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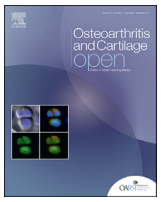

The OA Trial Bank: Update of individual patient data meta-analysis of intra-articular glucocorticoids in persons with knee and hip osteoarthritis

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ABSTRACT

Objective: To evaluate the efficacy of intra–articular (IA) glucocorticoid for knee or hip osteoarthritis (OA) in specific subgroups of patients according to the baseline severity of pain and inflammatory signs using individual patient data (IPD) from existing trials. Furthermore, this study aims to assess if a baseline pain cut-off was associated with clinically important effectiveness of IA glucocorticoid. This is an update of an IA glucocorticoid IPD meta-analysis by the OA Trial Bank.

Method: Randomized trials evaluating one or more IA glucocorticoid preparations in hip and knee OA, published to May 2018 were selected. IPD of patient and disease characteristics and outcome measures were acquired. The primary outcome was pain severity at short-term follow-up (up to 4 weeks). Potential interaction effect of severe pain (≥70 points, 0–100 scale) and signs of inflammation at baseline were studied using a two-stage approach with general liner model followed by random effects model. Analysis of trend was conducted, assessing if a baseline pain cut-off was associated with the threshold for clinically important treatment effect of IA glucocorticoid compared to placebo.

Results: Four out of 16 eligible randomized clinical trials (n = 641) were combined with the existing OA Trial Bank studies (n = 620), yielding 1261 participants from eleven studies. Participants with severe baseline pain compared to those with less severe pain had greater pain reduction at mid-term (around 12 weeks) (mean reduction: −6.90 (95%CI -10.91; −2.90)), but not at short- and long-term. No interaction effects were found between inflammatory signs and IA glucocorticoid injections compared to placebo at all follow-up time-points. Analysis of trend demonstrated treatment response to IA glucocorticoid from baseline pain levels >50 (0–100 scale) and above.

Conclusion: This updated IPD meta-analysis demonstrated that participants with severe pain compared to those with less severe pain at baseline experienced significantly more pain relief with IA glucocorticoid compared with placebo at mid-term.

1. Introduction

Intra-articular (IA) glucocorticoid injections are regularly employed in the management of knee or hip osteoarthritis (OA) patients, in whom conservative treatments or first-line pharmacological agents are not successful. IA glucocorticoid has shown short-term efficacy up to two-four weeks post-injection based on the Cochrane systematic review [1]. Furthermore, compared to IA placebo, IA glucocorticoid has some effect for pain and patient global assessment one-week post-injection. Based on the 2019 OARSI guideline, IA glucocorticoids is conditionally recommended in individuals with knee OA as per the *Good Clinical Practice Statement*, however, it is not recommended for individuals with hip or polyarticular joint OA [2]. Several guidelines also support its short-term use in the clinical setting of severe pain or acute exacerbation in knee OA [3,4].

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Due to the heterogeneity of OA patients, clinical guidelines have advocated for identifying predictors of response to different treatment modalities [5]. Understanding the relationship between baseline characteristics, such as pain severity or presence of inflammation and the magnitude of treatment effect, may lead to better patient selection for treatment. Systematic reviews of IA glucocorticoid trials have sought to identify subgroups with treatment effects [6–8], but overall, no reliable predictors of response were found. In part, methodological limitations of the studies account for the null findings as most individual studies conducted *post hoc* subgroup analysis, and thus were underpowered to detect such effects [6–8]. To overcome this, the individual patient data (IPD) meta-analysis method is increasingly applied in different research areas to test subgroup-treatment interaction effects using IPD from multiple published trials, as it allows for adjustments for confounders at both the individual and study level [9,10].

The OA Trial Bank, established in 2010, sought to collect existing studies in OA for the meta-analysis of the effect of treatment on predefined subgroups of OA participants. van Middlekoop et al. [11] reported on the effectiveness of IA glucocorticoid in knee and hip OA and demonstrated that participants with severe baseline pain (≥70, 0–100 scale) had a significantly larger reduction in short-term pain, compared with those with less pain at baseline (mean difference: 13.91; 95% confidence interval (CI) 1.50–26.31) when receiving IA glucocorticoid compared to placebo. The definition of severe pain was based on OA Trial Bank consensus and is comparable to the pain severity definition based on strata used in other OA clinical trials [12], and pain severity cut-off points for OA [13]. Whilst severe baseline pain has been predictive of response to IA glucocorticoid injection [14], the cut-off baseline pain for reaching clinically important treatment effects is unclear.

The purpose of this present study is to further expand and update the OA Trial Bank work of the IPD in IA glucocorticoid, including further published trials since the previous study. The primary aim is to use IPD to evaluate the efficacy of IA glucocorticoid for knee or hip OA in specific subgroups of patients according to the severity of pain and inflammatory signs at different follow-up time points. Furthermore, we want to assess whether there is a clear baseline pain cut-off associated with clinically important effectiveness of IA glucocorticoid.

2. Methods

An IPD meta-analysis of randomised controlled trials (RCT) was conducted to study the efficacy and subgroup effects of IA glucocorticoid injections in participants with hip or knee OA. Full study protocol has been published previously [9].

2.1. Type of studies

All RCTs, including crossover trials, evaluating one or more IA glucocorticoid preparations in participants with hip or knee OA. There were no language restrictions.

2.2. Participants

Participants must have a diagnosis of hip or knee OA either according to the American College of Rheumatology (ACR) classification criteria, EULAR evidence-based recommendations for the diagnosis of knee OA [15,16] or based on clinical and/or radiographic diagnosis.

2.3. Types of intervention

All IA glucocorticoid preparations utilised in the treatment of knee or hip OA compared with control agents, i.e., placebo, IA hyaluronic acid, other doses, or preparations of IA glucocorticoids, usual conservative treatments, or different injection procedures of glucocorticoids.

The trials were grouped into three different comparisons.

1. IA glucocorticoid versus placebo
2. IA glucocorticoid versus IA hyaluronic acid
3. IA glucocorticoid versus tidal irrigation

2.4. Baseline assessments

To be included in the IPD analysis, at a minimum, baseline severity of pain (and pain measures at subsequent follow up timeframes), age and sex.

If available, signs of inflammation at baseline, detected either by physical examination (effusion or warmth of the joint), or by other diagnostic testing (ultrasound – the presence of effusion/synovitis/synovial hypertrophy, MRI – the presence of effusion or synovitis, blood test with CRP and/or ESR levels).

2.5. Outcomes

The primary outcome was pain severity at short-term (up to 4 weeks follow-up). Secondary outcomes included: Pain severity at mid-term (closest to 12 weeks follow-up) and long-term (closest to 12 months follow-up). If available, physical function and patient global assessment.

2.6. Eligible studies

Databases were searched from June 2012 to May 2018 for RCTs of IA glucocorticoid versus control treatment for knee and hip OA. Identified and collected studies were then combined with the existing studies from the OA Trial Bank with searches from 1995 (based on the availability of data sets and authors) to June 19, 2012). MEDLINE (PubMed), EMBASE, Webs of Science, Cochrane Central Register of Controlled Trials. Reference lists were further searched for identification of published work. Potential studies underway were further searched via the ISRCTN Registry of clinical trials, ClinicalTrials.gov, Australian New Zealand Clinical Trials registry. Identified studies were imported to EndNote™ X8 for screening.

Two review authors (SPY, LD) independently selected citations based on titles and abstracts and assessed full articles that met the eligibility criteria independently before consensus was reached. If a consensus was not reached, the OA Trial Bank members (MvM) were the next point of consult.

2.7. Data collection and transfer and checks

The corresponding authors of eligible trials were invited to collaborate initially via email and subsequently by telephone. Listed authors and institutions were contacted if the corresponding authors were unreachable. IPD data was requested per OA Trial Bank protocol and terms [9], and data delivery licence agreements were signed between both parties. The original data were kept in their original versions and in a secured server at the University of Sydney, and the Erasmus MC University Medical Centre, and participant details were kept anonymously and confidentially. All data were checked for consistency with the published papers, and data quality was ensured through independent checking, assessing for data-entry mistakes and inconsistencies by reproducing the main baseline characteristics and the reported changes over time for the available outcomes.

2.8. Risk of bias assessment

The methodological quality of the studies was assessed using the 12 criteria risk of bias assessment recommended by the Cochrane Collaboration for randomised trials [17,18] by two review authors (SPY, LD). The domains assessed included 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. The risk of bias was scored as

'low', 'high' or 'unclear'. A study with a low risk of bias was defined as fulfilling six or more of the criteria items listed. Any disagreement between the reviewers was resolved by discussion and if required, further input from a OA Trial Bank member (MvM).

2.9. Data extraction

Information related to the interventions and comparator groups was obtained from the published papers. The data obtained from the original studies included participant baseline characteristics (age, sex, body mass index (BMI)), joint characteristics (radiographic grading, duration of disease and signs of inflammation), study characteristics (types of intervention and doses), and outcome measurements (pain, function). All participant data were pooled into a dataset and assigned an individual random trial number.

2.10. Data analyses

Data from the newly identified studies were combined with the existing IPD collected under the OA Trial Bank [11]. As this was an update study, analyses were only conducted for the treatment comparisons and interaction effects of IA glucocorticoid compared with placebo and hyaluronic acid due to the absence of new studies comparing IA glucocorticoid with tidal irrigation.

The primary outcome was pain severity at short-term follow-up. The outcomes measured on different scales were standardised - the visual analogue scale (VAS) pain measure was utilised if available. If only the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee injury and osteoarthritis outcome scores (KOOS) or other Likert scores were available, the pain subscales were converted to a 0–100 scale. Tests of heterogeneity were conducted using Q statistics, which is distributed as a chi-square random variable (assumption of homogeneity of effect sizes). The between-study heterogeneity was assessed with τ^2 (estimate of between-study variance) and I^2 (the percentage of total variation due to between study variance) with interpretation as follows: $I^2 < 25\%$ means no heterogeneity, $I^2 < 50\%$ means low heterogeneity, $I^2 < 75\%$ means moderate heterogeneity, $I^2 \geq 75\%$ indicates high heterogeneity [19]. Additional analysis was performed excluding trials causing heterogeneity to reach an $I^2 < 50\%$.

The overall effect between the different treatment comparative groups was estimated at all follow-up time points using standardised mean differences. The IPD analysis was conducted in a two-stage approach as the study sponsor of one trial stipulated their data to be analysed on a secure server. Due to participant confidentiality and data share agreement requirements, IPD from the included trials for this study could not be uploaded to the specified server for a one-stage analysis, thus a two-stage approach was decided. We tested one-stage and two-stage analyses of the trials not on the secure server and yielded similar results, which is compatible with prior research indicating that in most cases, comparable results will be obtained from a one-stage and two-stage analysis [20].

An ANCOVA model adjusting for baseline pain, age and sex was fitted and tested to obtain the adjusted treatment effect in each study separately (first-stage), then pooled using a random-effects model (second-stage). The analyses could not be adjusted for BMI, symptom duration or KL grade, as not all studies provided these data. All the eligible trials reported less than 15% missing values and data were not imputed.

Interaction effects were analysed using a two-stage approach: a general linear model in the first-stage, and a random effects model in the second-stage. The model specification included the main effects, the interaction of subgroup factors and the treatment effect. The following subgroups were defined: presence or absence of severe pain (defined as $\geq$70 points at baseline on the pain scale, pre-determined by the OA Trial Bank consensus), and presence or absence of inflammation. Baseline pain was not included in the interaction effect analysis as severe pain is based on a cut-off of baseline pain. Including baseline pain could induce severe multicollinearity and inflate the standard error. Interaction effects were only tested for treatment comparisons that included more than one trial.

All analyses were repeated for knee OA participants separately based on hip/knee OA trials. This was not conducted for hip OA participants due to the lack of new hip OA trials obtained for this study.

To assess whether there was a minimum baseline pain cut-off for clinically important treatement effect of IA glucocorticoid compared with placebo, a pairwise comparison of pain scores (grouped) was conducted. Baseline pain scores were distributed into groups of 10 points (i.e., VAS pain score 0–10 = 10, and 11–20 = 20 and onwards) and introduced as a factor along with the treatment group in the linear mixed effect model adjusting for age and gender. *Post hoc* comparisons were based on heteroscedastic consistent multiplicity adjustments using Dunnett's T3 method [21], which is based on the studentized maximum modulus and keeps tight Type I error control [22].

The analyses were conducted using the statistical software, SAS® Version 9.4 (SAS Institute Inc.) and Stata Version 17 (StataCorp. 2021).

3. Results

3.1. Study descriptions

The literature search yielded 418 study abstracts that were screened. 388 were excluded based on title and abstract. Full-text articles of 30 studies were evaluated. Of those, 16 studies that fulfilled the inclusion criteria were sought for IPD [23–38]. Three attempts were made to contact the corresponding authors/institutes and study sponsors, and four authors/sponsors agreed to participate and contributed data [29–31, 35]. Authors/institutions/sponsors of five studies did respond to the data share request, but were subsequently lost to further contact, or had data availability or access issues[25-28, 33 34]. No contact was established with six studies [23,24,32,36–38].

The IPD from the four studies (n = 621) were combined with the existing IPD from the OA Trial Bank for analyses [39–45] (Fig. 1). This yielded 1261 participants from eleven studies, fulfilling the eligibility criteria. The characteristics of the included studies are presented in Table 1. A total of six studies compared glucocorticoids (n = 190) with placebo (n = 232) [29,30,40,42,44,45], three studies compared glucocorticoids (n = 203) with hyaluronic acid (n = 330) [31,40,43], two studies compared glucocorticoids (n = 104) with tidal irrigation (n = 92) [39,45], one study compared glucocorticoids (n = 30) with botulinum toxin injections (n = 30) [41], and one study compared two different preparations of glucocorticoids — methylprednisolone (n = 50) versus triamcinolone (n = 50) [35]. Table 1 is an overview of the included studies. Nine studies were knee OA studies, whilst two studies were based on hip OA. All studies reported on pain at short-term follow-up. No issues were identified when checking transferred IPD data.

Table 2 details the baseline characteristics of the study participants for each treatment comparison. The average age was about 64 years, and 59.8% were women. 31.2% of participants reported severe pain ($\geq$70 on a 0–100 scale) at baseline, with the highest proportion of participants reporting severe pain in the treatment comparison group of glucocorticoid and tidal irrigation. Nine studies assessed for inflammatory signs either by physical examination or imaging, which were present in 36.3% of the participants.

The risk of bias scores of the studies are presented in Appendix 1. All studies were deemed to be of low bias. All studies scored low risk in relation to randomization, compliance, timing, and selective outcome reporting. Two studies scored negative on all blinding criteria [39,40].

3.2. Overall treatment effects

A significant overall treatment effect on the primary outcome pain severity at short-term follow-up was seen when comparing IA

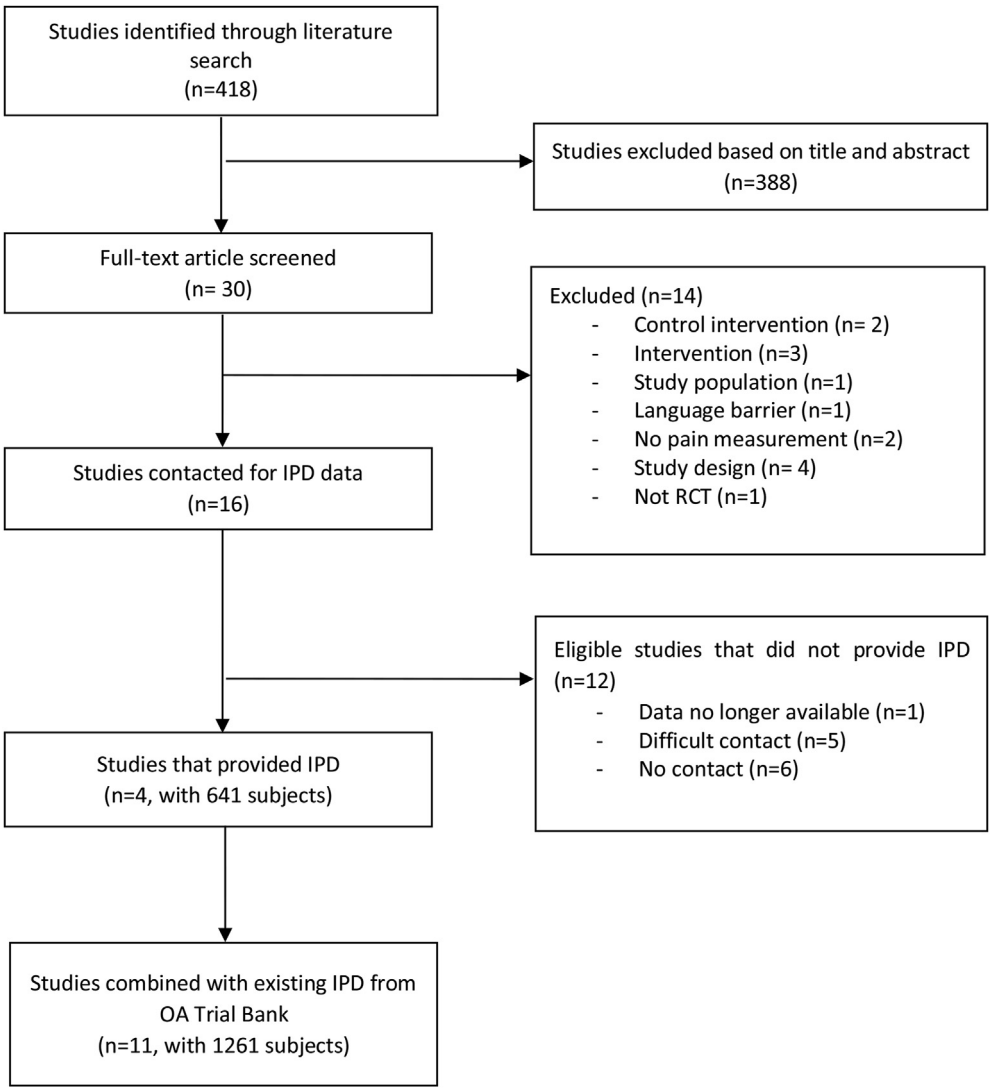

Fig. 1. Flow diagram of updated search and included studies.

glucocorticoid injection to placebo for both hip and knee OA (adjusted mean difference (on a 100-point scale): −11.85 (95% CI -21.40; −2.30)) (Fig. 2 and Table 3). No statistical differences were found at mid- or long-term follow-up when comparing IA glucocorticoid to placebo. No statistical differences were found when comparing glucocorticoid with hyaluronic acid at all follow-up time points. Comparison with tidal irrigation was not conducted due to absence of new studies.

Subgroup analyses of knee OA participants separately at short-term follow-up did not show significant overall effects of IA glucocorticoid injections compared to placebo (Mean difference: −7.36 (95%CI -18.06; 3.34)). Similar findings were seen at mid- and long-term follow-ups (data not shown).

3.3. Baseline pain severity and treatment effect

Significant interaction effects were found between severe pain at baseline and the treatment effect of IA glucocorticoid injections compared to placebo at mid-term follow-up with a greater reduction in pain observed in those with severe pain (i.e. >70 points on 0–100 point scale) (Mean reduction: −6.90 (95%CI -10.91; −2.90)); effect size was 0.68 (moderate). In contrast, this interaction effect was not seen at short- or long-term follow-ups, even though there was a reduction in pain across the different follow-up time points in participants with severe pain compared to less severe pain at baseline (Table 4).

No significant interaction effects were found between severe pain at baseline and the treatment effects of IA glucocorticoid injections compared to hyaluronic acid and tidal irrigation.

Subgroup analysis on knee OA participants based on three trials [30,42,45] did show a statistically significant interaction between severe pain and IA glucocorticoid injection compared to placebo at mid-term follow-up (Mean reduction: −7.77 (95%CI -7.70; −2.46, p = 0.014, I^2 0%)), but this was not seen at short- or long-term follow-up (data not shown).

3.4. Baseline inflammatory signs and treatment effect

At short-term follow-up, there were significant interaction effects found between inflammatory signs, and the treatment of IA glucocorticoid injections compared to hyaluronic acid (Mean reduction: −10.82 (95%CI -20.30; −1.33)); effect size was 0.47 (small). No significant interaction effects were found between inflammatory signs and the treatment of IA glucocorticoid injections compared to placebo (Table 4).

No significant interaction effects of inflammatory signs and IA glucocorticoid injections and placebo in the subgroup analysis of knee OA patients at both short-term and mid-term follow-ups based on four trials [29,30,42,45] (data not shown).

No statistically significant interaction effects were seen with ultrasound-detected inflammatory signs and IA glucocorticoid injections compared to placebo at short-or mid-term follow-ups (Table 4).

Table 1
Characteristics of included studies.

	Origin	N at baseline	Joint	OA diagnosis	N in Glucocorticoid	N in Control intervention	Interventions	Outcome	Inflammation	Follow-up	Funding source
Arden et al. [39] (2008)	United Kingdom	150	Knee	Clinical diagnosis of knee OA + radiographic evidence	79	71	Triamcinolone acetonide 40 mg + 2 ml lignocaine Vs Tidal irrigation	- Pain (VAS) - WOMAC pain, physical function, stiffness, total - Global assessment (5 pt Likert)	Presence of effusion by physical examination (Small/mod/large)	2, 4, 12 and 26 weeks	Government institution and funding agency
Atchia et al. [40] (2011)	United Kingdom	77	Hip	ACR criteria for hip OA (1991)	19	58 - n = 19, placebo - n = 20, standard care - n = 19, Hyaluronic acid	Methylprednisolone acetate 3 mL/120 mg Vs placebo (3 mg saline) Vs standard care Vs hyaluronic acid (Durolane)	- Pain (NRS) - WOMAC pain, physical function, stiffness, total	Presence of synovitis >7 mm on ultrasound	1, 4, 8 and 16 weeks	Governmental institution and funding agency
Boon et al. [41] (2010)	USA	60	Knee	Clinical diagnosis of knee OA + KL grade 2 or 3	20	40 - n = 20, low dose botulinum - n = 20, high dose botulinum	Methylprednisolone acetate 40 mg Vs low and high dose botulinum toxin type A (100 and 200 units)	- Pain (VAS) - WOMAC pain, physical function, stiffness, total	Presence of effusion by physical examination (mild/mod/large)	2,12 and 26 weeks	Funding agency
Chao et al. [42] (2010)	USA	79	Knee	ACR criteria for knee OA (1986) + radiograph within 1 year of enrolment	40	39	Triamcinolone acetonide 40 mg Vs Placebo (1 cc 0.9% saline)	- Pain (VAS) - WOMAC pain and total	Pathologic effusion of ≥5 mm present on ultrasound	4 and 12 weeks	Governmental institution and funding agency
De Campos et al. [43] (2013)	Brazil	104	Knee	ACR criteria for knee OA (1986)	52	52	Triamcinolone hexacetonide + Hylan GF20 (6 ml) Vs Hylan GF20 (6 ml)	- Pain (VAS) - WOMAC pain, physical function, stiffness, total	–	1, 4, 12 and 24 weeks	Governmental institution and funding agency
Hall et al. [29] (2014)[a]	United Kingdom	50	Knee	Clinical diagnosis of painful knee OA + KL grade ≥2	25	25	Methylprednisolone 40 mg Vs Placebo (1 ml, 0.9%)	- Pain (VAS) - WOMAC pain, physical function, stiffness	Presence of effusion/synovial hypertrophy on ultrasound	1 week	Governmental institution
Henriksen et al. [30] (2015)[a]	Denmark	100	Knee	ACR criteria for knee OA (1986) + radiographic confirmation	50	50	Methylprednisolone acetate 40 mg + 4 ml lidocaine hydrochloride (10 mg/ml) Vs Placebo (1 ml isotonic saline + 4 ml lidocaine hydrochloride (10 mg/ml)) Followed by 12-week exercise program starting at week 2	- KOOS pain, ADL, QOL, function in sports/recreation, symptoms	Presence of effusion/synovitis on MRI imaging	2, 14 and 26 weeks	Governmental institution
Housman et al. [31] (2014)[a]	USA	391	Knee	ACR criteria for knee OA (1986) + exclusion criteria of KL grade 0 and 4	132	259 - n = 129, 2 × 4 mL hylastan - n = 130, 1 × 4 mL hylastan	Methylprednisolone acetate 40 mg Vs 2 × 4 ml hylastan Vs 1 × 4 ml hylastan	- WOMAC A pain - WOMAC A1 walking pain - WOMAC A responders - OMERACT-OARSI response criteria - Patient global assessment Clinical observer global assessment	Presence of effusion or warmth by clinical assessment	4, 8, 12, 16, 20 and 26 weeks	Commercial party
Lambert et al. [44] (2007)	Canada	52	Hip	ACR criteria for hip OA (1991) + radiologic evidence of OA	31	21	Triamcinolone 40 mg + 10 mg bupivacaine Vs Placebo (10 mg bupivacaine + 2 ml saline)	- WOMAC pain, physical function, stiffness, total - Global Assessment	–	1, 2, 3 and 6 months	Funding agency

(*continued on next page*)

Table 1 (*continued*)

	Origin	N at baseline	Joint	OA diagnosis	N in Glucocorticoid	N in Control intervention	Interventions	Outcome	Inflammation	Follow-up	Funding source
Lomonte et al. [35] (2015)[a]	Brazil	100	Knee	ACR criteria for knee OA (1986) + inclusion criateri of KL grade 2 or 3	50	50	Triamcinolone hexacetonide 40 mg Vs Methylprednisolone acetate 40 mg	- Pain (VAS) - WOMAC pain, physical function, stiffness, total - Patient global and physician global assessment (VAS) - Lequesne index	Presence of effusion detected by arthrocentesis	4, 12 and 24 weeks	Governmental institution
Ravaud et al. [45] (1999)	France	98	Knee	ACR criteria for knee OA (1986) + inclusion criteria of KL grade ≥2	25	73 - n = 28, placebo - n = 21 joint lavage plus placebo - n = 24, joint lavage plus corticosteroid	Cortivazol 3.75 mg in 1.5 ml Vs placebo (1.5 ml 0.9% saline) Vs joint lavage plus IA placebo Vs joint lavage plus IA corticosteroid	- Pain (VAS) - Global status (VAS)	Evidence of effusion by clinical assessment (present or not)	1, 4, 12, and 24 weeks	Governmental institution and funding agency

[a] Indicate new studies added to OA Trial Bank.

3.5. Sensitivity analyses

By using a leave-one-out sensitivity analysis method along with qualitative assessment of the studies based on sample size and design, theexclusion of the study of Henriksen et al. [30]. For the comparison with placebo, resulted in a reduction of I^2 to 8.6%. Comparable significant pain reduction was still seen in the short-term for IA glucocorticoid and placebo with an effect estimate of −14.87 (95%CI -22.63; −7.12). For the comparison with hyaluronic acid, excluding the study of Housman et al. [31], rendered the I^2 to 33.4%. For the interaction of severe pain in the hyaluronic acid group, excluding the study of Atchia et al. [40], the I^2 reduced to 0%. For the interaction of inflammation in the placebo group, excluding the study of Atchia et al. [40], the I^2 reduced to 37.8%.

3.6. Pain level and clinical effectiveness of IA glucocorticoids

Comparison of marginal means of pain scores showed that clinically important response to IA glucocorticoid injections compared to placebo at short-term follow-up started to become evident from pain group 31–40 onwards. However, the difference in mean score between IA glucocorticoid and placebo only became significant from pain group 51–60 ($t(318) = -2.50$, $p = 0.013$), with the magnitude of effect becoming more prominent as the pain score increased, with pain group 91–100 ($t(318) = -4.37$, $p < 0.0001$) (Fig. 3 and Table 5).

4. Discussion

Despite the regular use of IA glucocorticoid in OA management, factors predicting responses to these injections remain poorly understood. This updated IPD meta-analysis aimed to build upon the knowledge from the prior IPD meta-analysis in IA glucocorticoid, focusing on the subgroup effects of severe pain and inflammatory signs.

This updated meta-analysis of eleven studies with an increased number of participants in both the placebo and hyaluronic acid comparison groups reaffirms the results of the original study that participants with and without severe pain at baseline benefited from glucocorticoid injection compared to placebo at short-term follow-up with an estimated reduction in pain of −11.9 points on a 0–100 pain scale. The initial IPD study showed an interaction effect of severe baseline pain than those with less severe pain when receiving IA glucocorticoid injection compared to placebo at short-term follow-up. In this updated study, even though there was a reduction in pain points when IA glucocorticoid injection was compared with placebo, an interaction effect of severe baseline pain was seen only at mid-term follow-up, suggesting that severe baseline pain likely still has an impact on predicting the treatment response of IA glucocorticoid and possibly leading to more sustained effects in the individual over time. The absence of interaction of severe pain in the short-term may be related to the newer studies included having lower effect estimates compared to placebo than the older studies (Fig. 2). This reduced effect is seen in other more recent (but not included in this analysis) glucocorticoid studies [33,46], which leads to the question of whether clinical trial conduct and protocol changes throughout the years may have an impact on trial outcomes and hence, our results compared to the initial study. The absence of effect for the interaction of severe pain in the hyaluronic acid group might be explained by the high heterogeneity in the short-term. The design, study sample size, and drug dosing/preparations are all influencing factors.

Analysis of trend demonstrated that as the baseline pain score increased, the larger the mean differences became between IA glucocorticoid and placebo. This finding indicates that even for individuals with moderate pain levels (i.e. >50 and above, 0–100 pain scale), treatment may be of benefit. This also gives potential for future studies to include participants with moderate pain levels.

In IA glucocorticoid trials, trial methodology issues with underpower of the studies and inconsistencies across the studies in terms of predictor

Table 2
Baseline characteristics of participants in the study.

	Total population, N = 1261	Treatment comparison 1 (corticosteroid vs placebo) N = 372	Treatment comparison 2 (corticosteroid vs hyaluronic acid) N = 533	Treatment comparison 3 (corticosteroid vs tidal irrigation) N = 196
Age (years)	63.79 (10.16)	65.21 (10.66)	61.76 (9.90)	66.28 (9.56)
Sex, % female	754 (59.8%)	182 (49.6%)[d]	360 (67.5%)	82 (41.8%)
BMI (kg/m^2)	30.21 (5.21)[a]	29.02 (4.35)	30.68 (6.14)	30.80 (5.09)
Knee OA, %	1132 (89.8%)	282 (75.8%)	495 (92.9%)	196 (100%)
Hip OA, %	129 (10.2%)	90 (24.2%)	38 (7.1%)	–
Duration of symptoms (months)	72.11 (91.23)[b]	86.62 (122.38)	37.11 (39.59)[i]	69.36 (87.22)
KL grade %				
0	2 (0.1%)	2 (0.5%)	0	0
1	56 (4.4%)	13 (3.5%)	38 (7.1%)	4 (2.0%)
2	342 (27.1%)	64 (17.2%)	155 (29.1%)	107 (54.6%)
3	640 (50.8%)	147 (39.5%)	312 (58.5%)	39 (19.9%)
4	113 (9.0%)	66 (17.7%)	26 (4.9%)	20 (10.2%)
Missing	108 (8.6%)	80 (21.5%)[f]	2 (0.4%)	26 (13.3%)
Inflammation, %	308 (36.3%)[e]	220 (69.8%)[g]	96 (25.5%)[h]	110 (56.1%)
Pain (0–100)	58.33 (17.24)	57.27 (21.19)	58.13 (14.45)	57.71 (23.02)[c]
Severe pain (≥70 points on VAS), %	394 (31.2%)	102 (28.0%)	109 (20.5%)	65 (33.2%)

[a] N = 1026.
[b] N = 857.
[c] N = 187.
[d] N = 367.
[e] N = 849.
[f] Not available for Chao.
[g] N = 315 (not available for Lambert).
[h] N = 376 (not available for de Campos).
[i] N = 429 (not available for de Campos).

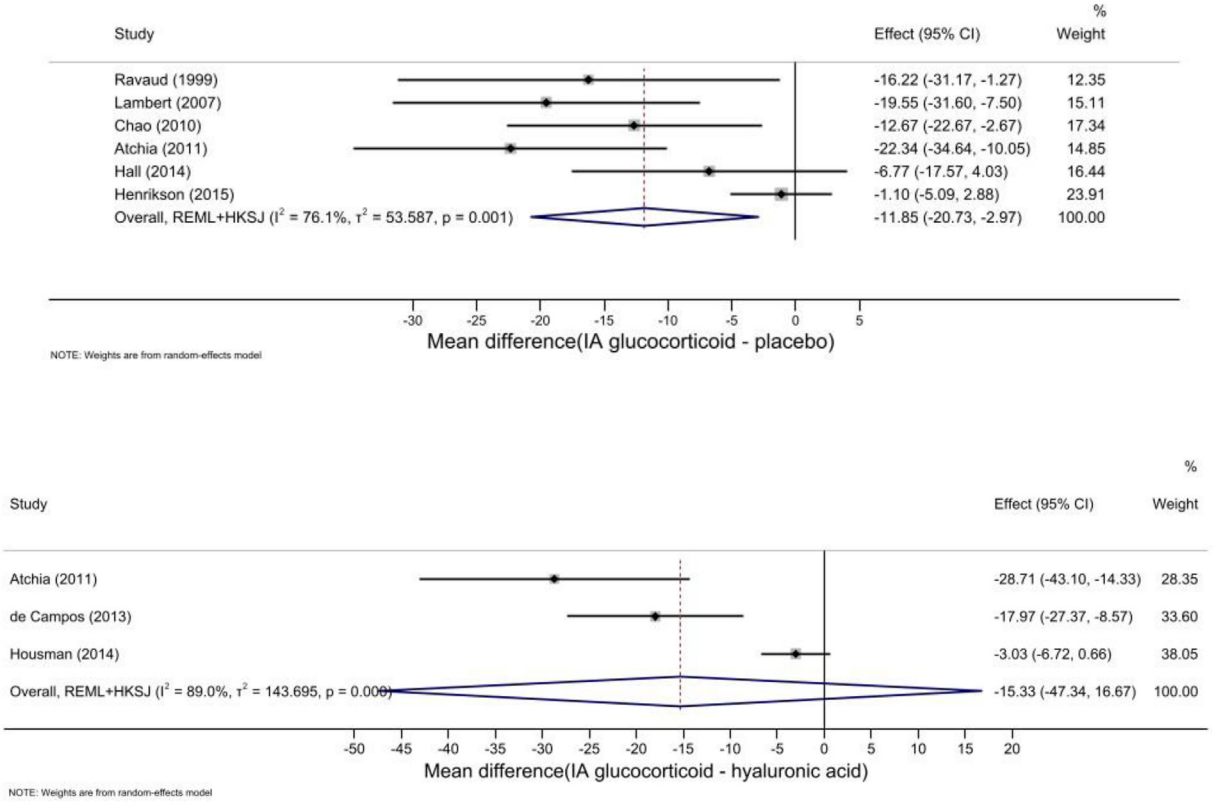

Fig. 2. Estimated pooled differences for pain between intra-articular glucocorticoid and placebo injections and intra-articular glucocorticoid and hyaluronic acid injections short-term follow-up.

Table 3
Estimated pooled differences between IA glucocorticoid versus comparison agents on pain severity (negative values indicate a greater reduction in the outcome measure of IA glucocorticoid).

	N Total	*N* intervention	*N* control	Estimated pooled differences (95%CI)	*P*-value	Cochran's Q (*P*-value)	I^2 (%)	Tau^2	Adjusted estimated pooled differences (95%CI)	*P*-value	Cochran's Q (*P*-value)	I^2 (%)	Tau^2
IA glucocorticoid versus placebo													
Short-term (six trials) [29,30,40,42,44,45]	351	176	175	**−11.47 (-21.16; -1.78)**	**0.029**	15.93 (0.007)	68.6	56.58	**−11.85 (-20.73; -2.97)**	**0.019**	20.96 (0.001)	76.1	53.59
Mid-term (five trials) [30,40,42,44,45]	274	144	130	−2.37 (−13.30; 8.57)	0.580	8.17 (0.086)	51.0	42.95	−0.66 (−9.61; 8.28)	0.847	6.33 (0.176)	36.8	22.74
Long term (three trials) [30,44,45]	160	88	72	3.33 (−12.41; 19.08)	0.458	1.39 (0.500)	0	15.65	3.81 (−10.0; 17.61)	0.357	2.15 (0.341)	6.9	0
IA glucocorticoid versus hyaluronic acid													
Short-term (three trials) [31,40,43]	513	199	314	−14.30 (−44.97; 16.37)	0.183	14.12 (0.001)	85.8	125.70	−15.33 (−47.34; 16.81)	0.176	18.25 (0.000)	89.0	143.69
Mid-term (three trials) [31,40,43]	471	186	285	−1.85 (−7.81; 4.11)	0.313	1.00 (0.606)	0	0	−2.161 (−5.93; 1.61)	0.132	0.41 (0.815)	0	0
Long term (two trials) [31,43]	456	170	286	0.87 (−0.91; 2.66)	0.101	0.00 (0.969)	0	0	0.685 (−6.46; 7.83)	0.438	0.08 (0.781)	0	0

Adjusted for age, sex, and baseline pain. Bold value signifies statistical significant differences ($P < 0.05$).

variables, trial design, and statistical analyses all impact on the ability to find reliable predictors of response to treatment. Thus, studies assessing predictors of response have showed conflicting results, with one study suggesting that radiographic severity of knee OA was predictive of response to treatment [39], whilst different studies negated that self-perceived symptom severity was a predictor of response [47]. In a systematic review of eleven publications that assessed the clinical predictors of response to IA glucocorticoid injections in knee OA [6], identification of specific predictors was not well established. Similar findings were seen in another systematic review of twenty-one studies [8]. Data from the individual publications within the reviews suggested that the presence of effusion, synovial fluid aspiration, the severity of disease, the absence of synovitis, injection delivery under ultrasound guidance and greater symptoms at baseline may all improve the likelihood of response to IA glucocorticoid.

Inflammation is recognised to play a role in the pathogenesis of OA, with increasing evidence that low-grade synovitis contributes to radiographic and pain progression [48]. Given the anti-inflammatory effects of IA glucocorticoid and its use in other inflammatory joint conditions, there is the expectation that it may be effective in relieving OA symptoms. To date, there is no consistent association between effusion or synovitis on outcome [7,14]. In this IPD analysis, apart from the significant interaction between signs of inflammation and IA glucocorticoid compared to hyaluronic acid at short-term, a non-significant trend of pain reduction was seen for the effectiveness of IA glucocorticoid when assessing the interaction effect of inflammation, and this was also noted for inflammatory signs measured by ultrasound. Comparable to the initial IPD analysis, no definite conclusions could be made on the subgroup effects of inflammation.

4.1. Strengths and limitations

The utilisation of IPD and the increased number of trials from the original IPD meta-analysis to eleven trials gave the study greater power than other studies that assessed potential predictors of response for the treatment of knee and hip OA with IA glucocorticoid.

There are several limitations to the study. Authors of 16 potential eligible publications were approached, and only IPD of four studies were obtained. Therefore, selection bias might be a possibility. As the intent of the OA Trial Bank is to include all OA intervention studies, studies by Boon et al. and Lomonte et al. were included in the study but were not included in the subgroup analyses as the studies compared different preparations of IA glucocorticoid and IA glucocorticoids with botulinum toxin.

There was high heterogeneity seen within the trials at short-term follow-up when comparing IA glucocorticoid and placebo, IA glucocorticoid and hyaluronic acid and in the interactions with severe pain in the hyaluronic acid comparison and inflammation in the placebo comparison. Heterogeneity is most likely due to the variances in the study design, intervention dosage and preparations, and sample sizes, i.e., the Henriksen et al. [30]. Trial integrated larger quantity of local anaesthetics and a 12-week exercises program. Due to the limited number of studies, analysis of re-group trials in homogeneous subgroups was not achievable. This is of consideration if more trials are available for future updates.

With this updated study, the additional study of hyaluronic acid comparison allowed for subgroup analysis of inflammation in this comparison group that was not conducted in the initial study. However, the subgroup analysis assessing severe pain and inflammation may be underpowered due to the low number of subjects included. Inflammation reporting was varied across the included studies and effusion and/or synovitis was utilised as a determinant for inflammation in our study, whether it is via clinical examination or imaging. Perhaps a more stringent definition of inflammation is required for future studies with more objective signs identified on imaging. A frequent issue in IPD analyses is that variables of interest or potential effect modifiers are often not

Table 4
Interaction effects of severe pain (≥70 points), inflammation and ultrasound measured inflammation with IA glucocorticoid for primary outcome of pain severity.

Interaction effect of severe pain with IA glucocorticoid[a]												
	Severe pain *n/N* glucocorticoid group	Severe pain *n/N* control group	Pooled mean reduction (β) (95%CI)	*P*-value	Cochran's Q (*P*-value)	I^2 (%)	Tau^2	Adjusted mean reduction (β) (95%CI)	*P*-value	Cochran's Q (*P*-value)	I^2 (%)	Tau^2
IA glucocorticoid versus placebo												
Short-term [29,30,40,42,44,45]	49/174	51/171	−5.98 (−17.17; 5.20)	0.227	3.75 (0.586)	0	0	−5.98 (−18.28; 6.31)	0.266	4.47 (0.484)	0	0
Mid-term [30,40,42,44,45]	34/140	32/130	−6.75 (−12.47; −1.03)	0.031	0.37 (0.985)	0	0	**−6.90 (-10.91; -2.90)**	**0.009**	0.17 (0.996)	0	0
Long term [30,44,45]	17/88	15/72	−5.05 (–52.90; 42.80)	0.694	1.75 (0.416)	0	0	−2.84 (−62.69; 57.01)	0.857	2.88 (0.24)	30.5	0
IA glucocorticoid versus hyaluronic acid												
Short-term [31,40,43]	47/199	59/314	8.49 (−58.87; 75.84)	0.642	11.36 (0.003)	82.4	594.71	7.50 (−56.58; 71.57)	0.665	9.41 (0.009)	78.8	508.88
Mid-term [31,40,43]	44/191	51/285	6.09 (−81.75; 93.92)	0.540	0.68 (0.410)	0	0	6.90 (−3.39; 17.20)	0.102	0.39 (0.822)	0	0
Long term [31,43]	42/170	55/286	9.24 (−29.20; 47.68)	0.201	0.29 (0.587)	0	0	8.42 (−28.03; 44.86)	0.209	0.27 (0.605)	0	0
Interaction effect of inflammation with IA glucocorticoid[b]												
	Inflammation *n/N* glucocorticoid group	Inflammation *n/N* control group	Mean reduction (β) (95%CI)	*P*-value	Cochran's Q	I^2 (%)	Tau^2	Adjusted mean reduction (β) (95%CI) (95%CI)	*P*-value	Cochran's Q	I^2 (%)	Tau^2
IA glucocorticoid versus placebo												
Short-term [29,30,40,42,45]	97/142	111/154	−4.48 (−22.72; 13.76)	0.533	4.33 (0.363)	7.7	0	−15.01 (−51.23; 21.21)	0.314	21.83 (0.00)	81.7	688.97
Mid-term [30,40,42,45]	80/117	78/113	3.39 (−23.15; 29.94)	0.711	3.62 (0.306)	17.1	45.11	−5.96 (−35.81; 23.91)	0.571	5.95 (0.114)	49.6	172.64
Long term [30,45]	53/66	50/60	−5.45 (−155.41; 144.51)	0.725	0.93 (0.335)	0	0	−7.43 (−125.49; 110.63)	0.571	0.64 (0.423)	0	0
IA glucocorticoid versus hyaluronic acid												
Short-term [31,40]	28/133	65/227	−11.04 (−72.28; 50.20)	0.262	0.79 (0.376)	0	0	**−10.82 (-20.30; -1.33)**	**0.044**	0.02 (0.885)	0	0
Mid-term [31,40]	28/125	57/209	−9.26 (−21.31; 2.80)	0.065	0.02 (0.881)	0	0	−9.22 (−70.10; 51.662)	0.305	0.62 (0.432)	0	0
Interaction effects of ultrasound measured inflammation with IA glucocorticoid[b]												
	Inflammation *n/N* glucocorticoid group	Inflammation *n/N* control group	Mean reduction (β) (95%CI)	*P*-value	Cochran's Q	I^2 (%)	Tau^2	Adjusted mean reduction (β) (95%CI)	*P*-value	Cochran's Q	I^2 (%)	Tau^2
IA glucocorticoid versus placebo												
Short-term [29,40,42]	46/75	48/76	−6.35 (−59.03; 46.33)	0.656	3.70 (0.157)	46.0	192.43	−20.16 (−118.61; 78.29)	0.471	21.08 (0.00)	90.5	1.4e+03
Mid-term [40,42]	29/49	25/47	1.94 (−267.25; 271.14)	0.942	3.31 (0.069)	69.8	635.99	−8.54 (−301.76; 284.67)	0.774	4.98 (0.026)	79.9	864.63

Bold value signifies statistical significant differences ($P < 0.05$).
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, and baseline pain.

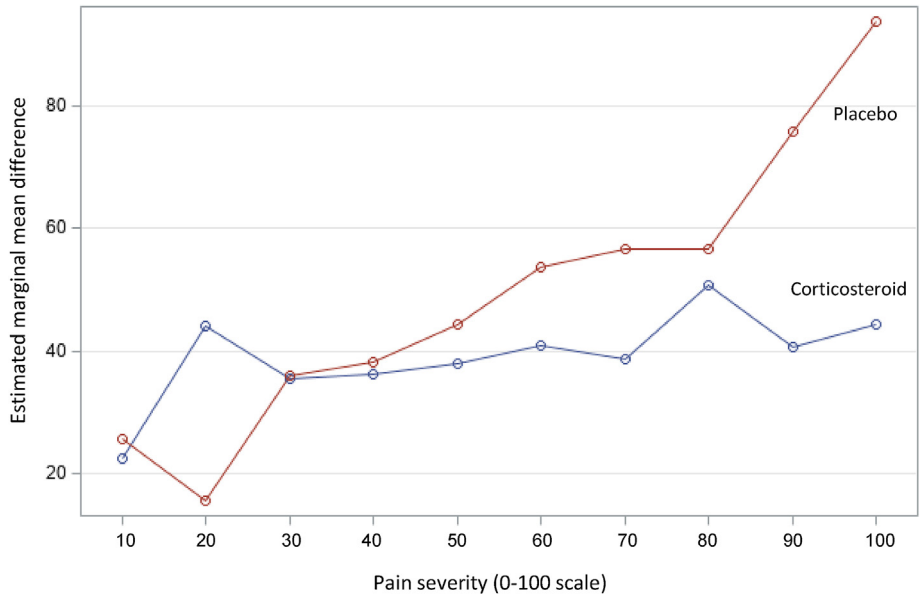

Fig. 3. Comparison of marginal means of pain scores (grouped) of IA glucocorticoid compared to placebo at short-term follow-up.

Table 5
Pairwise comparison of marginal means of pain scores (grouped) of IA glucocorticoid compared to placebo at short-term follow-up.

Pain Group	Estimate	Standard error	T value	P-score
0–10	−3.42	9.10	−0.34	0.732
11–20	28.58	14.05	2.03	0.042
21–30	−0.43	9.69	−0.04	0.965
31–40	−2.14	6.74	−0.32	0.751
41–50	−6.27	4.87	−1.29	0.199
51–60	−12.66	5.06	−2.50	0.013
61–70	−17.96	5.06	−3.55	0.0004
71–80	−5.90	5.43	−1.09	0.278
81–90	−35.22	7.75	−4.54	<0.0001
91–100	−49.37	11.29	−4.37	<0.0001

measured in the primary studies, or are not consistently available across the studies included, thus affecting the harmonisation of the variables [49]. Participant outcomes scores require standardisation from their original scores for data harmonisation despite potentially having different measurement sensitivities, which can have potential implications on the results. Ideally for clinical trials, there should be consistency across the board with baseline characteristics and outcome measurements, and interest groups should direct attention towards these measures, to enable greater accuracy for meta-analyses.

For the systematic review, an update of the search strategy may be ideal, but this was not feasible for the present study. Around 36 months was required for all data acquisition after completion of the systematic search at the end of 2018. Timing was affected by when contact was established, lengthy bureaucratic procedures with legal entities, repeated data share agreements alterations, obtaining institutional approvals and data supplier changes. Further three months were required for data extraction, checking and harmonisation before analyses commencement. In this timeframe, only one additional IA glucocorticoid/placebo randomised trial was published [50]. This highlights the acquisition of data in an IPD analysis being a time-consuming and resource-intensive process.

5. Conclusion

This IPD meta-analysis demonstrated that in participants with severe baseline pain, clinically relevant response is seen at mid-term follow-up, which is suggestive that sustained response to IA glucocorticoid injection may be seen in a subgroup of OA participants. As baseline pain score increases, the magnitude of effect of therapy is more pronounced and treatment response is seen in participants from moderate pain levels and beyond. No concrete conclusions can be made on inflammatory signs in OA. There is a need for ongoing IPD studies with increased study numbers, stringent standardisation of OA classification criteria, outcomes, effect modifiers and treatment protocols in clinical trials to facilitate higher precision in meta-analyses.

Author contributions

SPY, MvM, MF, LD, VV, SMAB-Z and DJH were involved in the study design and contributed to the interpretation of the results. SPY contacted the potential data-deliverers, coordinated the data collection, and performed the data analysis. VV contributed to data analysis. SPY and LD conducted the literature review. SPY wrote the manuscript together with MvM, MF, LD, VV, SMAB-Z and DJH.

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Conflict of interest

Professor David Hunter provides consulting advice to Merck Serono, Pfizer, Lilly, TLCBio, Novartis. Professor Sita receives consulting fees from Pfizer Infirst Healthcare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2023.100362.

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