp OR Rehabilitation/ OR "Rehabilitation".mp OR exp "Antirheumatic Agent"/ OR "Antirheumatic".mp OR exp analgesic agent/ OR Analgesic*.mp OR exp nonsteroid antiinflammatory agent/ OR "Nonsteroidal Antiinflammatory".mp OR "Nonsteroidal Anti-inflammatory".mp OR "Non-steroidal Antiinflammatory".mp OR "Non-steroidal Anti-inflammatory".mp OR NSAID*.mp OR exp Arthrodesis/ OR exp Arthroplasty/ OR "Arthrodesis".mp OR "Arthroplasty".mp OR "surgery".mp OR "surgical".mp OR "replacement".mp OR trapeziectom*.mp OR "exercise".mp OR "Health Education"/ OR "education".mp OR exp "Self Care"/ OR exp "Behavior Therapy"/ OR exp "Splint"/ OR exp "Orthosis"/ OR "Self-Help Device"/ OR splint*.mp OR orthos*.mp OR "assistive device".mp OR exp "Thermotherapy"/ OR "heat application".mp OR exp "Topical Drug Administration"/ OR exp "balneotherapy"/ OR "balneotherapy".mp OR "Paracetamol"/ OR "acetaminophen".mp OR "paracetamol".mp OR exp "Glucosamine"/ OR "glucosamine".mp OR "Chondroitin"/ OR "chondroitin".mp OR "chondroitin sulfate".mp OR "chondroitin sulphate".mp OR "avocado-soyabean unsaponifiables".mp OR "avocado-soybean unsaponifiables".mp OR "ASU".mp OR "diacerein"/ OR "diacerhein".mp OR "diacerein".mp OR "Dietary Supplement"/ OR exp "salicylic acid derivative "/ OR salicylate*.mp OR "Capsaicin"/ OR "Capsaicin".mp OR "Hydroxychloroquine"/ OR "Methotrexate"/ OR "Sulfasalazine"/ OR "Hydroxychloroquine".mp OR "Methotrexate".mp OR "Sulfasalazine".mp OR "Tramadol"/ OR "Tramadol".mp OR "opioid".mp OR "opioids".mp OR exp "bisphosphonic acid derivative"/ OR "bisphosphonates".mp OR "bisphosphonate".mp OR "Intra-Articular Injection".mp OR "Intraarticular Injections".mp OR "Intraarticular Injection".mp OR exp "Injection"/ OR "injection".mp OR "injections".mp OR inject*.mp OR Intraarticular*.mp OR Intra-articular*.mp OR "Viscosupplementation"/ OR "viscosupplementation".mp OR viscosupplement*.mp OR "Hyaluronic Acid"/ OR "Hyaluronic Acid".mp OR "Hyaluronic Acids".mp OR "Hyaluronate".mp OR "Hyaluronan".mp OR corticosteroid*.mp OR exp "Corticosteroid"/ OR "Methylprednisolone"/ OR "Prednisolone"/ OR exp "Prednisone"/ OR "Glucocorticoids".mp OR "Glucocorticoid".mp OR glucocorticoid*.mp OR exp "Biological Therapy"/ OR "infliximab".mp OR "adalimumab".mp OR "etanercept".mp OR "remicade".mp OR "humira".mp OR "enbrel".mp OR "infliximab".mp OR exp "monoclonal antibody"/ OR exp "Monokine"/ OR "Interleukin 1 receptor"/ OR "anakinra".mp OR "kineret".mp OR "non-pharmacological".mp OR "self-management".mp

OR "assistive devices".mp OR exp "Ultrasound Therapy"/ OR "therapeutic ultrasound" OR "pharmacological intervention".mp OR "pharmacological interventions".mp OR "diet therapy".mp OR exp "Diet Therapy"/ OR "DMARDs".mp OR DMARD*.mp OR "anti-IL-1".mp OR "anti-IL1".mp OR "anti-Interleukin-1".mp OR "anti-Interleukin1".mp OR exp "Osteotomy"/ OR "osteotomy".mp OR osteotom*.mp) AND (exp human/ OR human.mp.)

13.1.3 CENTRAL search strategy

CENTRAL search strategy with added relevant pharmacological interventions, searched without time restriction:

(("Hand" OR "hands" OR "Hand Joints" OR "hand joint" OR "intermetacarpal joint" OR "intermetacarpal joints" OR "finger" OR "fingers" OR "Finger Joint" OR "Carpal Joints" OR "Carpal Joint" OR "Carpal Joints" OR "Carpometacarpal Joint" OR "Carpometacarpal Joints" OR "Finger Joints" OR "Metacarpophalangeal Joint" OR "Metacarpophalangeal Joints" OR "thumb" OR "thumbs" OR "metacarpus" OR "trapeziometacarpal" OR "first metacarpal-carpal" OR "carpometacarpal" OR "interphalangeal" OR "distal interphalangeal" OR "proximal interphalangeal" OR Intermetacarp* OR Interphalang* OR Intercarp* OR Carpometacarp* OR Metacarpophalang* OR Metacarp* OR scaphotrapeziotrapezoid*) AND ("Osteoarthritis" OR osteoarthr* OR "osteoarthrosis" OR "osteoarthroses" OR "degenerative arthritis" OR rhizarthros* OR "arthrosis" OR "arthroses" OR Heberden OR Bouchard) AND ("Colchicine" OR "glucosamin" OR "estrogen" OR "shinbaro" OR "plant extracts" OR "lutikizumab" OR "ABT-981" OR "immunoglobulins" OR "tocilizumab" OR "cannabidiol" OR "cannabinoids" OR "apremilast" OR "thalidomide" OR "denosumab" OR "pregabalin" OR "duloxetine" OR "GSK3196165" OR "otilimab" OR "Gevokizumab" OR "ampion" OR "Serum Albumin, Human"))

CENTRAL search strategy from Kroon et al., searched from 2017 until present:

(("Hand" OR "hands" OR "Hand Joints" OR "hand joint" OR "intermetacarpal joint" OR "intermetacarpal joints" OR "finger" OR "fingers" OR "Finger Joint" OR "Carpal Joints" OR "Carpal Joint" OR "Carpal Joints" OR "Carpometacarpal Joint" OR "Carpometacarpal Joints" OR "Finger Joints" OR "Metacarpophalangeal Joint" OR "Metacarpophalangeal Joints" OR "thumb" OR "thumbs" OR "metacarpus" OR "trapeziometacarpal" OR "first metacarpal-carpal" OR "carpometacarpal" OR "interphalangeal" OR "distal interphalangeal" OR "proximal interphalangeal" OR Intermetacarp* OR Interphalang* OR Intercarp* OR Carpometacarp* OR Metacarpophalang* OR Metacarp* OR scaphotrapeziotrapezoid*) AND ("Osteoarthritis" OR osteoarthr* OR

"osteoarthrosis" OR "osteoarthroses" OR "degenerative arthritis" OR rhizarthros* OR "arthrosis" OR "arthroses" OR Heberden OR Bouchard) AND ("Treatment Outcome" OR "Treatment" OR "Treatments" OR "treated" OR "Therapeutics" OR "Therapeutic" OR "Therapy" OR "Therapies" OR therapy OR "drug" OR "drugs" OR medicament* OR kinesiotherapy OR kinesiotherapy OR "Exercise Therapy" OR Rehabilitation OR "Rehabilitation" OR "Antirheumatic Agent" OR "Antirheumatic" OR analgesic agent OR Analgesic* OR nonsteroid antiinflammatory agent OR "Nonsteroidal Antiinflammatory" OR "Nonsteroidal Anti-inflammatory" OR "Non-steroidal Antiinflammatory" OR "Non-steroidal Anti-inflammatory" OR NSAID* OR Arthrodesis OR Arthroplasty OR "Arthrodesis" OR "Arthroplasty" OR "surgery" OR "surgical" OR "replacement" OR trapeziectom* OR "exercise" OR "Health Education" OR "education" OR "Self Care" OR "Behavior Therapy" OR "Splint" OR "Orthosis" OR "Self-Help Device" OR splint* OR orthos* OR "assistive device" OR "Thermotherapy" OR "heat application" OR "Topical Drug Administration" OR "balneotherapy" OR "balneotherapy" OR "Paracetamol" OR "acetaminophen" OR "paracetamol" OR "Glucosamine" OR "glucosamine" OR "Chondroitin" OR "chondroitin" OR "chondroitin sulfate" OR "chondroitin sulphate" OR "avocado-soyabean unsaponifiables" OR "avocado-soybean unsaponifiables" OR "ASU" OR "diacerein" OR "diacerhein" OR "diacerein" OR "Dietary Supplement" OR "salicylic acid derivative " OR salicylate* OR "Capsaicin" OR "Capsaicin" OR "Hydroxychloroquine" OR "Methotrexate" OR "Sulfasalazine" OR "Hydroxychloroquine" OR "Methotrexate" OR "Sulfasalazine" OR "Tramadol" OR "Tramadol" OR "opioid" OR "opioids" OR "bisphosphonic acid derivative" OR "bisphosphonates" OR "bisphosphonate" OR "Intra-Articular Injection" OR "Intraarticular Injections" OR "Intraarticular Injection" OR "Injection" OR "injection" OR "injections" OR inject* OR Intraarticular* OR Intra-articular* OR "Viscosupplementation" OR "viscosupplementation" OR viscosupplement* OR "Hyaluronic Acid" OR "Hyaluronic Acid" OR "Hyaluronic Acids" OR "Hyaluronate" OR "Hyaluronan" OR corticosteroid* OR "Corticosteroid" OR "Methylprednisolone" OR "Prednisolone" OR "Prednisone" OR "Glucocorticoids" OR "Glucocorticoid" OR glucocorticoid* OR "Biological Therapy" OR "infliximab" OR "adalimumab" OR "etanercept" OR "remicade" OR "humira" OR "enbrel" OR "infliximab" OR "monoclonal antibody" OR "Monokine" OR "Interleukin 1 receptor" OR "anakinra" OR "kineret" OR "non-pharmacological" OR "self-management" OR "assistive devices" OR "Ultrasound Therapy" OR "therapeutic ultrasound" OR "pharmacological intervention" OR "pharmacological interventions" OR "diet therapy" OR "Diet Therapy" OR "DMARDs" OR DMARD* OR "anti-IL-1" OR "anti-IL1" OR "anti-Interleukin-1" OR "anti-Interleukin1" OR "Osteotomy" OR "osteotomy" OR osteotom*))

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