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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027372
Article Type:	Protocol
Date Submitted by the Author:	19-Oct-2018
Complete List of Authors:	Yu, Shirley; Royal North Shore Hospital, Rheumatology; 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, Academic Rheumatology Deveza, Leticia; University of Sydney, Royal North Shore Hospital, Rheumatology Department Hunter, David; The University of Sydney,
Keywords:	Osteoarthritis, Individual patient data meta-analysis, Intra-articular therapy, Placebo effect

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Manuscripts

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3 **Placebo effects of local (intra-articular) therapy in osteoarthritis – an individual**  
4 **patient data meta-analysis protocol**  
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46 **Word Count:** 2632  
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50 **Keywords:**  
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52 Osteoarthritis; individual patient data meta-analysis; intra-articular therapy; placebo effect  
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3 **Systemic review registration:**  
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5 PROSPERO registration number: CRD42018095188  
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For peer review only

## 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.
- 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.

## 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]

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

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



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3 considered to be superior, as it facilitates standardisation of analyses across different studies and  
4 allow derivation of the desired information.[15] Our IPD meta-analysis will examine the role of  
5 potential placebo effect modifiers, assessing patient, intervention and trial characteristics -  
6 contextual factors that are rarely measured and reported in clinical trials or analysed in existing  
7 meta-analyses.  
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16 This analysis will be conducted under the auspices of the OA Trial Bank, an international  
17 collaboration that is endorsed by the Osteoarthritis Research Society International (OARSI) and  
18 the European League Against Rheumatism (EULAR). The OA Trial Bank was initiated in 2010  
19 with the purpose of collecting and analysing IPD of published randomised controlled trials (RCTs)  
20 in OA to identify specific responsive subgroups for the different OA treatment. It brings together  
21 data from individuals with a diagnosis of OA, recruited for published RCTs from around the world  
22 to form a databank.[16, 17]  
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33 Therefore, the aim of this IPD analysis is to investigate the magnitude of the placebo effect and  
34 its potential predictors in intra-articular injection trials in osteoarthritis. This study will differ from  
35 the recently submitted IPD-meta-analysis protocol assessing placebo response in OA by  
36 University of Nottingham arthritis research group.[17] Based on their published protocol, their data  
37 extraction from the OA Trial Bank is targeted at OA therapies namely topical non-steroidal anti-  
38 inflammatory drugs, topical capsaicin, glucosamine and intra-articular glucocorticoids. Potential  
39 placebo effect modifiers that will be assessed are: patient baseline characteristics (age, gender,  
40 body mass index), disease (radiographic information, signs of inflammation, muscle strength,  
41 duration of complaints, pain severity, type of pain, central sensitisation, psychological  
42 assessments), placebo (oral, topical, injection, dose), and trial and outcome measures (pain,  
43 function, patient global assessment, and quality of life).[17] In contrast, intra-articular injection  
44 therapies will be the only therapies of interest in this analysis. While there will be some cross over  
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3 regarding patient-level characteristics, the incorporation of viscosupplementation/hyaluronic acid  
4 trials and an updated systematic review with the acquisition of newer glucocorticoid trials which  
5 will allow for a larger sample size, increased precision of the results and provide insight into the  
6 more commonly used injectables. In addition to patient-level characteristics, there will be a focus  
7 on interventional and trial characteristics i.e. Intervention characteristics (aspirate volume,  
8 frequency of injection, volume of injection, and intra-articular injection approach), and trial  
9 characteristics (clinical setting, blinding, use of intention to treat analysis, funder/sponsor).  
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## 22 **METHODS AND ANALYSIS**

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26 Individual patient data from trials comparing intra-articular injection to placebo for knee  
27 osteoarthritis will be extracted and re-analysed to ascertain the magnitude of the placebo effect  
28 and the role of potential predictors in these trials. The analysis will be conducted under the  
29 umbrella of the OA Trial Bank.  
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37 The IPD meta-analysis will be conducted in accordance with the methods recommended by the  
38 IPD Meta-analysis Methods Group.[15] Reporting of the meta-analysis will conform with the  
39 PRISMA-IPD checklist.[18]  
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45 The research question and study proposal of this study has been approved by the steering  
46 committee of the OA Trial Bank, before the development of the full study protocol.  
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### 51 **Participants**

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53 Participants from the identified randomised controlled trials must have a diagnosis of knee and  
54 hip OA, according to the criteria defined by the American College of Rheumatology, EULAR  
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3 evidence-based recommendations for the diagnosis of knee OA [19, 20] or fulfil specified  
4 radiological criteria of OA diagnosis.  
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### 9 **Types of baseline assessments**

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

27 The primary outcome of the IPD meta-analysis will be change in pain over time. Visual analogue  
28 scale (VAS) pain score will be preferentially used for the analysis. If unavailable, the WOMAC  
29 pain score will be used and converted into a VAS 0-100 scale as per previous OA Trial Bank  
30 Protocols.[21]  
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36 Secondary outcomes will be a change in function and patient global assessment.  
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### 41 **Language**

42 No language restrictions will apply.  
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### 47 **Literature search**

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3 A systematic literature search will be conducted using the following databases: Pubmed  
4 (Medline), EMBASE, Web of Science, Cochrane Central, and SCOPUS. The search will be from  
5 inception to September 2018. The search strategy was developed by the reviewers in consultation  
6 with the OA Trial Bank (Appendix 1).  
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13 Literature searches will be done separately for intra-articular glucocorticoid and  
14 viscosupplementation/hyaluronic acid. The literature search approach will comprise of an  
15 amalgamation of main search terms including identification of the osteoarthritis population group,  
16 intervention of intra-articular glucocorticoid and viscosupplementation/hyaluronic acid, and of  
17 randomised controlled trial design. Furthermore, efforts will be made to identify unpublished trials  
18 through Clinicaltrials.gov. and contacting pharmaceutical suppliers.  
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26 Identified studies will be imported to EndNote X8 for screening.  
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- 29 • Screening process  
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33 Studies eligible for inclusion will be assessed by two independent reviewers (SY, LD). Titles and  
34 abstracts for potential studies will be screened first, and subsequently, the full text of the selected  
35 studies will be reviewed for appropriateness to be included. If no consensus is reached, a third  
36 reviewer will be consulted (DJH). The results will be summarised as per the PRISMA  
37 guidelines.[22]  
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### 46 **Type of studies**

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49 Randomised placebo-controlled trials of intra-articular glucocorticoids and/or  
50 viscosupplementation/hyaluronic acid in knee or hip osteoarthritis will be included. Studies related  
51 to inflammatory arthritis (such as rheumatoid or psoriatic arthritis) will be excluded. Animal model  
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3 and biomarker studies will be excluded. Trials that are not randomised, literature or systematic  
4 reviews, and conference abstracts without available data will be excluded.  
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### 8 9 **Data collection and transfer**

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11 As per all other studies conducted by the OA Trial Bank,[16, 21, 23] the same method for data  
12 acquisition and transfer will be utilised. The corresponding authors of eligible trials will be invited  
13 to collaborate. Initial contact will be by email with two further successive email reminders. If the  
14 corresponding author is uncontactable, communication will be attempted with the other trial  
15 authors and/or institutions listed. Authors who are willing to collaborate will be asked to sign a  
16 data delivery agreement from the OA Trial Bank. This will include items of input data, ownership  
17 of data, obligation, terms, authorship, and subsequent publication intentions. The data obtained  
18 will be stored on a secure server at Erasmus MC University Medical Center, Rotterdam, the  
19 Netherlands, and participant details will be kept in an anonymous and confidential fashion. Data  
20 quality will be ensured through independent checking looking at data-entry mistakes and  
21 inconsistencies. Data received will be compared with the published summary results from the  
22 primary studies. In situations where there are differences found, the authors will be contacted to  
23 resolve the discrepancy issue.  
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41 With the existing intra-articular glucocorticoid trials that have been stored in the OA Trial Bank,  
42 the corresponding authors will be contacted and will be asked to sign a further data transfer  
43 agreement for the use of their data for the purpose of this analysis.  
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### 49 **Patient and public involvement**

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51 There have been no patient and/or public involvement in the design of this IPD meta-analysis.  
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### 56 **Risk and Quality assessment**

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

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24 A descriptive evaluation of each trial and study participants will be conducted. Publication bias  
25 will be investigated using a funnel plot analysis.[25, 26] Missing data will be assumed to be  
26 missing at random, thus patient characteristics will be used to impute missing data by means of  
27 multiple imputation at random.[27, 28]  
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35 Baseline and follow-up data from the placebo arm will be used to estimate the predictors of the  
36 placebo effect. When possible, and no-treatment data is available, those will be included as well  
37 to estimate a between-group placebo effect. Separate analyses will be conducted for  
38 glucocorticoids and viscosupplementation/hyaluronic acid, as well as different outcome measures  
39 (i.e. pain, function and patient global assessment). Trials will also be grouped by type of joint (i.e.  
40 knee or hip) and follow up duration (e.g. < 4 weeks or > 4 weeks for corticosteroid and <12 weeks  
41 or >12 weeks for viscosupplementation/hyaluronic acid).  
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51 A one-step approach will be applied, via the use of a multilevel logistic regression model to  
52 estimate the magnitude of the placebo effect. The use of the one step approach in this setting will  
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3 allow for a more cohesive modelling of covariates and account for the clustering of participants  
4 within the study.[15]  
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9 The primary outcome will be change in pain and will be determined as the dependent variable in  
10 the regression model. Secondary outcomes will be a change in function and patient global  
11 assessment. Change in pain will be determined as the dependent variable, and independent  
12 variables will be the potential predictors of placebo effect. These will be grouped as patient-level  
13 characteristics, peripheral pain mechanisms, central pain mechanisms, intervention  
14 characteristics and those related to trial design (blinding, funder/sponsor roles and intention to  
15 treat) (Table 1) and are as listed below. Each group will be forced into multivariate models with a  
16 final model including all groups.  
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- 27 1. Patient characteristics: age, gender, body mass index, bilateral versus unilateral disease,  
28 disease duration,  
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- 31 2. Pain mechanisms: peripheral (i.e. signs of inflammation, morning stiffness symptoms and  
32 radiographic findings), central pain mechanisms (i.e. other joint OA, comorbidities, pain  
33 severity),  
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- 38 3. Intervention characteristics: clinical setting (i.e. location of intervention), aspirate volume,  
39 frequency of injection, volume of injection, and intra-articular injection approach (i.e.  
40 medial vs lateral approach, use of ultrasound guided injection).  
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- 44 4. Trial characteristics: blinding (patients, assessors or physicians), dropout rates, role of  
45 funder/sponsor (i.e. pharmaceutical company) and use of 'intention to treat' analysis.  
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50 The trials that originate the individual patient data will also be coded and included as a level  
51 variable in all analyses. Analyses will be performed by intention to treat. Effect sizes and 95%  
52 confidence intervals will be generated for each outcome measure.  $P < 0.05$  will be considered  
53 statistically significant.  
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5 A sensitivity analysis will be conducted using pain scores (instead of change in pain scores) as a  
6 continuous dependent variable and repeating the approaches described above.  
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11 Statistical analyses will be performed using Stata SE 14 (StataCorp, College Station, TX).  
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## 14 15 **EXPECTED RESEARCH CONTRIBUTION**

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17 It is envisaged, that the investigators will deliver data to be used in the design and execution of  
18 future clinical trials. It will allow for better understanding of the placebo effect and subsequent  
19 implementation of clinical designs with lowered placebo responses.  
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## 26 27 **ETHICS AND DISSEMINATION**

28 This study does not include identifiable data. Ethical approval was obtained by the original  
29 investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-  
30 reviewed journal and by international conference presentations.  
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## 35 36 **AUTHORS' CONTRIBUTIONS**

37 Study design: SPY, MLF, SMZ, MvM, WZ and DJH contributed to the study design. SPY and LD  
38 will be conducting the systematic review, data extraction, and analysis. SPY drafted the first  
39 version of the manuscript and all the authors were involved in the critical revision of the  
40 manuscript for important intellectual content. The study proposal has been peer-reviewed and  
41 approved by the OA Trial Bank Steering Committee.  
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## 50 51 **FUNDING STATEMENT**

52 SPY holds a University of Sydney Postgraduate Research Scholarship (Part Time). MLF holds a  
53 National Health and Medical Research Council (NHMRC) Career Development Fellowship and  
54 is a Sydney Medical Foundation Fellow. DJH holds an NHMRC Practitioner Fellowship. SBZ  
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1  
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3 reports grants from European Union, The Netherlands Organisation for Health Research and  
4  
5 Development, Dutch Arthritis Foundation. WZ is supported by a grant from Arthritis Research  
6  
7 UK. The OA Trial Bank is supported by the Dutch Arthritis Society.  
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#### 10 11 **COMPETING INTERESTS STATEMENT**

12  
13 DJH reports personal fees from consulting fees from Merck Serono, Flexion and Tissuegene,  
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15 outside the submitted work. All other authors have nothing to disclose.  
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12 **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)

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For peer review only

## 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 osteoarthritis\*[tw] OR osteoporosis\*[tw] OR bone loss\*[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 gonarthr\*[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 adrenocorticosteroid\*[tw] OR corticosteroid\*[tw] OR cortico-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 osteoarthritis\*)) 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 osteoarthritis*)) 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 osteoarthritis*)) 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 osteoarthritis\*[tw] OR osteoporos\*[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 gonarthr\*[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 osteoarthritis\*)) 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 osteoarthritis*)) 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.
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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.#)
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 <sup>2</sup> , 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027372.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Jan-2019
Complete List of Authors:	Yu, Shirley; Royal North Shore Hospital, Rheumatology; 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, Academic Rheumatology Deveza, Leticia; University of Sydney, Royal North Shore Hospital, Rheumatology Department Hunter, David; The University of Sydney,
<b>Primary Subject Heading</b>:	Rheumatology
Secondary Subject Heading:	Research methods
Keywords:	Osteoarthritis, Individual patient data meta-analysis, Intra-articular therapy, Placebo effect

SCHOLARONE™  
Manuscripts

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3 **Placebo effects of local (intra-articular) therapy in osteoarthritis – an individual**  
4 **patient data meta-analysis protocol**  
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10 Shirley P. Yu<sup>1</sup>, Manuela L. Ferreira<sup>1</sup>, Marienke van Middelkoop<sup>2</sup>, Sita Bierma-Zeinstra<sup>2</sup>, Weiya  
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46 **Word Count:** 2877  
47  
48  
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50 **Keywords:**  
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52 Osteoarthritis; individual patient data meta-analysis; intra-articular therapy; placebo effect  
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56 **Systemic review registration:**  
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58 PROSPERO registration number: CRD42018095188  
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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, 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



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

### 9 **Ethics and dissemination:**

11 This study does not include identifiable data and ethical approval was obtained by the  
12 original investigators. Results of the IPD meta-analysis will be disseminated for publication in  
13 peer-reviewed journals and conference presentations.  
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### 26 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 29 • The use of an individual patient data (IPD) meta-analysis of randomised controlled  
30 trials will provide more precise estimates of the placebo effect. It also allows the  
31 identification of patient-level predictors of placebo effect in this population.  
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- 34 • The study will be conducted within the framework of the OA Trial Bank, an  
35 international organisation that initiates meta-analyses of effect on predefined  
36 subgroups of OA patients from existing trials.  
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- 39 • Identification of the predictors of placebo response in intra-articular injections for  
40 osteoarthritis may influence future clinical trial designs with a more tailored approach  
41 when classifying participants in future studies.  
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- 44 • Inclusion of frequently utilised intra-articular injection RCTs will allow for a larger  
45 sample size, increased precision of the results and provide insight into the more  
46 commonly used injectables.  
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- 49 • The limitation lies in the potential for bias due to lack of available IPDs obtainable  
50 despite the number of studies available due to study and company regulations, and  
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3 the inclusion of only corticosteroid and viscosupplements/hyaluronic acid trials may  
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5 affect our ability to identify predictors of response.  
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For peer review only

## 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

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3 in the context of a placebo-controlled intra-articular injection trial despite the concerns. The  
4 inclusion of a no-treatment/sham-injection group may be a way to discern the placebo effect  
5 of normal saline, however the presence of this design is rare in OA clinical trials.[13]  
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11 The inability to demonstrate a minimum clinically important difference over placebo, directly  
12 affects the development of potential pharmacological innovations and their translation to  
13 becoming commercially available treatment options for this disabling disease. The magnitude  
14 of the placebo effect in OA trials is significant with about 75% of treatment effect being  
15 attributable to placebo contextual effects.[14] In general, the more invasive and more frequent  
16 the administration of an intervention, the larger the placebo effect. For invasive therapies,  
17 patients' expectations and beliefs create even larger placebo/contextual effects.[13] When  
18 considering clinical trial design, the challenges of which placebo to choose, its volume,  
19 injection frequency, the use of injection guidance, concomitant local anaesthetic use, patient  
20 baseline disease presentation (bilateral versus unilateral disease, concomitant presence of  
21 inflammatory features/effusion, disease severity, baseline pain) all create substantial  
22 opportunity for heterogeneity in what is already a challenging clinical trial environment. The  
23 intervention itself is also subject to placebo effects; administration route, colour, branding and  
24 cost all have an effect, thus indicating that clinical trials may need more standardisation across  
25 the board to optimise the demonstration of treatment response.[15]  
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45 To date, placebo effects from clinical trials are ultimately measured as a change in outcome  
46 from baseline in the placebo group in comparison to the treatment group. Minimal trials  
47 incorporate a no-treatment group, which may allow for adequate clarification of the placebo  
48 effect. Meta-analysis of OA treatments has shown that the placebo effect varies greatly  
49 between individuals.[14] The main limitation of aggregate data meta-analysis is that the  
50 variations of the treatment/placebo effects across individuals cannot be scrutinised. As the  
51 placebo effect can be attributed to the individual or related to the study protocol, assessment  
52 of the placebo effect utilising individual patient data (IPD) meta-analysis will give insight into  
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3 the different predictors of placebo response. IPD analysis is now increasingly used over  
4 established meta-analysis and is considered to be superior, as it facilitates standardisation of  
5 analyses across different studies and allow derivation of the desired information.[16] Our IPD  
6 meta-analysis will examine the role of potential placebo effect modifiers, assessing patient,  
7 intervention and trial characteristics - contextual factors that are rarely measured and reported  
8 in clinical trials or analysed in existing meta-analyses.  
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18 This analysis will be conducted under the auspices of the OA Trial Bank, an international  
19 collaboration that is endorsed by the Osteoarthritis Research Society International (OARSI)  
20 and the European League Against Rheumatism (EULAR). The OA Trial Bank was initiated in  
21 2010 with the purpose of collecting and analysing IPD of published randomised controlled  
22 trials (RCTs) in OA to identify specific responseive subgroups for the different OA treatment.  
23 It brings together data from individuals with a diagnosis of OA, recruited for published RCTs  
24 from around the world to form a databank.[17, 18]  
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35 Therefore, the aim of this IPD analysis is to investigate the predictors of placebo effects in  
36 intra-articular injection trials in osteoarthritis. This study will differ from the recently submitted  
37 IPD-meta-analysis protocol assessing placebo response in OA by University of Nottingham  
38 arthritis research group.[18] Based on their published protocol, their data extraction from the  
39 OA Trial Bank is targeted at OA therapies namely topical non-steroidal anti-inflammatory  
40 drugs, topical capsaicin, glucosamine and intra-articular glucocorticoids. Potential placebo  
41 effect modifiers that will be assessed are: patient baseline characteristics (age, gender, body  
42 mass index), disease (radiographic information, signs of inflammation, muscle strength,  
43 duration of complaints, pain severity, type of pain, central sensitisation, psychological  
44 assessments), placebo (oral, topical, injection, dose), and trial and outcome measures (pain,  
45 function, patient global assessment, and quality of life).[18] In contrast, intra-articular injection  
46 therapies will be the only therapies of interest in this analysis. While there will be some cross  
47 over regarding patient-level characteristics, the incorporation of  
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3 viscosupplementation/hyaluronic acid trials and an updated systematic review with the  
4 acquisition of newer glucocorticoid trials which will allow for a larger sample size, increased  
5 precision of the results and provide insight into the more commonly used injectables. In  
6 addition to patient-level characteristics, there will be a focus on interventional and trial  
7 characteristics i.e. Intervention characteristics (aspirate volume, frequency of injection, volume  
8 of injection, and intra-articular injection approach), and trial characteristics (clinical setting,  
9 blinding, use of intention to treat analysis, funder/sponsor).

## 10 11 12 13 14 15 16 17 18 19 20 **METHODS AND ANALYSIS**

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

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

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

### 45 46 47 48 49 **Participants**

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51 Participants from the identified randomised controlled trials must have a diagnosis of knee  
52 and hip OA, according to the criteria defined by the American College of Rheumatology,  
53 EULAR evidence-based recommendations for the diagnosis of knee OA [20, 21] or fulfil  
54 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



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3 reminders. If the corresponding author is uncontactable, communication will be attempted with  
4 the other trial authors and/or institutions listed. Authors who are willing to collaborate will be  
5 asked to sign a data delivery agreement from the OA Trial Bank. This will include items of  
6 input data, ownership of data, obligation, terms, authorship, and subsequent publication  
7 intentions. The data obtained will be stored on a secure server at Erasmus MC University  
8 Medical Center, Rotterdam, the Netherlands, and participant details will be kept in an  
9 anonymous and confidential fashion. Data quality will be ensured through independent  
10 checking looking at data-entry mistakes and inconsistencies. Data received will be compared  
11 with the published summary results from the primary studies. In situations where there are  
12 differences found, the authors will be contacted to resolve the discrepancy issue.  
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26 With the existing intra-articular glucocorticoid trials that have been stored in the OA Trial Bank,  
27 the corresponding authors will be contacted and will be asked to sign a further data transfer  
28 agreement for the use of their data for the purpose of this analysis.  
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### 35 **Patient and public involvement**

36 There have been no patient and/or public involvement in the design of this IPD meta-  
37 analysis.  
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### 43 **Risk and Quality assessment**

44 The included trials will be assessed independently by two reviewers to assess the quality of  
45 evidence and the risk of biases through the use of the Cochrane Collaboration's tool.[25, 26]  
46 A third reviewer will be consulted if there is a disagreement. The domains assessed will  
47 include randomisation of procedure, blinding of participants, physicians and treatment  
48 allocation, use of intention to treat analysis, incomplete outcome data, baseline group  
49 similarity, reporting bias and other sources of biases. Studies will be categorised as 'low risk',  
50 'high risk' or 'unclear. As per previous studies with the OA trial bank, a low risk of bias study  
51 will be classified as fulfilling at least 6 of the 12 items in the Cochrane Collaboration's tool.[26]  
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## 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  $\geq$  4 weeks for corticosteroid and <12 weeks or  $\geq$ 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.

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3 The primary outcome will be change in pain from baseline and will be determined as the  
4 dependent variable in the regression model. The minimum clinically important difference  
5 (MCID) threshold will be a 20% or more reduction in pain based on the visual analogue scale  
6 (VAS) pain score with 0mm being no pain to 100mm being the worst pain ever. This level  
7 has been recommended for use in pain and function assessment in rheumatic diseases such  
8 as OA. [30, 31] In situations where WOMAC pain score is only available, it will be used  
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20 Secondary outcomes will be a change in function and patient global assessment. Change in  
21 pain will be determined as the dependent variable, and independent variables will be the  
22 potential predictors of placebo effect. These will be grouped as patient-level characteristics,  
23 peripheral pain mechanisms, central pain mechanisms, intervention characteristics and those  
24 related to trial design (blinding, funder/sponsor roles and intention to treat) (Table 1) and are  
25 as listed below. Each group will be forced into multivariate models with a final model including  
26 all groups.  
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- 36 1. Patient characteristics: age, gender, body mass index, bilateral versus unilateral  
37 disease, disease duration,  
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- 39 2. Pain mechanisms: peripheral pain mechanisms (i.e. signs of inflammation, morning  
40 stiffness symptoms and radiographic findings), central pain mechanisms (i.e. other  
41 joint OA, comorbidities, pain severity),  
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- 46 3. Intervention characteristics: clinical setting (i.e. location of intervention), aspirate  
47 volume, frequency of injection, volume of injection, and intra-articular injection  
48 approach (i.e. medial vs lateral approach, use of ultrasound guided injection).  
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- 52 4. Trial characteristics: blinding (patients, assessors or physicians), dropout rates, role of  
53 funder/sponsor (i.e. pharmaceutical company), randomisation ratio, trial duration,  
54 single centre/multi-centre study, parallel/cross-over trial, and use of 'intention to treat'  
55 analysis.  
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3 The trials that originate the individual patient data will also be coded and included as a level  
4 variable in all analyses. Effect sizes and 95% confidence intervals will be generated for each  
5 outcome measure.  $P < 0.05$  will be considered statistically significant.  
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11 A sensitivity analysis will be conducted using pain scores (instead of change in pain scores)  
12 as a continuous dependent variable and repeating the approaches described above.  
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18 Statistical analyses will be performed using Stata SE 14 (StataCorp, College Station, TX).  
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## 21 22 **EXPECTED RESEARCH CONTRIBUTION**

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24 It is envisaged, that the investigators will deliver data to be used in the design and execution  
25 of future clinical trials. It will allow for better understanding of the placebo effect and  
26 subsequent implementation of clinical designs with lowered placebo responses.  
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## 31 32 **ETHICS AND DISSEMINATION**

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34 This study does not include identifiable data. Ethical approval was obtained by the original  
35 investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-  
36 reviewed journal and by international conference presentations.  
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## 41 42 **AUTHORS' CONTRIBUTIONS**

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44 Study design: SPY, MLF, SMZ, MvM, WZ and DJH contributed to the study design. SPY and  
45 LD will be conducting the systematic review, data extraction, and analysis. SPY drafted the  
46 first version of the manuscript and all the authors were involved in the critical revision of the  
47 manuscript for important intellectual content. The study proposal has been peer-reviewed  
48 and approved by the OA Trial Bank Steering Committee.  
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## 58 59 **FUNDING STATEMENT**

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1  
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3 SPY holds a University of Sydney Postgraduate Research Scholarship (Part Time). MLF  
4  
5 holds a National Health and Medical Research Council (NHMRC) Career Development  
6  
7 Fellowship and is a Sydney Medical Foundation Fellow. DJH holds an NHMRC Practitioner  
8  
9 Fellowship. SBZ reports grants from European Union, The Netherlands Organisation for  
10  
11 Health Research and Development, Dutch Arthritis Foundation. WZ is supported by a grant  
12  
13 from Arthritis Research UK. The OA Trial Bank is supported by the Dutch Arthritis Society.  
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### 17 **COMPETING INTERESTS STATEMENT**

18  
19 DJH reports personal fees from consulting fees from Merck Serono, Flexion and  
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21 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)

For peer review only

## 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 osteoporos\*[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 gonarthr\*[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 adrenocorticosteroid\*[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 crossover 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)**

	<b>Searches</b>
<b>1</b>	((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]
<b>2</b>	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.
<b>3</b>	(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]
<b>4</b>	inject*.mp.
<b>5</b>	(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]
<b>6</b>	3 or 4
<b>7</b>	2 and 6
<b>8</b>	1 and 5 and 7
<b>9</b>	((case adj5 report*) or retrospect* or cadaver*).mp.
<b>10</b>	8 not 9
<b>11</b>	limit 10 to human

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

	<b>Searches</b>
<b>1</b>	((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.
<b>2</b>	exp adrenal cortex hormones/
<b>3</b>	(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.
<b>4</b>	((intraartic* or (intra adj5 artic*)) and inject*).mp
<b>5</b>	2 or 3
<b>6</b>	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 osteoarthritis\*[tw] OR osteoporosis\*[tw] OR bone loss\*[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 gonarthr\*[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 biotly\*[tw] OR go-on\*[tw] OR healon\*[tw] OR hyject\*[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 osteoarthritis\*)) 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 biotly\* OR go-on\* OR healon\* OR hyject\* 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 osteoarthritis*)) 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 osteoarthritis*)) 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.#)
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 $\tau$ )	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.*



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027372.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Mar-2019
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
<b>Primary Subject Heading</b>:	Rheumatology
Secondary Subject Heading:	Research methods
Keywords:	Osteoarthritis, Individual patient data meta-analysis, Intra-articular therapy, Placebo response

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Manuscripts

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3 **Predictors of placebo response to local (intra-articular) therapy in osteoarthritis**  
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5 **– an individual patient data meta-analysis protocol**  
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9 Shirley P. Yu<sup>1</sup>, Manuela L. Ferreira<sup>1</sup>, Marienke van Middelkoop<sup>2</sup>, Sita Bierma-Zeinstra<sup>2</sup>, Weiya  
10 Zhang<sup>3,4</sup>, Leticia A. Deveza<sup>1</sup>, David J. Hunter<sup>1</sup>  
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46 **Word Count:** 3061  
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50 **Keywords:**  
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52 Osteoarthritis; individual patient data meta-analysis; intra-articular therapy; placebo response  
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56 **Systemic review registration:**  
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58 PROSPERO registration number: CRD42018095188  
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## 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

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

### 9 **Ethics and dissemination:**

11 This study does not include identifiable data and ethical approval was obtained by the  
12 original investigators. Results of the IPD meta-analysis will be disseminated for publication in  
13 peer-reviewed journals and conference presentations.  
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### 26 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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29 • The use of an individual patient data (IPD) meta-analysis of randomised controlled  
30 trials will provide more precise estimates of the placebo response. It also allows the  
31 identification of patient-level predictors of placebo response in this population.  
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- 34 • The study will be conducted within the framework of the OA Trial Bank, an  
35 international organisation that initiates meta-analyses of effect on predefined  
36 subgroups of OA patients from existing trials.  
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- 39 • Identification of the predictors of placebo response in intra-articular injections for  
40 osteoarthritis may influence future clinical trial designs with a more tailored approach  
41 when classifying participants in future studies.  
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- 44 • Inclusion of frequently utilised intra-articular injection RCTs will allow for a larger  
45 sample size, increased precision of the results and provide insight into the more  
46 commonly used injectables.  
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- 49 • We have only included injections of corticosteroid and viscosupplements/hyaluronic  
50 acid trials because these are the standard intra-articular treatments for OA. There are  
51 other intra-articular injection treatments such as blood products, growth factors and  
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3 prolotherapy. As they are not established treatments with limited evidence in OA, we  
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5 will exclude them from this study.  
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For peer review only

## 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

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3 mechanisms such as those via endogenous opioid and dopamine,[11] as well as via possible  
4 dilution of the inflammatory element in the joint because of the volume of saline. [12, 13] Thus,  
5 intra-articular saline as a placebo can be considered to be an “impure placebo” in the context  
6 of a placebo-controlled intra-articular injection trial. The inclusion of a no-treatment/sham-  
7 injection group may be a way to discern the placebo effect of saline injections, however the  
8 presence of this design is rare in OA clinical trials. Despite this, previous meta-analysis of  
9 randomised controlled trials assessing the placebo response across a range of therapies in  
10 OA (non-pharmacological, pharmacological and surgical treatments) have confirmed that  
11 placebo response (Effect size (ES) = 0.51 95% CI 0.46-0.55) is greater than no treatment or  
12 spontaneous response (ES = 0.03, 95% CI -0.13-0.18) for pain in OA.[14]  
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26 The inability to demonstrate a minimum clinically important difference over placebo, directly  
27 affects the development of potential pharmacological innovations and their translation to  
28 becoming commercially available treatment options for this disabling disease. The magnitude  
29 of the placebo response in OA trials is significant with about 75% of treatment effect being  
30 attributable to placebo contextual effects.[15] In general, the more invasive and more frequent  
31 the administration of an intervention, the larger the placebo response. For invasive therapies,  
32 patients' expectations and beliefs create even larger placebo/contextual effects.[14] When  
33 considering clinical trial design, the challenges of which placebo to choose, its volume,  
34 injection frequency, the use of injection guidance, concomitant local anaesthetic use, patient  
35 baseline disease presentation (bilateral versus unilateral disease, concomitant presence of  
36 inflammatory features/effusion, disease severity, baseline pain) all create substantial  
37 opportunity for heterogeneity in what is already a challenging clinical trial environment. The  
38 intervention itself is also subject to contextual effects; administration route, colour, branding  
39 and cost all have an effect, thus indicating that clinical trials may need more standardisation  
40 across the board to optimise the demonstration of treatment response.[16]  
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3 To date, placebo responses from clinical trials are ultimately measured as a change in  
4 outcome from baseline in the placebo group in comparison to the treatment group and is  
5 potentially confounded by spontaneous effects such as the Hawthorne effect (ie, the effect  
6 due to being observed), natural fluctuation of disease and regression to the mean.[14, 16]  
7  
8 Minimal trials incorporate a no-treatment group, which may allow for adequate clarification of  
9 the placebo effect. Meta-analysis of OA treatments has shown that the placebo response  
10 varies greatly between individuals.[15] The main limitation of aggregate data meta-analysis is  
11 that the variations of the treatment/placebo responses across individuals cannot be  
12 scrutinised. As the placebo response can be attributed to the individual or related to the study  
13 protocol, assessment of the placebo response utilising individual patient data (IPD) meta-  
14 analysis will give insight into the different predictors of placebo response. IPD analysis is now  
15 increasingly used over established meta-analysis and is considered to be superior, as it  
16 facilitates standardisation of analyses across different studies and allow derivation of the  
17 desired information.[17] Our IPD meta-analysis will examine the role of potential placebo  
18 response modifiers, assessing patient, intervention and trial characteristics - contextual factors  
19 that are rarely measured and reported in clinical trials or analysed in existing meta-analyses.  
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39 This analysis will be conducted under the auspices of the OA Trial Bank, an international  
40 collaboration that is endorsed by the Osteoarthritis Research Society International (OARSI)  
41 and the European League Against Rheumatism (EULAR). The OA Trial Bank was initiated in  
42 2010 with the purpose of collecting and analysing IPD of published randomised controlled  
43 trials (RCTs) in OA to identify specific responseive subgroups for the different OA treatment.  
44 It brings together data from individuals with a diagnosis of OA, recruited for published RCTs  
45 from around the world to form a databank.[18, 19]  
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56 Therefore, the aim of this IPD analysis is to investigate the predictors of placebo response in  
57 intra-articular injection trials in osteoarthritis. This study will differ from the recently submitted  
58 IPD-meta-analysis protocol assessing placebo response in OA by University of Nottingham  
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3 arthritis research group.[19] Based on their published protocol, their data extraction from the  
4 OA Trial Bank is targeted at OA therapies namely topical non-steroidal anti-inflammatory  
5 drugs, topical capsaicin, glucosamine and intra-articular glucocorticoids. Potential placebo  
6 response modifiers that will be assessed are: patient baseline characteristics (age, gender,  
7 body mass index), disease (radiographic information, signs of inflammation, muscle strength,  
8 duration of complaints, pain severity, type of pain, central sensitisation, psychological  
9 assessments), placebo (oral, topical, injection, dose), and trial and outcome measures (pain,  
10 function, patient global assessment, and quality of life).[19] In contrast, intra-articular injection  
11 therapies will be the only therapies of interest in this analysis. While there will be some cross  
12 over regarding patient-level characteristics, the incorporation of  
13 viscosupplementation/hyaluronic acid trials and an updated systematic review with the  
14 acquisition of newer glucocorticoid trials which will allow for a larger sample size, increased  
15 precision of the results and provide insight into the more commonly used injectables. In  
16 addition to patient-level characteristics, there will be a focus on interventional and trial  
17 characteristics i.e. Intervention characteristics (aspirate volume, frequency of injection, volume  
18 of injection, and intra-articular injection approach), and trial characteristics (clinical setting,  
19 blinding, use of intention to treat analysis, funder/sponsor).  
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## 41 **METHODS AND ANALYSIS**

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45 Individual patient data from trials comparing intra-articular injection to placebo for knee  
46 osteoarthritis will be extracted and re-analysed to ascertain the magnitude of the placebo  
47 response and the role of potential predictors in these trials. The analysis will be conducted  
48 under the umbrella of the OA Trial Bank.  
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56 The IPD meta-analysis will be conducted in accordance with the methods recommended by  
57 the IPD Meta-analysis Methods Group.[17] Reporting of the meta-analysis will conform with  
58 the PRISMA-IPD checklist.[20]  
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5 The research question and study proposal of this study has been approved by the steering  
6 committee of the OA Trial Bank, before the development of the full study protocol.  
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## 10 11 **Participants**

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

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

42 The primary outcome of the IPD meta-analysis will be change in pain over time. Visual  
43 analogue scale (VAS) pain score will be preferentially used for the analysis. If unavailable, the  
44 WOMAC pain score will be used and converted into a VAS 0-100 scale as per previous OA  
45 Trial Bank Protocols.[23]  
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53 Secondary outcomes will be a change in function and patient global assessment.  
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## 58 **Language**

59 No language restrictions will apply.  
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## 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

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

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

57 There have been no patient and/or public involvement in the design of this IPD meta-  
58 analysis.  
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## 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  $\geq$  4 weeks for corticosteroid and <12 weeks or  $\geq$ 12 weeks for viscosupplementation/hyaluronic acid).

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3 A one-step approach will be applied, via the use of multilevel regression models to assess for  
4 predictors of the placebo response. The use of the one step approach in this setting will allow  
5 for a more cohesive modelling of covariates and account for the clustering of participants  
6 within the study.[17] This will be done by combining all the data from all the studies available  
7 after appropriate standardisation of the variables and a new dataset will be formed to allow for  
8 further analysis. To assess for the potential subgroup effects, a random effect model will be  
9 utilised given the hierarchical nature of the data to assess the interaction effects, with change  
10 in pain being a dependent variable, and potential predictors being independent variables. In  
11 the setting where a no-treatment control is available, we will include placebo-no-treatment as  
12 an independent variable. Responders to placebo will be compared with non-responders to  
13 identify predictors of response.  
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28 The primary outcome will be change in pain from baseline and will be determined as the  
29 dependent variable in the regression model. The minimum clinically important difference  
30 (MCID) threshold will be a 20% or more reduction in pain based on the visual analogue scale  
31 (VAS) pain score with 0mm being no pain to 100mm being the worst pain ever. This level  
32 has been recommended for use in pain and function assessment in rheumatic diseases such  
33 as OA, [31, 32] and we will use it to define the placebo response which is equivalent to an  
34 ES of 0.8,[33] that indicates the response unlikely to be caused by spontaneous effects. In  
35 situations where WOMAC pain score is only available, it will be used instead.  
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48 Secondary outcomes will be a change in function and patient global assessment. Change in  
49 pain will be determined as the dependent variable, and independent variables will be the  
50 potential predictors of placebo response. These will be grouped as patient-level  
51 characteristics, peripheral pain mechanisms, central pain mechanisms, intervention  
52 characteristics and those related to trial design (blinding, funder/sponsor roles and intention  
53 to treat) (Table 1) and are as listed below. Each group will be forced into multivariate models  
54 with a final model including all groups.  
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3 1. Patient characteristics: age, gender, body mass index, bilateral versus unilateral  
4 disease, disease duration,  
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- 7 2. Pain mechanisms: peripheral pain mechanisms (i.e. signs of inflammation, morning  
8 stiffness symptoms and radiographic findings), central pain mechanisms (i.e. other  
9 joint OA, comorbidities, pain severity),  
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- 12 3. Intervention characteristics: clinical setting (i.e. location of intervention), aspirate  
13 volume, frequency of injection, volume of injection, and intra-articular injection  
14 approach (i.e. medial vs lateral approach, use of ultrasound guided injection).  
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- 17 4. Trial characteristics: blinding (patients, assessors or physicians), dropout rates, role of  
18 funder/sponsor (i.e. pharmaceutical company), randomisation ratio, trial duration,  
19 single centre/multi-centre study, parallel/cross-over trial, and use of 'intention to treat'  
20 analysis.  
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30 The trials that originate the individual patient data will also be coded and included as a level  
31 variable in all analyses. Effect sizes and 95% confidence intervals will be generated for each  
32 outcome measure.  $P < 0.05$  will be considered statistically significant.  
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38 A sensitivity analysis will be conducted using pain scores (instead of change in pain scores)  
39 as a continuous dependent variable and repeating the approaches described above.  
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44 Statistical analyses will be performed using Stata SE 14 (StataCorp, College Station, TX).  
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#### 48 **EXPECTED RESEARCH CONTRIBUTION**

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50 It is envisaged, that the investigators will deliver data to be used in the design and execution  
51 of future clinical trials. It will allow for better understanding of the placebo response and  
52 subsequent implementation of clinical designs with lowered placebo responses.  
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#### 56 **ETHICS AND DISSEMINATION**

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3 This study does not include identifiable data. Ethical approval was obtained by the original  
4 investigators. Results of the IPD meta-analysis will be disseminated for publication in a peer-  
5 reviewed journal and by international conference presentations.  
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## 10 11 **AUTHORS' CONTRIBUTIONS**

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13 Study design: SPY, MLF, SBZ, MvM, WZ and DJH contributed to the study design. SPY and  
14 LD will be conducting the systematic review, data extraction, and analysis. SPY drafted the  
15 first version of the manuscript and all the authors were involved in the critical revision of the  
16 manuscript for important intellectual content. The study proposal has been peer-reviewed  
17 and approved by the OA Trial Bank Steering Committee.  
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## 26 27 **FUNDING STATEMENT**

28  
29 SPY holds a University of Sydney Postgraduate Research Scholarship (Part Time). MLF  
30 holds a National Health and Medical Research Council (NHMRC) Career Development  
31 Fellowship and is a Sydney Medical Foundation Fellow. DJH holds an NHMRC Practitioner  
32 Fellowship. SBZ reports grants from European Union, The Netherlands Organisation for  
33 Health Research and Development, Dutch Arthritis Foundation. WZ is supported by a grant  
34 from Arthritis Research UK. The OA Trial Bank is supported by the Dutch Arthritis Society.  
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## 43 44 **COMPETING INTERESTS STATEMENT**

45  
46 DJH reports personal fees from consulting fees from Merck Serono, Flexion and  
47 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)

For peer review only

## 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 osteoarthritis\*[tw] OR osteoporosis\*[tw] OR bone loss\*[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 gonarthr\*[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 adrenocorticosteroid\*[tw] OR corticosteroid\*[tw] OR cortico-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 (intraart\*[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 crossover 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 osteoarthritis\*)) 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 ((intraart\*[tw] 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 osteoarthritis\*[tw] OR osteoporosis\*[tw] OR bone loss\*[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 gonarthr\*[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 biotly\*[tw] OR go-on\*[tw] OR healon\*[tw] OR hyject\*[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 osteoarthritis\*)) 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 biotly\* OR go-on\* OR healon\* OR hyject\* 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 osteoarthritis*)) 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 osteoarthritis*)) 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.#)
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 $\tau$ )	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.*