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Placebo effects of local (intra-articular) therapy in osteoarthritis – an individual patient data meta-analysis protocol

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ABSTRACT

Introduction:

Osteoarthritis is a highly prevalent and disabling condition with limited safe and effective treatment options available. Intra-articular therapies are increasingly being utilised, especially in patients with mono or oligoarthritis. However, whether the effect of these agents is due to active treatment or placebo remains unclear. The placebo effect is part of treatment effect and identifying the magnitude and potential predictors of this effect in intra-articular therapies will inform the design of future trials and clinical practice. The aim of this individual patient data meta-analysis is to investigate the predictors of placebo effects in intra-articular injection trials in osteoarthritis.

Method and analysis:

A systematic literature search will be conducted for randomised clinical trials comparing corticosteroid and viscosupplementation/hyaluronic acid intra-articular injection with placebo for knee and hip osteoarthritis. Literature searches will be conducted through Pubmed (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS from inception to September 2018. Individual patient data from each study will be requested and obtained from the corresponding authors of the trials. Risk of bias will be assessed using the Cochrane Collaboration's tool.

The primary outcome will be change in pain from baseline. Secondary outcomes will be change in function and patient global assessment. Predictors of response to treatment that will be assessed include patient characteristics (age, gender, bilateral versus unilateral disease, other joints OA involvement, radiographic severity, pain severity and presence of inflammatory features based on imaging and physical examination), intervention characteristics (aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial design characteristics. We will report our results using the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA)-IPD guidelines.

Ethics and dissemination:

This study does not include identifiable data and ethical approval was obtained by the original investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-reviewed journal and international conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The use of an individual patient data (IPD) meta-analysis of randomised controlled trials will provide more precise estimates of the placebo effect. It also allows the identification of patient-level predictors of placebo effect in this population.
- The study will be conducted within the framework of the OA Trial Bank, an international organisation that initiates meta-analyses of effect on predefined subgroups of OA patients from existing trials.
- Identification of the predictors of placebo response in intra-articular injections for osteoarthritis may influence future study designs with a more tailored approach when classifying participants in future studies.
- nclusion of frequently utilised intra-articular injection RCTs will allow for a larger sample size, increased precision of the results and provide insight into the more commonly used injectables.
- The limitation lies in the potential for bias due to lack of available IPDs obtainable despite the number of studies available due to study and company regulations.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent condition that imposes a substantial burden on the individuals affected. It is estimated that by 2030, 25% of the population of the USA (67 million adults) will have OA.[1] Current management strategies suggest a focus towards conservative therapies including physiotherapy and weight loss, as well as pain palliation whether it is in the form of medications or ultimately joint replacement surgery.[2] However, for patients, especially with only symptomatic monoarthritis or oligoarthritis, the systematic effects of oral medications raises safety concerns [3-6]. Intra-articular injection therapies appear to be an attractive alternative in these patients, and there is a trend in the development of investigational intra-articular agents, aiming to improve symptoms and potentially alter disease progression.

Presently available intra-articular therapies are corticosteroids and viscosupplements (hyaluronic acid).[7, 8] Agents such as blood-derived products are also available in some countries. However, based on current guidelines for knee OA, intra-articular injections are not first-line therapies and are preferred as the last non-operative alternative where other conservative modalities have failed, or in some published treatment guidelines, not recommended at all based on their limited evidence, or controversial efficacy profiles.[9, 10]

There are a number of methodological limitations of clinical trials in OA that have constrained progress. Especially with intra-articular therapies in OA, most trials are small, thus affecting the strength of the studies. Another issue is the frequent practice of comparing one controversial agent versus another (i.e. platelet-rich plasma versus hyaluronate agent), which will not justify the agent to be superior in the overall treatment of OA. Furthermore, in intra-articular therapy trials, there are concerns of whether intra-articular injection of normal saline should be considered as the ideal agent to be employed as a placebo, given its potential volume/washout effects after injection.[11]

The inability to demonstrate a minimum clinically important difference over placebo, directly affects the development of potential pharmacological innovations and their translation to becoming commercially available treatment options for this disabling disease. The magnitude of the placebo effect in OA trials is significant with about 75% of treatment effect being attributable to placebo.[12] In general, the more invasive and more frequent the administration of an intervention, the larger the placebo effect. For invasive therapies, patients' expectations and beliefs create even larger placebo/contextual effects.[13] When considering clinical trial design, the challenges of which placebo to choose, its volume, injection frequency, the use of injection guidance, concomitant local anaesthetic use, patient baseline disease presentation (bilateral versus unilateral disease, concomitant presence of inflammatory features/effusion, disease severity, baseline pain) all create substantial opportunity for heterogeneity in what is already a challenging clinical trial environment. The intervention itself is also subject to placebo effects; administration route, colour, branding and cost all have an effect, thus indicating that clinical trials may need more standardisation across the board to optimise the demonstration of treatment response.[14]

To date, placebo effects from clinical trials are ultimately measured as a change in outcome from baseline in the placebo group in comparison to the treatment group. Minimal trials incorporate a no-treatment group, which may allow for adequate clarification of the placebo effect. Meta-analysis of OA treatments has shown that the placebo effect varies greatly between individuals.[12] The main limitation of aggregate data meta-analysis is that the variations of the treatment/placebo effects across individuals cannot be scrutinised. As the placebo effect can be attributed to the individual or related to the study protocol, assessment of the placebo effect utilising individual patient data (IPD) meta-analysis will give insight into the different predictors of placebo response. IPD analysis is now increasingly used over established meta-analysis and is

considered to be superior, as it facilitates standardisation of analyses across different studies and allow derivation of the desired information.[15] Our IPD meta-analysis will examine the role of potential placebo effect modifiers, assessing patient, intervention and trial characteristics - contextual factors that are rarely measured and reported in clinical trials or analysed in existing meta-analyses.

This analysis will be conducted under the auspices of the OA Trial Bank, an international collaboration that is endorsed by the Osteoarthritis Research Society International (OARSI) and the European League Against Rheumatism (EULAR). The OA Trial Bank was initiated in 2010 with the purpose of collecting and analysing IPD of published randomised controlled trials (RCTs) in OA to identify specific responseive subgroups for the different OA treatment. It brings together data from individuals with a diagnosis of OA, recruited for published RCTs from around the world to form a databank.[16, 17]

Therefore, the aim of this IPD analysis is to investigate the magnitude of the placebo effect and its potential predictors in intra-articular injection trials in osteoarthritis. This study will differ from the recently submitted IPD-meta-analysis protocol assessing placebo response in OA by University of Nottingham arthritis research group.[17] Based on their published protocol, their data extraction from the OA Trial Bank is targeted at OA therapies namely topical non-steroidal anti-inflammatory drugs, topical capsaicin, glucosamine and intra-articular glucocorticoids. Potential placebo effect modifiers that will be assessed are: patient baseline characteristics (age, gender, body mass index), disease (radiographic information, signs of inflammation, muscle strength, duration of complaints, pain severity, type of pain, central sensitisation, psychological assessments), placebo (oral, topical, injection, dose), and trial and outcome measures (pain, function, patient global assessment, and quality of life).[17] In contrast, intra-articular injection therapies will be the only therapies of interest in this analysis. While there will be some cross over

regarding patient-level characteristics, the incorporation of viscosupplementation/hyaluronic acid trials and an updated systematic review with the acquisition of newer glucocorticoid trials which will allow for a larger sample size, increased precision of the results and provide insight into the more commonly used injectables. In addition to patient-level characteristics, there will be a focus on interventional and trial characteristics i.e. Intervention characteristics (aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial characteristics (clinical setting, blinding, use of intention to treat analysis, funder/sponsor).

METHODS AND ANALYSIS

Individual patient data from trials comparing intra-articular injection to placebo for knee osteoarthritis will be extracted and re-analysed to ascertain the magnitude of the placebo effect and the role of potential predictors in these trials. The analysis will be conducted under the umbrella of the OA Trial Bank.

The IPD meta-analysis will be conducted in accordance with the methods recommended by the IPD Meta-analysis Methods Group.[15] Reporting of the meta-analysis will conform with the PRISMA-IPD checklist.[18]

The research question and study proposal of this study has been approved by the steering committee of the OA Trial Bank, before the development of the full study protocol.

Participants

Participants from the identified randomised controlled trials must have a diagnosis of knee and hip OA, according to the criteria defined by the American College of Rheumatology, EULAR

evidence-based recommendations for the diagnosis of knee OA [19, 20] or fulfil specified radiological criteria of OA diagnosis.

Types of baseline assessments

Participant baseline characteristics including age, gender, bilateral versus unilateral disease, other joint OA involvement, radiographic severity, pain severity at baseline and presence of inflammatory features (based on imaging and physical examination). Intervention characteristics (clinical setting, aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial design characteristics (blinding, dropout rate, use of intention to treat analysis, role of funder/sponsor) will also be extracted.

Types of outcomes

The primary outcome of the IPD meta-analysis will be change in pain over time. Visual analogue scale (VAS) pain score will be preferentially used for the analysis. If unavailable, the WOMAC pain score will be used and converted into a VAS 0-100 scale as per previous OA Trial Bank Protocols.[21]

Secondary outcomes will be a change in function and patient global assessment.

Language

No language restrictions will apply.

Literature search

- Identification of studies

A systematic literature search will be conducted using the following databases: Pubmed (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS. The search will be from inception to September 2018. The search strategy was developed by the reviewers in consultation with the OA Trial Bank (Appendix 1).

Literature searches will be done separately for intra-articular glucocorticoid and viscosupplementation/hyaluronic acid. The literature search approach will comprise of an amalgamation of main search terms including identification of the osteoarthritis population group, intervention of intra-articular glucocorticoid and viscosupplementation/hyaluronic acid, and of randomised controlled trial design. Furthermore, efforts will be made to identify unpublished trials through Clinicaltrials.gov. and contacting pharmaceutical suppliers.
Identified studies will be imported to EndNote X8 for screening.

- Screening process

Studies eligible for inclusion will be assessed by two independent reviewers (SY, LD). Titles and abstracts for potential studies will be screened first, and subsequently, the full text of the selected studies will be reviewed for appropriateness to be included. If no consensus is reached, a third reviewer will be consulted (DJH). The results will be summarised as per the PRISMA guidelines.[22]

Type of studies

Randomised placebo-controlled trials of intra-articular glucocorticoids and/or viscosupplementation/hyaluronic acid in knee or hip osteoarthritis will be included. Studies related to inflammatory arthritis (such as rheumatoid or psoriatic arthritis) will be excluded. Animal model

and biomarker studies will be excluded. Trials that are not randomised, literature or systematic reviews, and conference abstracts without available data will be excluded.

Data collection and transfer

As per all other studies conducted by the OA Trial Bank,[16, 21, 23] the same method for data acquisition and transfer will be utilised. The corresponding authors of eligible trials will be invited to collaborate. Initial contact will be by email with two further successive email reminders. If the corresponding author is uncontactable, communication will be attempted with the other trial authors and/or institutions listed. Authors who are willing to collaborate will be asked to sign a data delivery agreement from the OA Trial Bank. This will include items of input data, ownership of data, obligation, terms, authorship, and subsequent publication intentions. The data obtained will be stored on a secure server at Erasmus MC University Medical Center, Rotterdam, the Netherlands, and participant details will be kept in an anonymous and confidential fashion. Data quality will be ensured through independent checking looking at data-entry mistakes and inconsistencies. Data received will be compared with the published summary results from the primary studies. In situations where there are differences found, the authors will be contacted to resolve the discrepancy issue.

With the existing intra-articular glucocorticoid trials that have been stored in the OA Trial Bank, the corresponding authors will be contacted and will be asked to sign a further data transfer agreement for the use of their data for the purpose of this analysis.

Patient and public involvement

There have been no patient and/or public involvement in the design of this IPD meta-analysis.

Risk and Quality assessment

The included trials will be assessed independently by two reviewers to assess the quality of evidence and the risk of biases through the use of the Cochrane Collaboration's tool.[24, 25] A third reviewer will be consulted if there is a disagreement. The domains assessed will include randomisation of procedure, blinding of participants, physicians and treatment allocation, use of intention to treat analysis, incomplete outcome data, baseline group similarity, reporting bias and other sources of biases. Studies will be categorised as 'low risk', 'high risk' or 'unclear. As per previous studies with the OA trial bank, a low risk of bias study will be classified as fulfilling at least 6 of the 12 items in the Cochrane Collaboration's tool.[25]

Data analysis

A descriptive evaluation of each trial and study participants will be conducted. Publication bias will be investigated using a funnel plot analysis.[25, 26] Missing data will be assumed to be missing at random, thus patient characteristics will be used to impute missing data by means of multiple imputation at random.[27, 28]

Baseline and follow-up data from the placebo arm will be used to estimate the predictors of the placebo effect. When possible, and no-treatment data is available, those will be included as well to estimate a between-group placebo effect. Separate analyses will be conducted for glucocorticoids and viscosupplementation/hyaluronic acid, as well as different outcome measures (i.e. pain, function and patient global assessment). Trials will also be grouped by type of joint (i.e. knee or hip) and follow up duration (e.g. < 4 weeks or > 4 weeks for corticosteroid and <12 weeks or >12 weeks for viscosupplementation/hyaluronic acid).

A one-step approach will be applied, via the use of a multilevel logistic regression model to estimate the magnitude of the placebo effect. The use of the one step approach in this setting will

allow for a more cohesive modelling of covariates and account for the clustering of participants within the study.[15]

The primary outcome will be change in pain and will be determined as the dependent variable in the regression model. Secondary outcomes will be a change in function and patient global assessment. Change in pain will be determined as the dependent variable, and independent variables will be the potential predictors of placebo effect. These will be grouped as patient-level characteristics, peripheral pain mechanisms, central pain mechanisms, intervention characteristics and those related to trial design (blinding, funder/sponsor roles and intention to treat) (Table 1) and are as listed below. Each group will be forced into multivariate models with a final model including all groups.

1. Patient characteristics: age, gender, body mass index, bilateral versus unilateral disease, disease duration,
2. Pain mechanisms: peripheral (i.e. signs of inflammation, morning stiffness symptoms and radiographic findings), central pain mechanisms (i.e. other joint OA, comorbidities, pain severity),
3. Intervention characteristics: clinical setting (i.e. location of intervention), aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach (i.e. medial vs lateral approach, use of ultrasound guided injection).
4. Trial characteristics: blinding (patients, assessors or physicians), dropout rates, role of funder/sponsor (i.e. pharmaceutical company) and use of 'intention to treat' analysis.

The trials that originate the individual patient data will also be coded and included as a level variable in all analyses. Analyses will be performed by intention to treat. Effect sizes and 95% confidence intervals will be generated for each outcome measure. $P < 0.05$ will be considered statistically significant.

A sensitivity analysis will be conducted using pain scores (instead of change in pain scores) as a continuous dependent variable and repeating the approaches described above.

Statistical analyses will be performed using Stata SE 14 (StataCorp, College Station, TX).

EXPECTED RESEARCH CONTRIBUTION

It is envisaged, that the investigators will deliver data to be used in the design and execution of future clinical trials. It will allow for better understanding of the placebo effect and subsequent implementation of clinical designs with lowered placebo responses.

ETHICS AND DISSEMINATION

This study does not include identifiable data. Ethical approval was obtained by the original investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-reviewed journal and by international conference presentations.

AUTHORS' CONTRIBUTIONS

Study design: SPY, MLF, SMZ, MvM, WZ and DJH contributed to the study design. SPY and LD will be conducting the systematic review, data extraction, and analysis. SPY drafted the first version of the manuscript and all the authors were involved in the critical revision of the manuscript for important intellectual content. The study proposal has been peer-reviewed and approved by the OA Trial Bank Steering Committee.

FUNDING STATEMENT

SPY holds a University of Sydney Postgraduate Research Scholarship (Part Time). MLF holds a National Health and Medical Research Council (NHMRC) Career Development Fellowship and is a Sydney Medical Foundation Fellow. DJH holds an NHMRC Practitioner Fellowship. SBZ

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COMPETING INTERESTS STATEMENT

DJH reports personal fees from consulting fees from Merck Serono, Flexion and Tissuegene, outside the submitted work. All other authors have nothing to disclose.

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Table 1: Potential placebo effect modifiers

Study Features	Description
Patient domain	Age Gender Body mass index Bilateral versus unilateral disease Disease duration
Central pain mechanisms	OA on other joints Comorbidities Pain severity
Peripheral pain mechanisms	Radiographic information Presence of inflammatory features (ultrasound versus physician assessed joint swelling) Morning stiffness symptoms
Trial characteristics	Blinding Dropout rates per group Inclusion of a 'no treatment' group Use of 'intention to treat analysis' Funding/Sponsor (i.e. pharmaceutical funding)

APPENDIX 1

Search strategies for placebo response intra-articular corticosteroid injections in knee and/or hip osteoarthritis

Pubmed (Medline): 299 hits (30-09-2018)

((arthrit*[tw] OR arthros*[tw] OR arthrot*[tw] OR osteoarthro*[tw] OR osteoarthrit*[tw] OR osteoporo*[tw] OR boneloss*[tw] OR bone-loss*[tw] OR osteopen*[tw]) AND (hip[tw] OR hips[tw] OR knee[tw] OR knees[tw])) OR coxarthr*[tw] OR cox-arthr*[tw] OR gonarthr*[tw] OR gon-arthr*[tw]) AND (adrenal cortex hormones[mesh] OR adrenal cortex hormone*[tw] OR adrenal cortical hormone*[tw] OR adrenal cortical steroid*[tw] OR adrenal steroid*[tw] OR adrenocortical hormone*[tw] OR adrenocortical steroid*[tw] OR adrenocorticosteroid*[tw] OR adreno-corticosteroid*[tw] OR cortical steroid*[tw] OR cortico-steroid[tw] OR corticoid*[tw] OR corticosteroid*[tw] OR cortico-steroid*[tw] OR dermocorticosteroid*[tw] OR glucocortic*[tw] OR hydroxycorticosteroid*[tw] OR ketosteroid*[tw] OR androstenedion*[tw]) AND (intraartic*[tw] OR intra-artic*[tw]) AND inject*[tw] AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])) NOT (case report*[tw] OR retrospect*[tw] OR cadaver*[tw])

Web of Science – 383 hits (30-09-2018)

((((hip OR hips OR knee OR knees) NEAR/3 (arthrit* OR arthros* OR arthrot* OR osteoarthro* OR osteoarthrit*)) OR coxarthro* OR (cox NEAR/1 arthro*) OR gonarthro* OR (gon NEAR/1 arthro*)) AND (adrenocorticosteroid* OR corticoid* OR corticosteroid* OR dermocorticosteroid* OR glucocortic* OR hydroxycorticosteroid* OR ketosteroid* OR androstenedion* OR (adrenal OR adrenocortical OR adreno OR cortical OR cortico) NEAR/3 (hormone* OR steroid* OR corticosteroid*)) AND ((intraartic* OR (intra NEAR/1 artic*)) AND inject*) AND (randomi* OR ((singl* OR doubl* OR tripl*) NEAR/3 (mask* OR blind*)) OR "latin square" OR "crossover procedure" OR control* OR prospectiv* OR volunteer* OR placebo* OR "comparative study" OR "evaluation research" OR "follow up") NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR retrospect* OR cadaver*))

Embase – 558 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	corticosteroid/ or ((adrenocorticosteroid* or corticoid* or corticosteroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or (adrenal or adrenocortical or adreno or cortical or cortico)) adj5 (hormone* or steroid* or corticosteroid*)).mp.
3	(intraartic* or (intra adj5 artic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	inject*.mp.
5	(random* or (clinical adj5 trial*) or ((singl* or doubl* or tripl*) adj5 (mask* or blind*)) or latin square or crossover procedure or control* or prospectiv* or volunteer* or placebo*).mp. or comparative study/ or evaluation research/ or 'follow up'.mp. or followup:ti,ab,de.mp. or 'prospective study'/syn [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	3 or 4
7	2 and 6
8	1 and 5 and 7
9	((case adj5 report*) or retrospect* or cadaver*).mp.
10	8 not 9
11	limit 10 to human

Cochrane Central – 163 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp.
2	exp adrenal cortex hormones/
3	(adrenocorticosteroid* or corticoid* or corticosteroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or ((adrenal or adrenocortical or adreno or cortical or cortico) adj5 (hormone* or steroid* or corticosteroid*))).mp.
4	((intraartic* or (intra adj5 artic*)) and inject*).mp
5	2 or 3
6	1 and 4 and 5

Search strategies for placebo response intra-articular hyaluronic acid/viscosupplementation injections in knee and/or hip osteoarthritis

Pubmed (Medline): 776 hits (30-09-2018)

((arthrit*[tw] OR arthros*[tw] OR arthrot*[tw] OR osteoarthro*[tw] OR osteoarthrit*[tw] OR osteoporo*[tw] OR boneloss*[tw] OR bone-loss*[tw] OR osteopen*[tw]) AND (hip[tw] OR hips[tw] OR knee[tw] OR knees[tw])) OR coxarthr*[tw] OR cox-arthr*[tw] OR gonarthr*[tw] OR gon-arthr*[tw]) AND (hyaluronic acid*[tw] OR viscosupplementation*[tw] OR hyaluronate*[tw] OR hyaluron*[tw] OR hylan*[tw] OR synvisc*[tw] OR orthovisc*[tw] OR ostenil* [tw] OR suplasyn*[tw] OR arthrum*[tw] OR synovial*[tw] OR artz*[tw] OR biotty*[tw] OR go-on*[tw] OR healon*[tw] OR hyaject*[tw] OR hyalgan*[tw] OR hyalart*[tw] OR hyalectin*[tw] OR nuflexxa*[tw] OR euflexxa*[tw] OR polireumin*[tw] OR hygag*[tw] OR replasyn*[tw] OR supartz*[tw] OR artzal*[tw] OR nrd101*[tw] AND (intraartic*[tw] OR intra-artic*[tw]) AND inject*[tw]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])) NOT (case report*[tw] OR retrospect*[tw] OR cadaver*[tw]))

Web of Science – 596 hits (30-09-2018)

((((hip OR hips OR knee OR knees) NEAR/3 (arthrit* OR arthros* OR arthrot* OR osteoarthro* OR osteoarthrit*)) OR coxarthro* OR (cox NEAR/1 arthro*) OR gonarthro* OR (gon NEAR/1 arthro*)) AND (hyaluronic acid* OR viscosupplementation* OR hyaluronate* OR hyaluron* OR hylan* OR synvisc* OR orthovisc* OR ostenil* OR suplasyn* OR arthrum* OR synovial*OR artz* OR biotty* OR go-on* OR healon* OR hyaject* OR hyalgan* OR hyalart* OR hyalectin* OR nuflexxa* OR euflexxa* OR polireumin* OR hygag* OR replasyn* OR supartz* OR artzal* OR nrd101*) AND ((intraartic* OR (intra NEAR/1 artic*)) AND inject*) AND (randomi* OR ((singl* OR doubl* OR tripl*) NEAR/3 (mask* OR blind*)) OR "latin square" OR "crossover procedure" OR control* OR prospectiv* OR volunteer* OR placebo* OR "comparative study" OR "evaluation research" OR "follow up") NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR retrospect* OR cadaver*))

Embase – 1209 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	hyaluronic acid/ or viscosupplementation*.mp. or hyaluronate*.mp. or hyaluron*.mp. or hylan*.mp. or synvisc*.mp. or orthovisc*.mp. or ostenil.mp. or suplasyn*.mp. or arthrum*.mp. or synovial*OR artz*.mp. or biotty*.mp. or go-on*.mp. or healon*.mp. or hyaject*.mp. or hyalgan*.mp. or hyalart*.mp. or hyalectin*.mp. or nuflexxa*.mp. or euflexxa*.mp. or polireumin*.mp. or hygag*.mp. or replasyn*.mp. or supartz*.mp. or artzal*.mp. or nrd101*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3	(intraartic* or (intra adj5 artic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	inject*.mp.
5	(random* or (clinical adj5 trial*) or ((singl* or doubl* or tripl*) adj5 (mask* or blind*)) or latin square or crossover procedure or control* or prospectiv* or volunteer* or placebo*).mp. or comparative study/ or evaluation research/ or 'follow up'.mp. or followup:ti,ab,de.mp. or 'prospective study'/syn [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	3 or 4
7	2 and 6
8	1 and 5 and 7
9	((case adj5 report*) or retrospect* or cadaver*).mp.
10	8 not 9
11	limit 10 to human

Cochrane Central – 377 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp.
2	hyaluronic acid/ or viscosupplementation*.mp. or hyaluronate*.mp. or hyaluron*.mp. or hylan*.mp. or synvisc*.mp. or orthovisc*.mp. or ostenil.mp. or suplasyn*.mp. or arthrum*.mp. or synovial*OR artz*.mp. or biotty*.mp. or go-on*.mp. or healon*.mp. or hyaject*.mp. or hyalgan*.mp. or hyalart*.mp. or hyalectin*.mp. or nuflexxa*.mp. or euflexxa*.mp. or polireumin*.mp. or hygag*.mp. or replasyn*.mp. or supartz*.mp. or artzal*.mp. or nrd101*.mp.
3	((intraartic* or (intra adj5 artic*)) and inject*).mp
4	1 and 2 and 3

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 No.#)
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
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	13
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
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	7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8-9 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
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)	9
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	9
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	11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** 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.

BMJ Open

Placebo effects of local (intra-articular) therapy in osteoarthritis - an individual patient data meta-analysis protocol

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Research methods
Keywords:	Osteoarthritis, Individual patient data meta-analysis, Intra-articular therapy, Placebo effect

Placebo effects of local (intra-articular) therapy in osteoarthritis – an individual patient data meta-analysis protocol

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Word Count: 2877

Keywords:

Osteoarthritis; individual patient data meta-analysis; intra-articular therapy; placebo effect

Systemic review registration:

PROSPERO registration number: CRD42018095188

ABSTRACT

Introduction:

Osteoarthritis is a highly prevalent and disabling condition with limited safe and effective treatment options available. Intra-articular therapies are increasingly being utilised, however whether the effect of these agents is due to active treatment or placebo remains unclear. As the placebo effect can be attributed to multiple factors, assessment of the placebo effect utilising individual patient data (IPD) meta-analysis will give insight into the different modifiers of response to placebo. The aim of this IPD meta-analysis is to investigate the predictors of placebo effects in intra-articular injection trials in osteoarthritis. IPD meta-analysis is considered to be superior to conventional meta-analysis, as it facilitates standardisation of analyses across different studies and allows derivation of the desired information.

Method and analysis:

A systematic literature search will be conducted for randomised clinical trials comparing corticosteroid and viscosupplementation/hyaluronic acid intra-articular injections with placebo for knee and hip osteoarthritis. Pubmed (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS will be searched from inception to September 2018. Corresponding authors of the original trials will be contacted to obtain individual patient data. Risk of bias will be assessed using the Cochrane Collaboration's tool.

The primary outcome will be change in pain from baseline. Secondary outcomes will be change in function and patient global assessment. Potential placebo effect modifiers assessed will include patient characteristics, pain mechanism characteristics, radiographic severity, pain severity, intervention characteristics and trial design characteristics. A multilevel logistic regression analyses will be applied. Results will be reported using the

Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA)-IPD guidelines.

Ethics and dissemination:

This study does not include identifiable data and ethical approval was obtained by the original investigators. Results of the IPD meta-analysis will be disseminated for publication in peer-reviewed journals and conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The use of an individual patient data (IPD) meta-analysis of randomised controlled trials will provide more precise estimates of the placebo effect. It also allows the identification of patient-level predictors of placebo effect in this population.
- The study will be conducted within the framework of the OA Trial Bank, an international organisation that initiates meta-analyses of effect on predefined subgroups of OA patients from existing trials.
- Identification of the predictors of placebo response in intra-articular injections for osteoarthritis may influence future clinical trial designs with a more tailored approach when classifying participants in future studies.
- Inclusion of frequently utilised intra-articular injection RCTs will allow for a larger sample size, increased precision of the results and provide insight into the more commonly used injectables.
- The limitation lies in the potential for bias due to lack of available IPDs obtainable despite the number of studies available due to study and company regulations, and

the inclusion of only corticosteroid and viscosupplements/hyaluronic acid trials may affect our ability to identify predictors of response.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent condition that imposes a substantial burden on the individuals affected. It is estimated that by 2030, 25% of the population of the USA (67 million adults) will have OA.[1] Current management strategies suggest a focus towards conservative therapies including physiotherapy and weight loss, as well as pain palliation whether it is in the form of medications or ultimately joint replacement surgery.[2] However, for patients, especially with only symptomatic monoarthritis or oligoarthritis, the systematic effects of oral medications raises safety concerns [3-6]. Intra-articular injection therapies appear to be an attractive alternative in these patients, and there is a trend in the development of investigational intra-articular agents, aiming to improve symptoms and potentially alter disease progression.

Presently available intra-articular therapies are corticosteroids and viscosupplements (hyaluronic acid).[7, 8] Agents such as blood-derived products are also available in some countries. However, based on current guidelines for knee OA, intra-articular injections are not first-line therapies and are preferred as the last non-operative alternative where other conservative modalities have failed, or in some published treatment guidelines, not recommended at all based on their limited evidence, or controversial efficacy profiles.[9, 10]

There are a number of methodological limitations of clinical trials in OA that have constrained progress. Especially with intra-articular therapies in OA, most trials are small, thus affecting the strength of the studies. Another issue is the frequent practice of comparing one controversial agent versus another (i.e. platelet-rich plasma versus hyaluronate agent), which will not justify the agent to be superior in the overall treatment of OA. Furthermore, in intra-articular therapy trials, there are concerns of whether intra-articular injection of normal saline should be considered as the ideal agent to be employed as a placebo, given its potential volume/washout and possible biological effects after injection.[11, 12] However, without other more appropriate alternatives at present, normal saline is still the standard agent to be used

in the context of a placebo-controlled intra-articular injection trial despite the concerns. The inclusion of a no-treatment/sham-injection group may be a way to discern the placebo effect of normal saline, however the presence of this design is rare in OA clinical trials.[13]

The inability to demonstrate a minimum clinically important difference over placebo, directly affects the development of potential pharmacological innovations and their translation to becoming commercially available treatment options for this disabling disease. The magnitude of the placebo effect in OA trials is significant with about 75% of treatment effect being attributable to placebo contextual effects.[14] In general, the more invasive and more frequent the administration of an intervention, the larger the placebo effect. For invasive therapies, patients' expectations and beliefs create even larger placebo/contextual effects.[13] When considering clinical trial design, the challenges of which placebo to choose, its volume, injection frequency, the use of injection guidance, concomitant local anaesthetic use, patient baseline disease presentation (bilateral versus unilateral disease, concomitant presence of inflammatory features/effusion, disease severity, baseline pain) all create substantial opportunity for heterogeneity in what is already a challenging clinical trial environment. The intervention itself is also subject to placebo effects; administration route, colour, branding and cost all have an effect, thus indicating that clinical trials may need more standardisation across the board to optimise the demonstration of treatment response.[15]

To date, placebo effects from clinical trials are ultimately measured as a change in outcome from baseline in the placebo group in comparison to the treatment group. Minimal trials incorporate a no-treatment group, which may allow for adequate clarification of the placebo effect. Meta-analysis of OA treatments has shown that the placebo effect varies greatly between individuals.[14] The main limitation of aggregate data meta-analysis is that the variations of the treatment/placebo effects across individuals cannot be scrutinised. As the placebo effect can be attributed to the individual or related to the study protocol, assessment of the placebo effect utilising individual patient data (IPD) meta-analysis will give insight into

the different predictors of placebo response. IPD analysis is now increasingly used over established meta-analysis and is considered to be superior, as it facilitates standardisation of analyses across different studies and allow derivation of the desired information.[16] Our IPD meta-analysis will examine the role of potential placebo effect modifiers, assessing patient, intervention and trial characteristics - contextual factors that are rarely measured and reported in clinical trials or analysed in existing meta-analyses.

This analysis will be conducted under the auspices of the OA Trial Bank, an international collaboration that is endorsed by the Osteoarthritis Research Society International (OARSI) and the European League Against Rheumatism (EULAR). The OA Trial Bank was initiated in 2010 with the purpose of collecting and analysing IPD of published randomised controlled trials (RCTs) in OA to identify specific responseive subgroups for the different OA treatment. It brings together data from individuals with a diagnosis of OA, recruited for published RCTs from around the world to form a databank.[17, 18]

Therefore, the aim of this IPD analysis is to investigate the predictors of placebo effects in intra-articular injection trials in osteoarthritis. This study will differ from the recently submitted IPD-meta-analysis protocol assessing placebo response in OA by University of Nottingham arthritis research group.[18] Based on their published protocol, their data extraction from the OA Trial Bank is targeted at OA therapies namely topical non-steroidal anti-inflammatory drugs, topical capsaicin, glucosamine and intra-articular glucocorticoids. Potential placebo effect modifiers that will be assessed are: patient baseline characteristics (age, gender, body mass index), disease (radiographic information, signs of inflammation, muscle strength, duration of complaints, pain severity, type of pain, central sensitisation, psychological assessments), placebo (oral, topical, injection, dose), and trial and outcome measures (pain, function, patient global assessment, and quality of life).[18] In contrast, intra-articular injection therapies will be the only therapies of interest in this analysis. While there will be some cross over regarding patient-level characteristics, the incorporation of

viscosupplementation/hyaluronic acid trials and an updated systematic review with the acquisition of newer glucocorticoid trials which will allow for a larger sample size, increased precision of the results and provide insight into the more commonly used injectables. In addition to patient-level characteristics, there will be a focus on interventional and trial characteristics i.e. Intervention characteristics (aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial characteristics (clinical setting, blinding, use of intention to treat analysis, funder/sponsor).

METHODS AND ANALYSIS

Individual patient data from trials comparing intra-articular injection to placebo for knee osteoarthritis will be extracted and re-analysed to ascertain the magnitude of the placebo effect and the role of potential predictors in these trials. The analysis will be conducted under the umbrella of the OA Trial Bank.

The IPD meta-analysis will be conducted in accordance with the methods recommended by the IPD Meta-analysis Methods Group.[16] Reporting of the meta-analysis will conform with the PRISMA-IPD checklist.[19]

The research question and study proposal of this study has been approved by the steering committee of the OA Trial Bank, before the development of the full study protocol.

Participants

Participants from the identified randomised controlled trials must have a diagnosis of knee and hip OA, according to the criteria defined by the American College of Rheumatology, EULAR evidence-based recommendations for the diagnosis of knee OA [20, 21] or fulfil specified radiological criteria of OA diagnosis.

Types of baseline assessments

Participant baseline characteristics including age, gender, bilateral versus unilateral disease, other joint OA involvement, radiographic severity, pain severity at baseline and presence of inflammatory features (based on imaging and physical examination). Intervention characteristics (clinical setting, aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial design characteristics (blinding, dropout rate, use of intention to treat analysis, role of funder/sponsor) will also be extracted.

Types of outcomes

The primary outcome of the IPD meta-analysis will be change in pain over time. Visual analogue scale (VAS) pain score will be preferentially used for the analysis. If unavailable, the WOMAC pain score will be used and converted into a VAS 0-100 scale as per previous OA Trial Bank Protocols.[22]

Secondary outcomes will be a change in function and patient global assessment.

Language

No language restrictions will apply.

Literature search

- Identification of studies

A systematic literature search will be conducted using the following databases: Pubmed (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS. The search will be from inception to September 2018. The search strategy was developed by the reviewers in consultation with the OA Trial Bank (Appendix 1).

Literature searches will be done separately for intra-articular glucocorticoid and viscosupplementation/hyaluronic acid. The literature search approach will comprise of an amalgamation of main search terms including identification of the osteoarthritis population group, intervention of intra-articular glucocorticoid and viscosupplementation/hyaluronic acid, and of randomised controlled trial design. Furthermore, efforts will be made to identify unpublished trials through Clinicaltrials.gov, European Union Clinical Trials Register (EUCTR) and ISRCTN registry, and contacting pharmaceutical suppliers.

Identified studies will be imported to EndNote X8 for screening.

- Screening process

Studies eligible for inclusion will be assessed by two independent reviewers (SY, LD). Titles and abstracts for potential studies will be screened first, and subsequently, the full text of the selected studies will be reviewed for appropriateness to be included. If no consensus is reached, a third reviewer will be consulted (DJH). The results will be summarised as per the PRISMA guidelines.[23]

Type of studies

Randomised placebo-controlled trials of intra-articular glucocorticoids and/or viscosupplementation/hyaluronic acid in knee or hip osteoarthritis will be included. Studies related to inflammatory arthritis (such as rheumatoid or psoriatic arthritis) will be excluded. Animal model and biomarker studies will be excluded. Trials that are not randomised, literature or systematic reviews, and conference abstracts without available data will be excluded.

Data collection and transfer

As per all other studies conducted by the OA Trial Bank,[17, 22, 24] the same method for data acquisition and transfer will be utilised. The corresponding authors of eligible trials will be invited to collaborate. Initial contact will be by email with two further successive email

reminders. If the corresponding author is uncontactable, communication will be attempted with the other trial authors and/or institutions listed. Authors who are willing to collaborate will be asked to sign a data delivery agreement from the OA Trial Bank. This will include items of input data, ownership of data, obligation, terms, authorship, and subsequent publication intentions. The data obtained will be stored on a secure server at Erasmus MC University Medical Center, Rotterdam, the Netherlands, and participant details will be kept in an anonymous and confidential fashion. Data quality will be ensured through independent checking looking at data-entry mistakes and inconsistencies. Data received will be compared with the published summary results from the primary studies. In situations where there are differences found, the authors will be contacted to resolve the discrepancy issue.

With the existing intra-articular glucocorticoid trials that have been stored in the OA Trial Bank, the corresponding authors will be contacted and will be asked to sign a further data transfer agreement for the use of their data for the purpose of this analysis.

Patient and public involvement

There have been no patient and/or public involvement in the design of this IPD meta-analysis.

Risk and Quality assessment

The included trials will be assessed independently by two reviewers to assess the quality of evidence and the risk of biases through the use of the Cochrane Collaboration's tool.[25, 26] A third reviewer will be consulted if there is a disagreement. The domains assessed will include randomisation of procedure, blinding of participants, physicians and treatment allocation, use of intention to treat analysis, incomplete outcome data, baseline group similarity, reporting bias and other sources of biases. Studies will be categorised as 'low risk', 'high risk' or 'unclear. As per previous studies with the OA trial bank, a low risk of bias study will be classified as fulfilling at least 6 of the 12 items in the Cochrane Collaboration's tool.[26]

Data analysis

A descriptive evaluation of each trial and study participants will be conducted. Publication bias will be investigated using a funnel plot analysis.[26, 27] Missing data will be assumed to be missing at random, thus patient characteristics will be used to impute missing data by means of multiple imputation at random.[28, 29]

Baseline and follow-up data from the placebo arm will be used to estimate the predictors of the placebo effect. When possible, and no-treatment data is available, those will be included as well to estimate a between-group placebo effect. Separate analyses will be conducted for glucocorticoids and viscosupplementation/hyaluronic acid, as well as different outcome measures (i.e. pain, function and patient global assessment). Trials will also be grouped by type of joint (i.e. knee or hip) and follow up duration (e.g. < 4 weeks or ≥ 4 weeks for corticosteroid and <12 weeks or ≥12 weeks for viscosupplementation/hyaluronic acid).

A one-step approach will be applied, via the use of multilevel regression models to assess for predictors of the placebo effect. The use of the one step approach in this setting will allow for a more cohesive modelling of covariates and account for the clustering of participants within the study.[16] This will be done by combining all the data from all the studies available after appropriate standardisation of the variables and a new dataset will be formed to allow for further analysis. To assess for the potential subgroup effects, a random effect model will be utilised given the hierarchical nature of the data to assess the interaction effects, with change in pain being a dependent variable, and all potential predictors being independent variables. In the setting where a no-treatment control is available, we will include placebo/no-treatment as an independent variable. Responders to placebo will be compared with non-responders to identify predictors of response.

The primary outcome will be change in pain from baseline and will be determined as the dependent variable in the regression model. The minimum clinically important difference (MCID) threshold will be a 20% or more reduction in pain based on the visual analogue scale (VAS) pain score with 0mm being no pain to 100mm being the worst pain ever. This level has been recommended for use in pain and function assessment in rheumatic diseases such as OA. [30, 31] In situations where WOMAC pain score is only available, it will be used instead.

Secondary outcomes will be a change in function and patient global assessment. Change in pain will be determined as the dependent variable, and independent variables will be the potential predictors of placebo effect. These will be grouped as patient-level characteristics, peripheral pain mechanisms, central pain mechanisms, intervention characteristics and those related to trial design (blinding, funder/sponsor roles and intention to treat) (Table 1) and are as listed below. Each group will be forced into multivariate models with a final model including all groups.

1. Patient characteristics: age, gender, body mass index, bilateral versus unilateral disease, disease duration,
2. Pain mechanisms: peripheral pain mechanisms (i.e. signs of inflammation, morning stiffness symptoms and radiographic findings), central pain mechanisms (i.e. other joint OA, comorbidities, pain severity),
3. Intervention characteristics: clinical setting (i.e. location of intervention), aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach (i.e. medial vs lateral approach, use of ultrasound guided injection).
4. Trial characteristics: blinding (patients, assessors or physicians), dropout rates, role of funder/sponsor (i.e. pharmaceutical company), randomisation ratio, trial duration, single centre/multi-centre study, parallel/cross-over trial, and use of 'intention to treat' analysis.

The trials that originate the individual patient data will also be coded and included as a level variable in all analyses. Effect sizes and 95% confidence intervals will be generated for each outcome measure. *P* <0.05 will be considered statistically significant.

A sensitivity analysis will be conducted using pain scores (instead of change in pain scores) as a continuous dependent variable and repeating the approaches described above.

Statistical analyses will be performed using Stata SE 14 (StataCorp, College Station, TX).

EXPECTED RESEARCH CONTRIBUTION

It is envisaged, that the investigators will deliver data to be used in the design and execution of future clinical trials. It will allow for better understanding of the placebo effect and subsequent implementation of clinical designs with lowered placebo responses.

ETHICS AND DISSEMINATION

This study does not include identifiable data. Ethical approval was obtained by the original investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-reviewed journal and by international conference presentations.

AUTHORS' CONTRIBUTIONS

Study design: SPY, MLF, SMZ, MvM, WZ and DJH contributed to the study design. SPY and LD will be conducting the systematic review, data extraction, and analysis. SPY drafted the first version of the manuscript and all the authors were involved in the critical revision of the manuscript for important intellectual content. The study proposal has been peer-reviewed and approved by the OA Trial Bank Steering Committee.

FUNDING STATEMENT

SPY holds a University of Sydney Postgraduate Research Scholarship (Part Time). MLF holds a National Health and Medical Research Council (NHMRC) Career Development Fellowship and is a Sydney Medical Foundation Fellow. DJH holds an NHMRC Practitioner Fellowship. SBZ reports grants from European Union, The Netherlands Organisation for Health Research and Development, Dutch Arthritis Foundation. WZ is supported by a grant from Arthritis Research UK. The OA Trial Bank is supported by the Dutch Arthritis Society.

COMPETING INTERESTS STATEMENT

DJH reports personal fees from consulting fees from Merck Serono, Flexion and Tissuegene, outside the submitted work. All other authors have nothing to disclose.

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Table 1: Potential placebo effect modifiers

Study Features	Description
Patient domain	Age Gender Body mass index Bilateral versus unilateral disease Disease duration
Pain mechanisms	Central pain mechanisms: Osteoarthritis in other joints Comorbidities Pain severity
	Peripheral pain mechanisms: Radiographic information Presence of inflammatory features (ultrasound versus physician assessed joint swelling) Morning stiffness symptoms
Intervention characteristics	Clinical setting (i.e. location of intervention) Aspirate volume Frequency of injection Volume of injection Intra-articular injection approach (i.e. medial vs. lateral approach, use of ultrasound guided injection).
Trial characteristics	Blinding Dropout rates per group Inclusion of a 'no treatment' group Use of 'intention to treat analysis'

	Randomisation ratio Trial duration Single centre/multi-centre study Parallel/crossover trial Funding/Sponsor (i.e. pharmaceutical funding)

Search strategies for placebo response intra-articular corticosteroid injections in knee and/or hip OA

Pubmed (Medline): 299 hits (30-09-2018)

((arthrit*[tw] OR arthros*[tw] OR arthrot*[tw] OR osteoarthro*[tw] OR osteoarthrit*[tw] OR osteoporo*[tw] OR boneloss*[tw] OR bone-loss*[tw] OR osteopen*[tw]) AND (hip[tw] OR hips[tw] OR knee[tw] OR knees[tw])) OR coxarthr*[tw] OR cox-arthr*[tw] OR gonarthr*[tw] OR gon-arthr*[tw]) AND (adrenal cortex hormones[mesh] OR adrenal cortex hormone*[tw] OR adrenal cortical hormone*[tw] OR adrenal cortical steroid*[tw] OR adrenal steroid*[tw] OR adrenocortical hormone*[tw] OR adrenocortical steroid*[tw] OR adrenocorticosteroid*[tw] OR adreno-corticosteroid*[tw] OR cortical steroid*[tw] OR cortico-steroid[tw] OR corticoid*[tw] OR corticosteroid*[tw] OR cortico-steroid*[tw] OR dermocorticosteroid*[tw] OR glucocortic*[tw] OR hydroxycorticosteroid*[tw] OR ketosteroid*[tw] OR androstenedion*[tw]) OR triamcinolone acetonide*[tw] OR betamethasone acetate*[tw] OR extended release*[tw] AND (intraartic*[tw] OR intra-artic*[tw]) AND inject*[tw] AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])) NOT (case report*[tw] OR retrospect*[tw] OR cadaver*[tw])

Web of Science – 383 hits (30-09-2018)

((((hip OR hips OR knee OR knees) NEAR/3 (arthrit* OR arthros* OR arthrot* OR osteoarthro* OR osteoarthrit*)) OR coxarthro* OR (cox NEAR/1 arthro*) OR gonarthro* OR (gon NEAR/1 arthro*)) AND (adrenocorticosteroid* OR corticoid* OR corticosteroid* OR dermocorticosteroid* OR glucocortic* OR hydroxycorticosteroid* OR ketosteroid* OR triamcinolone acetonide* OR betamethasone acetate* OR extended release* OR androstenedion* OR (adrenal OR adrenocortical OR adreno OR cortical OR cortico) NEAR/3 (hormone* OR steroid* OR corticosteroid*)) AND ((intraartic* OR (intra NEAR/1 artic*)) AND inject*) AND (randomi* OR ((singl* OR doubl* OR tripl*) NEAR/3 (mask* OR blind*)) OR "latin square" OR "crossover procedure" OR control* OR prospectiv* OR volunteer* OR placebo* OR "comparative study" OR "evaluation research" OR "follow up") NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR retrospect* OR cadaver*))

Embase – 558 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	corticosteroid/ or ((adrenocorticosteroid* or corticoid* or corticosteroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or triamcinolone acetonide* or betamethasone acetate* or (adrenal or adrenocortical or adreno or cortical or cortico)) adj5 (hormone* or steroid* or corticosteroid*)).mp.
3	(intraartic* or (intra adj5 artic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	inject*.mp.
5	(random* or (clinical adj5 trial*) or ((singl* or doubl* or tripl*) adj5 (mask* or blind*)) or latin square or crossover procedure or control* or prospectiv* or volunteer* or placebo*).mp. or comparative study/ or evaluation research/ or 'follow up'.mp. or followup:ti,ab,de.mp. or 'prospective study'/syn [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	3 or 4
7	2 and 6
8	1 and 5 and 7
9	((case adj5 report*) or retrospect* or cadaver*).mp.
10	8 not 9
11	limit 10 to human

Cochrane Central – 163 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp.
2	exp adrenal cortex hormones/
3	(adrenocorticosteroid* or corticoid* or corticosteroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or triamcinolone acetonide* or betamethasone acetate* androstenedion* or ((adrenal or adrenocortical or adreno or cortical or cortico) adj5 (hormone* or steroid* or corticosteroid*))).mp.
4	((intraartic* or (intra adj5 artic*)) and inject*).mp
5	2 or 3
6	1 and 4 and 5

Search strategies for placebo response intra-articular hyaluronic acid/viscosupplementation injections in knee and/or hip OA

Pubmed (Medline): 776 hits (30-09-2018)

((arthrit*[tw] OR arthros*[tw] OR arthrot*[tw] OR osteoarthro*[tw] OR osteoarthrit*[tw] OR osteoporo*[tw] OR boneloss*[tw] OR bone-loss*[tw] OR osteopen*[tw]) AND (hip[tw] OR hips[tw] OR knee[tw] OR knees[tw])) OR coxarthr*[tw] OR cox-arthr*[tw] OR gonarthr*[tw] OR gon-arthr*[tw]) AND (hyaluronic acid*[tw] OR viscosupplementation*[tw] OR hyaluronate*[tw] OR hyaluron*[tw] OR hylan*[tw] OR synvisc*[tw] OR orthovisc*[tw] OR ostenil* [tw] OR suplasyn*[tw] OR arthrum*[tw] OR synovial*[tw] OR artz*[tw] OR biotty*[tw] OR go-on*[tw] OR healon*[tw] OR hyaject*[tw] OR hyalgan*[tw] OR hyalart*[tw] OR hyalectin*[tw] OR nuflexxa*[tw] OR euflexxa*[tw] OR polireumin*[tw] OR hygag*[tw] OR replasyn*[tw] OR supartz*[tw] OR artzal*[tw] OR nrd101*[tw] AND (intraartic*[tw] OR intra-artic*[tw]) AND inject*[tw]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])) NOT (case report*[tw] OR retrospect*[tw] OR cadaver*[tw]))

Web of Science – 596 hits (30-09-2018)

((((hip OR hips OR knee OR knees) NEAR/3 (arthrit* OR arthros* OR arthrot* OR osteoarthro* OR osteoarthrit*)) OR coxarthro* OR (cox NEAR/1 arthro*) OR gonarthro* OR (gon NEAR/1 arthro*)) AND (hyaluronic acid* OR viscosupplementation* OR hyaluronate* OR hyaluron* OR hylan* OR synvisc* OR orthovisc* OR ostenil* OR suplasyn* OR arthrum* OR synovial*OR artz* OR biotty* OR go-on* OR healon* OR hyaject* OR hyalgan* OR hyalart* OR hyalectin* OR nuflexxa* OR euflexxa* OR polireumin* OR hygag* OR replasyn* OR supartz* OR artzal* OR nrd101*) AND ((intraartic* OR (intra NEAR/1 artic*)) AND inject*) AND (randomi* OR ((singl* OR doubl* OR tripl*) NEAR/3 (mask* OR blind*)) OR "latin square" OR "crossover procedure" OR control* OR prospectiv* OR volunteer* OR placebo* OR "comparative study" OR "evaluation research" OR "follow up") NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR retrospect* OR cadaver*))

Embase – 1209 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	hyaluronic acid/ or viscosupplementation*.mp. or hyaluronate*.mp. or hyaluron*.mp. or hylan*.mp. or synvisc*.mp. or orthovisc*.mp. or ostenil.mp. or suplasyn*.mp. or arthrum*.mp. or synovial*OR artz*.mp. or biotty*.mp. or go-on*.mp. or healon*.mp. or hyaject*.mp. or hyalgan*.mp. or hyalart*.mp. or hyalectin*.mp. or nuflexxa*.mp. or euflexxa*.mp. or polireumin*.mp. or hygag*.mp. or replasyn*.mp. or supartz*.mp. or artzal*.mp. or nrd101*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3	(intraartic* or (intra adj5 artic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	inject*.mp.
5	(random* or (clinical adj5 trial*) or ((singl* or doubl* or tripl*) adj5 (mask* or blind*)) or latin square or crossover procedure or control* or prospectiv* or volunteer* or placebo*).mp. or comparative study/ or evaluation research/ or 'follow up'.mp. or followup:ti,ab,de.mp. or 'prospective study'/syn [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	3 or 4
7	2 and 6
8	1 and 5 and 7
9	((case adj5 report*) or retrospect* or cadaver*).mp.
10	8 not 9
11	limit 10 to human

Cochrane Central – 377 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp.
2	hyaluronic acid/ or viscosupplementation*.mp. or hyaluronate*.mp. or hyaluron*.mp. or hylan*.mp. or synvisc*.mp. or orthovisc*.mp. or ostenil.mp. or suplasyn*.mp. or arthrum*.mp. or synovial*OR artz*.mp. or biotty*.mp. or go-on*.mp. or healon*.mp. or hyaject*.mp. or hyalgan*.mp. or hyalart*.mp. or hyalectin*.mp. or nuflexxa*.mp. or euflexxa*.mp. or polireumin*.mp. or hygag*.mp. or replasyn*.mp. or supartz*.mp. or artzal*.mp. or nrd101*.mp.
3	((intraartic* or (intra adj5 artic*)) and inject*).mp
4	1 and 2 and 3

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 No.#)
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
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	14
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
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	9-10 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
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)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13
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	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	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)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

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

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BMJ Open

Predictors of placebo response to local (intra-articular) therapy in osteoarthritis - an individual patient data meta-analysis protocol

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Complete List of Authors:	Yu, Shirley; University of Sydney Department of Rheumatology at Royal North Shore Hospital; University of Sydney Institute of Bone and Joint Research, Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research van Middelkoop, Marienke; Erasmus MC Univ Med Ctr Rotterdam Bierma-Zeinstra, Sita; Erasmus University Medical Centre, Department of General Practice Zhang, Weiya; University of Nottingham Division of Academic Rheumatology Deveza, Leticia; University of Sydney Department of Rheumatology at Royal North Shore Hospital; University of Sydney Institute of Bone and Joint Research Hunter, David; University of Sydney Institute of Bone and Joint Research; University of Sydney Department of Rheumatology at Royal North Shore Hospital
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Research methods
Keywords:	Osteoarthritis, Individual patient data meta-analysis, Intra-articular therapy, Placebo response

Predictors of placebo response to local (intra-articular) therapy in osteoarthritis – an individual patient data meta-analysis protocol

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Word Count: 3061

Keywords:

Osteoarthritis; individual patient data meta-analysis; intra-articular therapy; placebo response

Systemic review registration:

PROSPERO registration number: CRD42018095188

ABSTRACT

Introduction:

Osteoarthritis is a highly prevalent and disabling condition with limited safe and effective treatment options. Intra-articular therapies are increasingly being utilised, however whether the effect of these agents is due to active treatment or placebo remains unclear. As the placebo response can be attributed to multiple factors, assessment of the placebo response utilising individual patient data (IPD) meta-analysis will give insight into the different modifiers of response to placebo. The aim of this IPD meta-analysis is to investigate the predictors of placebo response in intra-articular injection trials in osteoarthritis. IPD meta-analysis is considered to be superior to conventional meta-analysis, as it combines multiple trial data, facilitates the standardisation of analyses across different studies and allows measuring derivation of the desired information.

Method and analysis:

A systematic literature search will be conducted for randomised clinical trials comparing corticosteroid and viscosupplementation/hyaluronic acid intra-articular injections with placebo for knee and hip osteoarthritis. Pubmed (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS will be searched from inception to September 2018. Corresponding authors of the original trials will be contacted to obtain individual patient data. Risk of bias will be assessed using the Cochrane Collaboration's tool.

The primary outcome will be change in pain from baseline. Secondary outcomes will be change in function and patient global assessment. Potential predictors of placebo response assessed will include patient characteristics, pain mechanism characteristics, radiographic severity, pain severity, intervention characteristics and trial design characteristics. A multilevel logistic regression analyses will be applied. Results will be reported using the

Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA)-IPD guidelines.

Ethics and dissemination:

This study does not include identifiable data and ethical approval was obtained by the original investigators. Results of the IPD meta-analysis will be disseminated for publication in peer-reviewed journals and conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The use of an individual patient data (IPD) meta-analysis of randomised controlled trials will provide more precise estimates of the placebo response. It also allows the identification of patient-level predictors of placebo response in this population.
- The study will be conducted within the framework of the OA Trial Bank, an international organisation that initiates meta-analyses of effect on predefined subgroups of OA patients from existing trials.
- Identification of the predictors of placebo response in intra-articular injections for osteoarthritis may influence future clinical trial designs with a more tailored approach when classifying participants in future studies.
- Inclusion of frequently utilised intra-articular injection RCTs will allow for a larger sample size, increased precision of the results and provide insight into the more commonly used injectables.
- We have only included injections of corticosteroid and viscosupplements/hyaluronic acid trials because these are the standard intra-articular treatments for OA. There are other intra-articular injection treatments such as blood products, growth factors and

prolotherapy. As they are not established treatments with limited evidence in OA, we will exclude them from this study.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent condition that imposes a substantial burden on the individuals affected. It is estimated that by 2030, 25% of the population of the USA (67 million adults) will have OA.[1] Current management strategies suggest a focus towards conservative therapies including physiotherapy and weight loss, as well as pain palliation whether it is in the form of medications or ultimately joint replacement surgery.[2] However, for patients, especially with only symptomatic monoarthritis or oligoarthritis, the systematic effects of oral medications raises safety concerns [3-6]. Intra-articular injection therapies appear to be an attractive alternative in these patients, and there is a trend in the development of investigational intra-articular agents, aiming to improve symptoms and potentially alter disease progression.

Presently available intra-articular therapies are corticosteroids and viscosupplements (hyaluronic acid).[7, 8] Agents such as blood-derived products are also available in some countries. However, based on current guidelines for knee OA, intra-articular injections are not first-line therapies and are preferred as the last non-operative alternative where other conservative modalities have failed, or in some published treatment guidelines, not recommended at all based on their limited evidence, or controversial efficacy profiles.[9, 10]

There are a number of methodological limitations of clinical trials in OA that have constrained progress. Especially with intra-articular therapies in OA, most trials are small, thus affecting the strength of the studies. Another issue is the frequent practice of comparing one controversial agent versus another (i.e. platelet-rich plasma versus hyaluronate agent), which will not justify the agent to be superior in the overall treatment of OA. Furthermore, in intra-articular therapy trials, there are concerns of whether intra-articular injection of normal saline should be considered as the ideal agent to be employed as a placebo. There are increasing number of studies contributing to the evidence of intra-articular saline having a potential biological effect. The biological effect in this setting is likely secondary to neurobiological

mechanisms such as those via endogenous opioid and dopaine,[11] as well as via possible dilution of the inflammatory element in the joint because of the volume of saline. [12, 13] Thus, intra-articular saline as a placebo can be considered to be an “impure placebo” in the context of a placebo-controlled intra-articular injection trial. The inclusion of a no-treatment/sham-injection group may be a way to discern the placebo effect of saline injections, however the presence of this design is rare in OA clinical trials. Despite this, previous meta-analysis of randomised controlled trials assessing the placebo response across a range of therapies in OA (non-pharmacological, pharmacological and surgical treatments) have confirmed that placebo response (Effect size (ES) = 0.51 95% CI 0.46-0.55) is greater than no treatment or spontaneous response (ES = 0.03, 95% CI -0.13-0.18) for pain in OA.[14]

The inability to demonstrate a minimum clinically important difference over placebo, directly affects the development of potential pharmacological innovations and their translation to becoming commercially available treatment options for this disabling disease. The magnitude of the placebo response in OA trials is significant with about 75% of treatment effect being attributable to placebo contextual effects.[15] In general, the more invasive and more frequent the administration of an intervention, the larger the placebo response. For invasive therapies, patients’ expectations and beliefs create even larger placebo/contextual effects.[14] When considering clinical trial design, the challenges of which placebo to choose, its volume, injection frequency, the use of injection guidance, concomitant local anaesthetic use, patient baseline disease presentation (bilateral versus unilateral disease, concomitant presence of inflammatory features/effusion, disease severity, baseline pain) all create substantial opportunity for heterogeneity in what is already a challenging clinical trial environment. The intervention itself is also subject to contextual effects; administration route, colour, branding and cost all have an effect, thus indicating that clinical trials may need more standardisation across the board to optimise the demonstration of treatment response.[16]

To date, placebo responses from clinical trials are ultimately measured as a change in outcome from baseline in the placebo group in comparison to the treatment group and is potentially confounded by spontaneous effects such as the Hawthorne effect (ie, the effect due to being observed), natural fluctuation of disease and regression to the mean.[14, 16] Minimal trials incorporate a no-treatment group, which may allow for adequate clarification of the placebo effect. Meta-analysis of OA treatments has shown that the placebo response varies greatly between individuals.[15] The main limitation of aggregate data meta-analysis is that the variations of the treatment/placebo responses across individuals cannot be scrutinised. As the placebo response can be attributed to the individual or related to the study protocol, assessment of the placebo response utilising individual patient data (IPD) meta-analysis will give insight into the different predictors of placebo response. IPD analysis is now increasingly used over established meta-analysis and is considered to be superior, as it facilitates standardisation of analyses across different studies and allow derivation of the desired information.[17] Our IPD meta-analysis will examine the role of potential placebo response modifiers, assessing patient, intervention and trial characteristics - contextual factors that are rarely measured and reported in clinical trials or analysed in existing meta-analyses.

This analysis will be conducted under the auspices of the OA Trial Bank, an international collaboration that is endorsed by the Osteoarthritis Research Society International (OARSI) and the European League Against Rheumatism (EULAR). The OA Trial Bank was initiated in 2010 with the purpose of collecting and analysing IPD of published randomised controlled trials (RCTs) in OA to identify specific responseive subgroups for the different OA treatment. It brings together data from individuals with a diagnosis of OA, recruited for published RCTs from around the world to form a databank.[18, 19]

Therefore, the aim of this IPD analysis is to investigate the predictors of placebo response in intra-articular injection trials in osteoarthritis. This study will differ from the recently submitted IPD-meta-analysis protocol assessing placebo response in OA by University of Nottingham

arthritis research group.[19] Based on their published protocol, their data extraction from the OA Trial Bank is targeted at OA therapies namely topical non-steroidal anti-inflammatory drugs, topical capsaicin, glucosamine and intra-articular glucocorticoids. Potential placebo response modifiers that will be assessed are: patient baseline characteristics (age, gender, body mass index), disease (radiographic information, signs of inflammation, muscle strength, duration of complaints, pain severity, type of pain, central sensitisation, psychological assessments), placebo (oral, topical, injection, dose), and trial and outcome measures (pain, function, patient global assessment, and quality of life).[19] In contrast, intra-articular injection therapies will be the only therapies of interest in this analysis. While there will be some cross over regarding patient-level characteristics, the incorporation of viscosupplementation/hyaluronic acid trials and an updated systematic review with the acquisition of newer glucocorticoid trials which will allow for a larger sample size, increased precision of the results and provide insight into the more commonly used injectables. In addition to patient-level characteristics, there will be a focus on interventional and trial characteristics i.e. Intervention characteristics (aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial characteristics (clinical setting, blinding, use of intention to treat analysis, funder/sponsor).

METHODS AND ANALYSIS

Individual patient data from trials comparing intra-articular injection to placebo for knee osteoarthritis will be extracted and re-analysed to ascertain the magnitude of the placebo response and the role of potential predictors in these trials. The analysis will be conducted under the umbrella of the OA Trial Bank.

The IPD meta-analysis will be conducted in accordance with the methods recommended by the IPD Meta-analysis Methods Group.[17] Reporting of the meta-analysis will conform with the PRISMA-IPD checklist.[20]

The research question and study proposal of this study has been approved by the steering committee of the OA Trial Bank, before the development of the full study protocol.

Participants

Participants from the identified randomised controlled trials must have a diagnosis of knee and hip OA, according to the criteria defined by the American College of Rheumatology, EULAR evidence-based recommendations for the diagnosis of knee OA [21, 22] or fulfil specified radiological criteria of OA diagnosis.

Types of baseline assessments

Participant baseline characteristics including age, gender, bilateral versus unilateral disease, other joint OA involvement, radiographic severity, pain severity at baseline and presence of inflammatory features (based on imaging and physical examination). Intervention characteristics (clinical setting, aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach), and trial design characteristics (blinding, dropout rate, use of intention to treat analysis, role of funder/sponsor) will also be extracted.

Types of outcomes

The primary outcome of the IPD meta-analysis will be change in pain over time. Visual analogue scale (VAS) pain score will be preferentially used for the analysis. If unavailable, the WOMAC pain score will be used and converted into a VAS 0-100 scale as per previous OA Trial Bank Protocols.[23]

Secondary outcomes will be a change in function and patient global assessment.

Language

No language restrictions will apply.

Literature search

- Identification of studies

A systematic literature search will be conducted using the following databases: Pubmed (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS. The search will be from inception to September 2018. The search strategy was developed by the reviewers in consultation with the OA Trial Bank (Appendix 1).

Literature searches will be done separately for intra-articular glucocorticoid and viscosupplementation/hyaluronic acid. The literature search approach will comprise of an amalgamation of main search terms including identification of the osteoarthritis population group, intervention of intra-articular glucocorticoid and viscosupplementation/hyaluronic acid, and of randomised controlled trial design. Furthermore, efforts will be made to identify unpublished trials through Clinicaltrials.gov, European Union Clinical Trials Register (EUCTR) and ISRCTN registry and contacting pharmaceutical suppliers.
Identified studies will be imported to EndNote X8 for screening.

- Screening process

Studies eligible for inclusion will be assessed by two independent reviewers (SY, LD). Titles and abstracts for potential studies will be screened first, and subsequently, the full text of the selected studies will be reviewed for appropriateness to be included. If no consensus is reached, a third reviewer will be consulted (DJH). The results will be summarised as per the PRISMA guidelines.[24]

Type of studies

Randomised placebo-controlled trials of intra-articular glucocorticoids and/or viscosupplementation/hyaluronic acid in knee or hip osteoarthritis will be included. Studies related to inflammatory arthritis (such as rheumatoid or psoriatic arthritis) will be excluded. Animal model and biomarker studies will be excluded. Trials that are not randomised, literature or systematic reviews, and conference abstracts without available data will be excluded.

Data collection and transfer

As per all other studies conducted by the OA Trial Bank,[18, 23, 25] the same method for data acquisition and transfer will be utilised. The corresponding authors of eligible trials will be invited to collaborate. Initial contact will be by email with two further successive email reminders. If the corresponding author is uncontactable, communication will be attempted with the other trial authors and/or institutions listed. Authors who are willing to collaborate will be asked to sign a data delivery agreement from the OA Trial Bank. This will include items of input data, ownership of data, obligation, terms, authorship, and subsequent publication intentions. The data obtained will be stored on a secure server at Erasmus MC University Medical Center, Rotterdam, the Netherlands, and participant details will be kept in an anonymous and confidential fashion. Data quality will be ensured through independent checking looking at data-entry mistakes and inconsistencies. Data received will be compared with the published summary results from the primary studies. In situations where there are differences found, the authors will be contacted to resolve the discrepancy issue.

With the existing intra-articular glucocorticoid trials that have been stored in the OA Trial Bank, the corresponding authors will be contacted and will be asked to sign a further data transfer agreement for the use of their data for the purpose of this analysis.

Patient and public involvement

There have been no patient and/or public involvement in the design of this IPD meta-analysis.

Risk and Quality assessment

The included trials will be assessed independently by two reviewers to assess the quality of evidence and the risk of biases through the use of the Cochrane Collaboration's tool.[26, 27] A third reviewer will be consulted if there is a disagreement. The domains assessed will include randomisation of procedure, blinding of participants, physicians and treatment allocation, use of intention to treat analysis, incomplete outcome data, baseline group similarity, reporting bias and other sources of biases. Studies will be categorised as 'low risk', 'high risk' or 'unclear. As per previous studies with the OA trial bank, a low risk of bias study will be classified as fulfilling at least 6 of the 12 items in the Cochrane Collaboration's tool.[27]

Data analysis

A descriptive evaluation of each trial and study participants will be conducted. Publication bias will be investigated using a funnel plot analysis as this will specify the potential impact of both known and unknown missing trials on the results.[27, 28] Missing data will be assumed to be missing at random, thus patient characteristics will be used to impute missing data by means of multiple imputation at random.[29, 30] In addition, we will compare the effect sizes pooled from those responded versus the overall (ie, the ES pooled from all trials systematically searched from the literature) to examine the deviation.

Baseline and follow-up data from the placebo arm will be used to estimate the predictors of the placebo response. Separate analyses will be conducted for glucocorticoids and viscosupplementation/hyaluronic acid, as well as different outcome measures (i.e. pain, function and patient global assessment). Trials will also be grouped by type of joint (i.e. knee or hip) and follow up duration (e.g. < 4 weeks or ≥ 4 weeks for corticosteroid and <12 weeks or ≥12 weeks for viscosupplementation/hyaluronic acid).

A one-step approach will be applied, via the use of multilevel regression models to assess for predictors of the placebo response. The use of the one step approach in this setting will allow for a more cohesive modelling of covariates and account for the clustering of participants within the study.[17] This will be done by combining all the data from all the studies available after appropriate standardisation of the variables and a new dataset will be formed to allow for further analysis. To assess for the potential subgroup effects, a random effect model will be utilised given the hierarchical nature of the data to assess the interaction effects, with change in pain being a dependent variable, and potential predictors being independent variables. In the setting where a no-treatment control is available, we will include placebo-no-treatment as an independent variable. Responders to placebo will be compared with non-responders to identify predictors of response.

The primary outcome will be change in pain from baseline and will be determined as the dependent variable in the regression model. The minimum clinically important difference (MCID) threshold will be a 20% or more reduction in pain based on the visual analogue scale (VAS) pain score with 0mm being no pain to 100mm being the worst pain ever. This level has been recommended for use in pain and function assessment in rheumatic diseases such as OA, [31, 32] and we will use it to define the placebo response which is equivalent to an ES of 0.8,[33] that indicates the response unlikely to be caused by spontaneous effects. In situations where WOMAC pain score is only available, it will be used instead.

Secondary outcomes will be a change in function and patient global assessment. Change in pain will be determined as the dependent variable, and independent variables will be the potential predictors of placebo response. These will be grouped as patient-level characteristics, peripheral pain mechanisms, central pain mechanisms, intervention characteristics and those related to trial design (blinding, funder/sponsor roles and intention to treat) (Table 1) and are as listed below. Each group will be forced into multivariate models with a final model including all groups.

1. Patient characteristics: age, gender, body mass index, bilateral versus unilateral disease, disease duration,
2. Pain mechanisms: peripheral pain mechanisms (i.e. signs of inflammation, morning stiffness symptoms and radiographic findings), central pain mechanisms (i.e. other joint OA, comorbidities, pain severity),
3. Intervention characteristics: clinical setting (i.e. location of intervention), aspirate volume, frequency of injection, volume of injection, and intra-articular injection approach (i.e. medial vs lateral approach, use of ultrasound guided injection).
4. Trial characteristics: blinding (patients, assessors or physicians), dropout rates, role of funder/sponsor (i.e. pharmaceutical company), randomisation ratio, trial duration, single centre/multi-centre study, parallel/cross-over trial, and use of 'intention to treat' analysis.

The trials that originate the individual patient data will also be coded and included as a level variable in all analyses. Effect sizes and 95% confidence intervals will be generated for each outcome measure. P <0.05 will be considered statistically significant.

A sensitivity analysis will be conducted using pain scores (instead of change in pain scores) as a continuous dependent variable and repeating the approaches described above.

Statistical analyses will be performed using Stata SE 14 (StataCorp, College Station, TX).

EXPECTED RESEARCH CONTRIBUTION

It is envisaged, that the investigators will deliver data to be used in the design and execution of future clinical trials. It will allow for better understanding of the placebo response and subsequent implementation of clinical designs with lowered placebo responses.

ETHICS AND DISSEMINATION

This study does not include identifiable data. Ethical approval was obtained by the original investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-reviewed journal and by international conference presentations.

AUTHORS' CONTRIBUTIONS

Study design: SPY, MLF, SBZ, MvM, WZ and DJH contributed to the study design. SPY and LD will be conducting the systematic review, data extraction, and analysis. SPY drafted the first version of the manuscript and all the authors were involved in the critical revision of the manuscript for important intellectual content. The study proposal has been peer-reviewed and approved by the OA Trial Bank Steering Committee.

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SPY holds a University of Sydney Postgraduate Research Scholarship (Part Time). MLF holds a National Health and Medical Research Council (NHMRC) Career Development Fellowship and is a Sydney Medical Foundation Fellow. DJH holds an NHMRC Practitioner Fellowship. SBZ reports grants from European Union, The Netherlands Organisation for Health Research and Development, Dutch Arthritis Foundation. WZ is supported by a grant from Arthritis Research UK. The OA Trial Bank is supported by the Dutch Arthritis Society.

COMPETING INTERESTS STATEMENT

DJH reports personal fees from consulting fees from Merck Serono, Flexion and Tissuegene, outside the submitted work. All other authors have nothing to disclose.

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Table 1: Potential placebo response modifiers

Study Features	Description
Patient domain	Age Gender Body mass index Bilateral versus unilateral disease Disease duration
Pain mechanisms	Central pain mechanisms: Osteoarthritis in other joints Comorbidities Pain severity
	Peripheral pain mechanisms: Radiographic information Presence of inflammatory features (ultrasound versus physician assessed joint swelling) Morning stiffness symptoms
Intervention characteristics	Clinical setting (i.e. location of intervention) Aspirate volume Frequency of injection Volume of injection Intra-articular injection approach (i.e. medial vs. lateral approach, use of ultrasound guided injection).
Trial characteristics	Blinding Dropout rates per group Inclusion of a 'no treatment' group Use of 'intention to treat analysis'

	Randomisation ratio Trial duration Single centre/multi-centre study Parallel/crossover trial Funding/Sponsor (i.e. pharmaceutical funding)

Search strategies for placebo response intra-articular corticosteroid injections in knee and/or hip OA

Pubmed (Medline): 299 hits (30-09-2018)

((arthrit*[tw] OR arthros*[tw] OR arthrot*[tw] OR osteoarthro*[tw] OR osteoarthrit*[tw] OR osteoporo*[tw] OR boneloss*[tw] OR bone-loss*[tw] OR osteopen*[tw]) AND (hip[tw] OR hips[tw] OR knee[tw] OR knees[tw])) OR coxarthr*[tw] OR cox-arthr*[tw] OR gonarthr*[tw] OR gon-arthr*[tw]) AND (adrenal cortex hormones[mesh] OR adrenal cortex hormone*[tw] OR adrenal cortical hormone*[tw] OR adrenal cortical steroid*[tw] OR adrenal steroid*[tw] OR adrenocortical hormone*[tw] OR adrenocortical steroid*[tw] OR adrenocorticosteroid*[tw] OR adreno-corticosteroid*[tw] OR cortical steroid*[tw] OR cortico-steroid[tw] OR corticoid*[tw] OR corticosteroid*[tw] OR cortico-steroid*[tw] OR dermocorticosteroid*[tw] OR glucocortic*[tw] OR hydroxycorticosteroid*[tw] OR ketosteroid*[tw] OR androstenedion*[tw]) OR triamcinolone acetonide*[tw] OR betamethasone acetate*[tw] OR extended release*[tw] AND (intraartic*[tw] OR intra-artic*[tw]) AND inject*[tw] AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])) NOT (case report*[tw] OR retrospect*[tw] OR cadaver*[tw])

Web of Science – 383 hits (30-09-2018)

((((hip OR hips OR knee OR knees) NEAR/3 (arthrit* OR arthros* OR arthrot* OR osteoarthro* OR osteoarthrit*)) OR coxarthro* OR (cox NEAR/1 arthro*) OR gonarthro* OR (gon NEAR/1 arthro*)) AND (adrenocorticosteroid* OR corticoid* OR corticosteroid* OR dermocorticosteroid* OR glucocortic* OR hydroxycorticosteroid* OR ketosteroid* OR triamcinolone acetonide* OR betamethasone acetate* OR extended release* OR androstenedion* OR (adrenal OR adrenocortical OR adreno OR cortical OR cortico) NEAR/3 (hormone* OR steroid* OR corticosteroid*)) AND ((intraartic* OR (intra NEAR/1 artic*)) AND inject*) AND (randomi* OR ((singl* OR doubl* OR tripl*) NEAR/3 (mask* OR blind*)) OR "latin square" OR "crossover procedure" OR control* OR prospectiv* OR volunteer* OR placebo* OR "comparative study" OR "evaluation research" OR "follow up") NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR retrospect* OR cadaver*))

Embase – 558 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	corticosteroid/ or ((adrenocorticosteroid* or corticoid* or corticosteroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or triamcinolone acetonide* or betamethasone acetate* or (adrenal or adrenocortical or adreno or cortical or cortico)) adj5 (hormone* or steroid* or corticosteroid*)).mp.
3	(intraartic* or (intra adj5 artic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	inject*.mp.
5	(random* or (clinical adj5 trial*) or ((singl* or doubl* or tripl*) adj5 (mask* or blind*)) or latin square or crossover procedure or control* or prospectiv* or volunteer* or placebo*).mp. or comparative study/ or evaluation research/ or 'follow up'.mp. or followup:ti,ab,de.mp. or 'prospective study'/syn [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	3 or 4
7	2 and 6
8	1 and 5 and 7
9	((case adj5 report*) or retrospect* or cadaver*).mp.
10	8 not 9
11	limit 10 to human

Cochrane Central – 163 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp.
2	exp adrenal cortex hormones/
3	(adrenocorticosteroid* or corticoid* or corticosteroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or triamcinolone acetonide* or betamethasone acetate* androstenedion* or ((adrenal or adrenocortical or adreno or cortical or cortico) adj5 (hormone* or steroid* or corticosteroid*))).mp.
4	((intraartic* or (intra adj5 artic*)) and inject*).mp
5	2 or 3
6	1 and 4 and 5

Search strategies for placebo response intra-articular hyaluronic acid/viscosupplementation injections in knee and/or hip OA

Pubmed (Medline): 776 hits (30-09-2018)

((arthrit*[tw] OR arthros*[tw] OR arthrot*[tw] OR osteoarthro*[tw] OR osteoarthrit*[tw] OR osteoporo*[tw] OR boneloss*[tw] OR bone-loss*[tw] OR osteopen*[tw]) AND (hip[tw] OR hips[tw] OR knee[tw] OR knees[tw])) OR coxarthr*[tw] OR cox-arthr*[tw] OR gonarthr*[tw] OR gon-arthr*[tw]) AND (hyaluronic acid*[tw] OR viscosupplementation*[tw] OR hyaluronate*[tw] OR hyaluron*[tw] OR hylan*[tw] OR synvisc*[tw] OR orthovisc*[tw] OR ostenil* [tw] OR suplasyn*[tw] OR arthrum*[tw] OR synovial*[tw] OR artz*[tw] OR biotty*[tw] OR go-on*[tw] OR healon*[tw] OR hyaject*[tw] OR hyalgan*[tw] OR hyalart*[tw] OR hyalectin*[tw] OR nuflexxa*[tw] OR euflexxa*[tw] OR polireumin*[tw] OR hygag*[tw] OR replasyn*[tw] OR supartz*[tw] OR artzal*[tw] OR nrd101*[tw] AND (intraartic*[tw] OR intra-artic*[tw]) AND inject*[tw]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])) NOT (case report*[tw] OR retrospect*[tw] OR cadaver*[tw]))

Web of Science – 596 hits (30-09-2018)

((((hip OR hips OR knee OR knees) NEAR/3 (arthrit* OR arthros* OR arthrot* OR osteoarthro* OR osteoarthrit*)) OR coxarthro* OR (cox NEAR/1 arthro*) OR gonarthro* OR (gon NEAR/1 arthro*)) AND (hyaluronic acid* OR viscosupplementation* OR hyaluronate* OR hyaluron* OR hylan* OR synvisc* OR orthovisc* OR ostenil* OR suplasyn* OR arthrum* OR synovial*OR artz* OR biotty* OR go-on* OR healon* OR hyaject* OR hyalgan* OR hyalart* OR hyalectin* OR nuflexxa* OR euflexxa* OR polireumin* OR hygag* OR replasyn* OR supartz* OR artzal* OR nrd101*) AND ((intraartic* OR (intra NEAR/1 artic*)) AND inject*) AND (randomi* OR ((singl* OR doubl* OR tripl*) NEAR/3 (mask* OR blind*)) OR "latin square" OR "crossover procedure" OR control* OR prospectiv* OR volunteer* OR placebo* OR "comparative study" OR "evaluation research" OR "follow up") NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR retrospect* OR cadaver*))

Embase – 1209 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	hyaluronic acid/ or viscosupplementation*.mp. or hyaluronate*.mp. or hyaluron*.mp. or hylan*.mp. or synvisc*.mp. or orthovisc*.mp. or ostenil.mp. or suplasyn*.mp. or arthrum*.mp. or synovial*OR artz*.mp. or biotty*.mp. or go-on*.mp. or healon*.mp. or hyaject*.mp. or hyalgan*.mp. or hyalart*.mp. or hyalectin*.mp. or nuflexxa*.mp. or euflexxa*.mp. or polireumin*.mp. or hygag*.mp. or replasyn*.mp. or supartz*.mp. or artzal*.mp. or nrd101*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3	(intraartic* or (intra adj5 artic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	inject*.mp.
5	(random* or (clinical adj5 trial*) or ((singl* or doubl* or tripl*) adj5 (mask* or blind*)) or latin square or crossover procedure or control* or prospectiv* or volunteer* or placebo*).mp. or comparative study/ or evaluation research/ or 'follow up'.mp. or followup:ti,ab,de.mp. or 'prospective study'/syn [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	3 or 4
7	2 and 6
8	1 and 5 and 7
9	((case adj5 report*) or retrospect* or cadaver*).mp.
10	8 not 9
11	limit 10 to human

Cochrane Central – 377 hits (30-09-2018)

	Searches
1	(((hip or hips or knee or knees) adj5 (arthrit* or arthros* or arthrot* or osteoarthro* or osteoarthrit*)) or coxarthro* or (cox adj5 arthro*) or gonarthro* or (gon adj5 arthro*)).mp.
2	hyaluronic acid/ or viscosupplementation*.mp. or hyaluronate*.mp. or hyaluron*.mp. or hylan*.mp. or synvisc*.mp. or orthovisc*.mp. or ostenil.mp. or suplasyn*.mp. or arthrum*.mp. or synovial*OR artz*.mp. or biotty*.mp. or go-on*.mp. or healon*.mp. or hyaject*.mp. or hyalgan*.mp. or hyalart*.mp. or hyalectin*.mp. or nuflexxa*.mp. or euflexxa*.mp. or polireumin*.mp. or hygag*.mp. or replasyn*.mp. or supartz*.mp. or artzal*.mp. or nrd101*.mp.
3	((intraartic* or (intra adj5 artic*)) and inject*).mp
4	1 and 2 and 3

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 No.#)
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
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	14
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
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	9-10 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
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)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13
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	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	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)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

*** 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.