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Health Technology Assessment (HTA)

HTA Report

Intra-articular glucocorticoid injections for osteoarthritis of the hip or knee

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

Background and objectives

Intra-articular glucocorticoid injection (IAGI) is utilised and publicly reimbursed in Switzerland for patients with knee or hip osteoarthritis (OA). However, systematic reviews on the efficacy and safety of IAGI indicate limited or unclear benefits compared to placebo or no treatment. This health technology assessment (HTA) investigates the safety, efficacy, cost-effectiveness, budget impact and other issues related to IAGI in patients with hip or knee OA compared to sham, placebo or no treatment.

Methods

The clinical evaluation included a systematic review of randomised controlled trials (RCTs) by searching Embase, Medline and the Cochrane Library up to 4 October 2023. Outcomes of interest included function, pain, health-related quality of life (HRQoL), joint replacement surgery, care utilisation, treatment satisfaction, adverse events (AE) and serious adverse events (SAE).

Longitudinal meta-analyses (LMA) were conducted where possible; otherwise, separate pairwise meta-analyses were conducted at individual timepoints. Continuous outcomes were reported as standardised mean differences (SMD) or mean differences (MD), and dichotomous outcomes were reported as risk ratios (RR), all with corresponding 95% confidence intervals (CI). For SMDs, a difference of 0.2 was considered to be a small effect, 0.5 moderate and 0.8 large.

For efficacy outcomes, treatment effects were evaluated at 3 months (primary endpoint), as well as at 1, 6 and 12 months (secondary endpoints); safety outcomes were reported at longest follow-up. While the 3-month data provide information in line with the treatment goals of IAGI, it is worth highlighting that other timepoints also provide information on the durability of the treatment effect and should not be considered as less clinically relevant than the primary endpoint. Heterogeneity was evaluated qualitatively (forest plots) and quantitatively (I^2, χ^2, T^2). Risk of bias (RoB) was assessed using Cochrane RoB 2.0, and the overall strength of evidence for important outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach at the primary endpoint.

The economic evaluation included a systematic review of economic studies, which was undertaken in the same databases plus Econlit and the International Network of Agencies for Health Technology Assessment (INAHTA) database. The websites of HTA institutes and database searches were conducted up to 16 October 2023. Modelling was undertaken to explore the cost-utility of a single IAGI in the management of knee OA as an exemplar case. The analysis examined IAGI as an adjunct to standard care compared to standard care alone. To derive quality-adjusted life year (QALY) estimates, reported outcomes were mapped into a preference-based utility measure. Expected per patient costs for the delivery of a single injection were

estimated for both knee and hip OA. Current utilisation of IAGI among Swiss patients diagnosed with primary OA of the knee or hip was estimated and extrapolated to predict the future budget impact of IAGI to the Swiss healthcare payer. No limitation or disinvestment scenario modelling was undertaken.

Clinical evaluation

Sixteen RCTs comprising 1,522 patients were evaluated for knee OA, and 4 RCTs with a total of 239 patients were included for hip OA.

For **knee OA**, the evidence suggests that IAGI results in little to no difference in pain at 3 months (SMD -0.04, 95% CI: -0.29 to 0.21, low certainty evidence); however, there may be a small reduction in pain in patients receiving IAGI at 1 month (SMD -0.30, 95% CI: -0.52 to -0.08, with substantial heterogeneity, I^2 = 65.25). IAGI may result in little to no difference in function (MD 0.00, 95% CI: -1.08 to 1.09, low certainty evidence), and likely results in little to no difference in HRQoL (MD 1.80, 95% CI: -2.88 to 6.48, moderate certainty evidence) at 3 months, or at any other timepoints. The evidence suggests IAGI probably results in little to no difference in care utilisation at 3 months (MD -0.19, 95% CI -0.59 to 0.21, moderate certainty of evidence); however, IAGI likely reduces care utilisation up to 1 month (MD -0.43, 95% CI -0.81 to -0.05). There is probably no difference in the rate of AEs (moderate certainty evidence), and a high degree of uncertainty in the rate of SAEs (low certainty evidence) for IAGI compared to sham. No studies reported joint replacement surgery or treatment satisfaction.

For **hip OA**, there is no evidence of a difference between IAGI and sham injection in relation to pain at 3 months (SMD -0.28, 95% CI: -0.76 to 0.20, very low certainty evidence), but the evidence is very uncertain; there is a large difference favouring IAGI at 1 month (SMD -1.60, 95% CI -2.70 to -0.51). No other timepoints were reported. Regarding function, 3-month data were not reported. IAGI may improve function at 1 month (SMD -1.74, 95% CI: -3.08 to -0.41, very low certainty evidence), but the evidence is very uncertain. Data at other timepoints were not reported. Regarding HRQoL, 3-month data were not reported. Evidence suggests HRQoL may be improved with IAGI at 1 month (MD 5.29, 95% CI: -0.10 to 10.68, very low certainty evidence). Data at other timepoints were not reported. There was no evidence of a difference for care utilisation (very low certainty evidence), AEs (very low certainty evidence) and SAEs (very low certainty evidence), noting that the incidence of AEs and SAEs was low in both groups. No studies reported joint replacement surgery or treatment satisfaction.

Economic evaluation

Only one cost-effectiveness study meeting the PICO criteria (population, intervention, comparator, outcome) for knee OA was identified. This study, from the New Zealand healthcare payer perspective, assessed the cost-utility of IAGI as an adjunct to core treatment compared to core treatment alone, finding IAGI to be a cost-effective adjunctive therapy. Despite differences in the modelling methodologies between the current HTA and the New Zealand study, the overall

findings appear to be in broad alignment, with incremental cost-effectiveness ratios (ICER) of NZD24,532 (CHF17,774) and CHF12,456 per QALY gained, respectively. In probabilistic analysis, 22.0% of iterations fell in the fourth quadrant of the cost-effectiveness plane, where IAGI is dominated (i.e. is more expensive and less effective than standard care). Mean expected incremental QALYs gained was estimated at 0.013 (95% CI: -0.019 to 0.044). Results from the current HTA suggest IAGI has 71.9% and 75.0% probability of being cost-effective at hypothetical willingness-to-pay thresholds of CHF50,000 and CHF100,000 per QALY gained, respectively.

The net financial impact of IAGI for knee OA under current policy conditions was estimated at CHF0.82 million in 2025, increasing to CHF0.97 million in 2029. For hip OA, the net financial impact was estimated at CHF0.52 million in 2025, increasing to CHF0.57 million in 2029.

Ethical, legal, social and organisational evaluation

Thirteen publications relating to ethical and social issues were identified; none were identified relating to legal or organisational considerations. Regarding ethical issues, informed consent was emphasised. Social issues identified that patient education highlighting the benefits of exercise and weight loss for treating hip and knee OA was an important factor in empowering individuals to maintain social activities. Survey findings indicate that individuals who derived benefits from exercise also generated positive beliefs and motivated others to persist in exercise routines. Knowledge about the importance of exercise and weight loss in managing OA served as a significant facilitator. Conversely, the belief that exercise could worsen the condition hindered physical activity, especially when individuals perceived OA as an inevitable ‘wear and tear’ issue.

Conclusions

Overall, neither of the populations reported improvements in pain, function or HRQoL at 3 months or beyond; however, both groups reported improvements in pain favouring IAGI at 1 month, and HRQoL may be improved in hip patients at 1 month. Patients with knee OA also experienced a decrease in care utilisation at 1 month; however, patients with hip OA may not experience a change in care utilisation. There were no significant safety concerns associated with IAGI in patients with either knee or hip OA at the longest follow-up. Other outcomes were not reported.

Economic modelling explored the cost utility of a single IAGI in the management of knee OA as an exemplar case. The estimated base case ICER (CHF12,456 per QALY gained) broadly aligned with the results from the available published literature. However, probabilistic analysis performed for the present evaluation highlighted uncertainty in the treatment benefit attributed to IAGI, contrasting with the existing study, which indicated confidence that IAGI was associated with a positive treatment effect. There is also uncertainty in the applicability of the estimated benefit to the Swiss population.

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Abbreviations and acronyms

AAOS	American Academy of Orthopedic Surgeons
ACR	American College of Rheumatology
AE	adverse event
BAG	Bundesamt für Gesundheit
BMI	body mass index
CI	confidence interval
CUA	cost-utility analysis
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis
ELSO	ethical, legal, social and organisational
EQ-5D	EuroQol 5-dimension health-related quality of life questionnaire
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
EULAR	European League Against Rheumatism
FOPH	Federal Office of Public health
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HOOS	Hip dysfunction and Osteoarthritis Outcome Score
HRQoL	health-related quality of life
HTA	health technology assessment
IAGI	intra-articular glucocorticoid injection
ICER	incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
KOOS	Knee injury and Osteoarthritis Outcome Score
LMA	longitudinal meta-analysis
MCID	minimal clinically important difference

MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OKP	Obligatorische Krankenpflegeversicherung (mandatory health insurance)
PICO	population, intervention, comparator, outcome
PICO (EO)	population, intervention, comparator, outcome, (economic outcomes)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
RCT	randomised controlled trial
RoB	risk of bias
RR	risk ratio
SAE	serious adverse event
SD	standard deviation
SMD	standardised mean difference
THA	total knee arthroplasty
VAS	visual analogue scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Arthritis index
WTP	willingness to pay

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described, their execution and the results. The analytical process is comparative, systematic and transparent, and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety; costs; cost-effectiveness and budget impact; and ethical, legal, social and organisational (ELSO) issues. The purpose of an HTA is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

Patients diagnosed with knee or hip osteoarthritis (OA) may be managed with non-surgical interventions including intra-articular glucocorticoid injections (IAGI), oral analgesics and/or physiotherapy.[1-4] These interventions aim to reduce pain, increase function and improve health-related quality of life (HRQoL). In Switzerland, IAGI with betamethasone acetate, dexamethasone, methylprednisolone and triamcinolone are currently covered by mandatory health insurance (OKP) for the treatment of patients diagnosed with knee or hip OA.[5] However, systematic reviews and studies on the clinical efficacy and safety of IAGI indicate limited or unclear benefits of this therapy compared to placebo or no treatment.[1 2] This HTA has been commissioned to determine whether the effectiveness, appropriateness and economic viability criteria are met.

2 Medical background

OA is a degenerative joint disease that affects the cartilage, bones and other tissues in the joints. It is the most common form of musculoskeletal disease, with knees, hips and hands most affected.[3] While it was previously viewed as a disease that solely caused mechanical cartilage degradation, it is now known to be a complex, fluctuating condition of the entire joint.[6]

2.1 Pathogenesis, risk factors and diagnosis

The cause of OA is not fully understood. It is believed to result from a complex interplay of genetic, biochemical, metabolic and mechanical factors. Some of the most recognised risk factors for the development of OA include genetic predisposition, age, obesity, joint injury, joint malalignment, joint instability and occupational or recreational activities that place excessive stress on the joints.[7] For example, participation in sports such as football, long distance running, wrestling and competitive weight lifting increases the risk of developing knee OA.[8] Individuals who are obese have a 66% chance of developing symptomatic knee OA, compared with a 45% chance for individuals with a healthy weight or normal body mass index (BMI).[9]

Inflammation plays a major role in OA and correlates with pain.[10] During the disease course, so called ‘activated OA’ occurs with increased pain, swelling (i.e. joint effusion) and redness. Joint effusion and synovial thickening can be observed through imaging such as ultrasound or magnetic resonance imaging (MRI).[11]

The major clinical features of OA include chronic relapsing joint pain, stiffness and joint deformities; however, the presentation and progression of OA varies greatly between patients.[12] Other features

include crepitus, joint deformity or effusion. In early-stage knee OA, pain is related to activity and becomes more constant over time; in late-stage OA this background pain is interspersed with unpredictable intense pain.[13] Pain is typically activity-related and resolves with rest. Early morning stiffness is transient, lasting <30 minutes.[14] As the disease progresses, pain may become more continuous and begin to affect activities of daily living.[7] This can lead to functional decline, reduced participation in daily activities and HRQoL and increased cardiovascular risk due to immobility.

Although the pathogenesis of OA remains largely unclear, pathologic changes in affected joints include degradation of the articular cartilage, thickening of the subchondral bone, bone marrow lesions, osteophyte formation, varying degrees of synovial inflammation, degeneration of ligaments, and hypertrophy of the joint capsule especially in the knee and menisci.[15]

Calcification within the cartilage is observed in >90% cases in end-stage OA. The release of crystals in the joint space leads to subsequent synovitis and joint effusion.[16] On the other hand, chondrocalcinosis or other types of intra-articular calcification can be detected in 10% of OA cases by computed tomography (CT) scan and 5% by radiography.[17]

Blood test measurements, including complete blood count, erythrocyte sedimentation rate and rheumatoid factor, typically show normal results in patients with OA. However, these tests may be requested to exclude inflammatory arthritis. The gold-standard method for diagnosing OA remains radiographic evaluation of the affected joint, typically with plain film radiography or ultrasound. Features include narrowing of the joint space width, osteophyte formation, and the development of subchondral sclerosis and cysts.[6] MRI can also be used to examine cartilage and bony changes during disease progression.[18] Cartilage depth and quality can be used as a possible radiological indicator for worsening disease in OA patients; however, a clear association between cartilage depth and quality, and how it translates to clinical progression, has not been established.[19] Arthrocentesis usually is performed for new onset joint effusion, in order to rule out inflammatory or crystal arthritis.[20]

2.2 Incidence and prevalence of OA

The global prevalence of knee and hip OA has increased from 141.3 million cases in 1990 (95% uncertainty interval 126.2–158.8 million) to approximately 303.1 million cases in 2017 (95% uncertainty interval 273.3–338.6 million).[21] Prevalence estimates for Western Europe and Central Europe are 3,866.5 cases and 3,164.5 cases per 100,000 head of population, respectively—an increase of 7.2% and 7.4%, respectively, between 1990 and 2017.[21] OA is a common degenerative disease in Switzerland, although estimates of the prevalence of OA show a decline from 8.4% in 2007 to 7.3% in 2012.[22] The cause of this decline is unclear.

2.3 Natural course of OA

OA of the knee is a heterogeneous disease that presents with a wide range of clinical symptoms and varying rates of progression. Some patients remain stable, while others will worsen clinically or even improve.[23] It is considered a lifelong disease, so patients that experience ongoing disease progression may ultimately require joint replacement.

Several factors have been identified as predictors for progression, including older age, the presence of OA in multiple joints, varus malalignment of the knee, higher BMI, presence of comorbidities, MRI-detected infrapatellar synovitis and joint effusion.[24, 25] Some studies also suggest that serum hyaluronic acid and tumour necrosis factor-α are associated with knee OA progression.[24, 26] However, conflicting evidence exists regarding the association of BMI and age with knee OA progression, and only limited evidence supports the association of joint alignment (varus/valgus) with progression.[26]

The clinical progression of hip OA has been found to be associated with comorbidities, a higher Kellgren–Lawrence (KL) grade (classification of the severity of OA), superior or lateral femoral head migration and subchondral sclerosis.[27] An evidence synthesis of cohort and case-control studies indicates that clinical progression is not associated with gender, social support, baseline use of pain medication, baseline HRQoL, or limited range of motion of internal or external hip rotation.[27]

2.4 Treatment pathway

IAGI is usually provided as a pain management intervention for patients with hip and knee OA who have not responded to oral or topical analgesics. In clinical practice, IAGI is performed in patients with joint effusion and other signs of inflammation. However, there is discordance in guideline recommendations for management of hip and knee OA by scientific organisations such as the American College of Rheumatology (ACR),[28] the American Academy of Orthopedic Surgeons (AAOS),[29] the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO),[30] the European Alliance of Associations for Rheumatology (EULAR)[31] and the Osteoarthritis Research Society International (OARSI).[32] While it is acknowledged that a range of treatment options exist in this population (including but not limited to oral pain medication, non-steroidal anti-inflammatory drugs [NSAIDs] and physiotherapy), this HTA focuses on evaluating the efficacy of IAGI in relation to placebo (including oral placebo and sham injection) or no treatment.

3 Technology

3.1 Technology description

IAGI is a non-surgical option for treating OA symptoms, with a primary aim to provide short-term improvement in pain, function and HRQoL.[33, 34] IAGI is used to treat patients with knee and hip OA, particularly those who cannot tolerate long-term therapy with paracetamol and NSAIDs, those for whom drugs are no longer effective, those who are contraindicated for surgical interventions, and those who want to delay or avoid surgical treatment.[33, 35]

3.2 Types of glucocorticoids for intra-articular injection

The various IAGI preparations publicly reimbursed in Switzerland are outlined in ***Appendix 13.1***, ***Table 39***.[36-38] The most frequently used are methylprednisolone acetate (Depo Medrol) and triamcinolone acetonide (Kenacort). Typical dosage is 40 mg, with an interval of at least 3 months between injections.[39, 40] IAGI can be administered with an equal volume of 1% or 2% anaesthetic (usually lidocaine or ropivacaine, as they provide more rapid onset and longer-lasting effects) to reduce discomfort and provide immediate relief;[40] however, current evidence suggests that multiple intra-articular local anaesthetic injections may be associated with an increased risk of chondrolysis.[35, 41] There is no consensus on the optimal dose for IAGI, which may depend on the size of the joint or body region, the severity of inflammation, or the amount of articular fluid present.

3.3 Mechanism of action

Glucocorticoids have immunosuppressive and anti-inflammatory effects. Anti-inflammatory and analgesic mechanisms include reduction of synovial blood flow, alteration of synovial fluid composition, inhibition of leukocyte traffic to the inflammation site, production of protease and cytokine, and alteration of collagen synthesis.[36] Synovitis is observed in 50% of patients with knee OA. The reason for this inflammatory status is not fully understood. Articular calcium crystal deposition, which includes calcium pyrophosphate dihydrate and basic calcium phosphate crystals, occurs in over 90% of patients with advanced knee or hip OA. These calcifications are believed to trigger OA ‘activation’ by interacting directly with synovial cells and chondrocytes to produce pro-inflammatory substances.[42] Similar to gout or pseudogout, intra-articular application of glucocorticoids is a potent treatment of microcrystalline inflammation.[43, 44]

IAGI has local and systemic effects. By binding to nuclear steroid receptors, glucocorticoids interrupt the inflammatory and immune cascades at many levels and modulate several pro-inflammatory cytokines involved in cartilage damage and degradation. They also interfere with the

production of inflammatory mediators such as prostaglandins and leukotrienes and may lead to downregulation of immune function.[45]

Certain pre-existing conditions reportedly increase the risk of negative joint outcome after IAGI. Older age, comorbid conditions such as diabetes mellitus (type 1 or 2), concomitant use of other immunosuppressive agents, severity and nature of the underlying disease, and poor nutritional status can all influence the occurrence and severity of side effects.[35, 46]

3.4 IAGI administration to the knee or hip

Intra-articular injection of the hip or knee can be a diagnostic and therapeutic procedure. It can be used to identify or exclude the cause of pain or to treat pain due to OA, and to distinguish inflammatory arthropathies from crystal arthritis or OA.[47] Administration of IAGI is usually guided by ultrasound or fluoroscopy to accurately identify the trajectory and depth of needle placement in the knee or hip.

Ultrasound uses high frequency sounds to create images of tissues within the body. Once the hip or knee joint is visualised, ultrasound enables correct placement of the needle, accurate delivery of medications, and visualisation of the steroid suspension before and after the procedure.[48] Advantages of ultrasound over fluoroscopy include the following: a) patient positioning and the needle trajectory are easily adjusted, b) the needle can be moved in real time, c) soft tissues can be targeted or avoided, d) no exposure to ionising radiation.[49]

Fluoroscopy is a radiologic imaging modality that uses X-rays to produce real-time images. A radiopaque object is placed on the skin overlaying the target to mark an appropriate entry site. Contrast medium is used to determine the correct intra-articular needle position in the joint. A major criticism of the use of fluoroscopy is the radiation risk or exposure to ionising radiation. For patients with allergy to iodinated contrast material, a full-strength gadolinium contrast or the use of ultrasound may be used.

3.5 Contraindications

There are several known contraindications to the use of glucocorticoid injections in musculoskeletal disorders. Absolute contraindications include active superficial skin or soft-tissue infection, suspected joint infection, unstable coagulopathy, anticoagulant therapy, septic arthritis, periarticular or intra-articular fracture, juxta-articular osteoporosis, severe joint destruction, hypersensitivity to the injection agent, uncontrolled diabetes mellitus (type 1 or 2) and broken skin at the injection site. Of note, anticoagulation treatment is a relative contraindication as a smaller-gauge needle is used for IAGI.[35, 39] Other relative contraindications include severe juxta-articular osteoporosis and injection of the joint 3 times that year or injections within 6 weeks.[37]

Contraindications associated with the use of specific glucocorticoids are presented in ***Appendix 13.1***, ***Table 39***.

3.6 Regulatory status/provider

In Switzerland, the glucocorticoid preparations triamcinolone (Kenacort ®-A 10/A 40, Triamcort®, Triamject), methylprednisolone (Depo Medrol®, Depo Medrol® Lidocaine), betamethasone (Celestone®, Chronodose®, Diprophos®) and dexamethasone (Dexamethasone Zentiva®, Dexamethasone Galepharm Amp, Mephamesone Injektionslösung), are listed on the Spezialitätenliste and are currently reimbursed through mandatory health insurance. Details regarding the coverage conditions according to the SwissMedic and the Spezialitätenliste are reported in ***Appendix 13.1***, ***Table 39***. Reimbursement in other European countries is outlined in ***Table 1***.

Table 1 Reimbursement of IAGI preparations for knee and hip OA in European countries

Country*	Triamcinolone	Methylprednisolone	Betamethasone	Dexamethasone
Switzerland	Reimbursed	Reimbursed	Reimbursed	Reimbursed
Denmark Danish Medicines Agency [50]	Reimbursed	Reimbursed	Reimbursed	Reimbursed
France Agence nationale de sécurité du médicament et des produits de santé [51]	Reimbursed	Reimbursed	Reimbursed	Reimbursed
Italy Italian Medicines Agency [52]	Reimbursed	Reimbursed	Reimbursed	Reimbursed
Norway Norwegian Medical Products Agency [53]	Reimbursed	Reimbursed	Reimbursed	Not reimbursed

Abbreviations: IAGI: intra-articular glucocorticoid injection; **OA**: osteoarthritis.
*Countries were chosen based on having similar demographic profiles to Switzerland, and published and retrievable data via targeted searches.

4 Population, Intervention, Comparator, Outcome (PICO)

The eligible population, intervention, comparator and outcomes (PICO) criteria for this HTA are shown in ***Table 2***.

Table 2 PICO criteria

Population(s)	Adult patients (≥18 years of age) with primary OA of the knee or hip *Exclusion criteria: OA in other joints (e.g. shoulder, wrist, neck, spine), secondary OA (e.g. caused by another disease, condition or injury), mixed populations (e.g. knee and hip)*
Intervention(s)	Intra-articular glucocorticoid injections (including triamcinolone, methylprednisolone, betamethasone acetate, betamethasone sodium phosphate, dexamethasone and dexamethasone sodium phosphate)
Comparator(s)	• No treatment • Sham injection (e.g. saline injection) • Oral placebo
Outcome(s)	**Clinical outcomes** • Pain – measured using NRS and VAS etc. • Function – measured using HOOS, KOOS, WOMAC etc. • Health-related quality of life – measured using EQ-5D, SF-12, VR-12 etc. • Joint replacement surgery (i.e. disease progression) • Care utilisation – measured via number of care providers visited within a certain time period (e.g. general practitioner, orthopaedic surgeon, dietician, physiotherapist, rheumatologist) • Treatment satisfaction – measured using the ARTS questionnaire or patient-reported satisfaction with treatment etc. • Adverse events • Serious adverse events **Health economic outcomes** • Direct medical costs of the technology and associated services • Incremental costs • Incremental effectiveness – incremental QALYs or incremental effect expressed using another relevant unit of health outcome • Cost-effectiveness/cost utility – expressed as ICER • Total costs to the Swiss healthcare payer

Abbreviations: **ARTS**: osteoARthritis Treatment Satisfaction; **EQ-5D**: EuroQol 5-dimension health-related quality of life questionnaire; **HOOS**: Hip dysfunction and Osteoarthritis Outcome Score; **ICER**: incremental cost-effectiveness ratio; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **NRS**: numerical rating scale; **NSAIDs**: non-steroidal anti-inflammatory drugs; **OA**: osteoarthritis; **QALY**: quality-adjusted life year; **SF-12**: 12-item short form health survey; **VAS**: visual analogue scale; **VR-12**: Veterans RAND 12-item health survey; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

4.1 Population

There are 2 key populations of interest: adult patients (≥18 years old) diagnosed with primary OA of the knee and adult patients diagnosed with primary OA of the hip, as defined by the ACR clinical classification criteria, KL stage, EULAR or the National Institute for Health and Care Excellence (NICE) criteria. Studies that include patients with secondary OA, or mixed populations (i.e. hip and knee combined) were excluded. The definition of primary OA and secondary OA was taken as defined in the included trials.

4.2 Intervention

The intervention of interest is IAGI. The pharmaceuticals used for IAGI were limited to triamcinolone, methylprednisolone, betamethasone acetate, betamethasone sodium phosphate, dexamethasone and dexamethasone sodium phosphate, as used and listed in Switzerland.[5]

4.3 Comparators

No treatment: No active or passive interventions provided to patients with OA of the knee or hip.

Sham injection: A commonly reported intra-articular (IA) placebo is 1 ml of 0.9% saline solution. Other IA placebos include polysorbate, sorbitol, benzyl alcohol and water.[54]

Oral placebo: An oral placebo usually takes the form of a tablet or pill that resembles the oral analgesics used in the treatment of OA of the hip or knee but is made of an inactive substance such as starch or sugar.[55, 56]

Sham injection and oral placebo can be grouped together and subgroup analysis conducted to investigate the impact of the different comparators on the result.

4.4 Clinical outcomes

The included clinical outcomes are based on recommendations by the International Consortium for Health Outcomes Measurement (ICHOM) working group on hip and knee OA.[57]

Pain: Pain is a common symptom of OA. It is caused by the decreased ability of the cartilage to act as a shock absorber, and by synovitis and bone marrow oedema.[58] OA pain can lead to functional limitation and fatigue, which contributes to depressed mood and worsening pain and function.[59] Pain can be measured using several scales. Where a study reported more than one pain scale, data were extracted preferentially for the first outcome listed according to the following hierarchy, based on Jüni 2015:[34]

1. global pain
2. pain on walking

3. Western Ontario and McMaster Universities Arthritis Index (WOMAC) OA pain subscore
4. composite pain scores other than WOMAC
5. pain on activities other than walking
6. rest pain or pain during the night
7. WOMAC global algofunctional score
8. Lequesne OA index global score
9. other algofunctional scales
10. participant's global assessment
11. physician's global assessment.

Function: Pain and stiffness caused by structural changes within the joint in patients with OA can contribute to limitations in physical function.[60] Assessment of a patient's functional status may give the healthcare provider information on disease progression and severity, allowing the provider to suggest optimal treatment approaches. Functional assessment tools used in patients with OA may include the WOMAC score, and the knee injury (Knee Injury and Osteoarthritis Outcome Score—KOOS) or hip injury (Knee Injury and Osteoarthritis Outcome Score—HOOS) OA outcome score. Where a study reported more than one function scale, data were extracted preferentially for the first outcome listed according to the following hierarchy, based on Jüni 2015:[34]

1. global disability score
2. walking disability
3. WOMAC disability subscore
4. composite disability scores other than WOMAC
5. disability other than walking
6. WOMAC global scale
7. Lequesne OA index global score
8. other algofunctional scale
9. participant's global assessment
10. physician's global assessment.

Health-related quality of life: HRQoL can provide patient-centred information on physical, emotional and mental health to guide clinical practice. The tools used to quantify and gather patient-centred information can be disease-specific or generic. OA-specific instruments may include the OA knee and hip HRQoL questionnaire (OAKHQOL).[61-63] Generic instruments that measure general HRQoL may include the EuroQol 5-dimension questionnaire (EQ-5D) and the 12-item short form health survey (SF-12).[64-66] No limitations were placed on the type of HRQoL tools included. Where a study reported more than one HRQoL measure, data were extracted preferentially for the

first outcome listed according to the following hierarchy, based on relative ease and reliability for calculating quality-adjusted life years (QALYs) for the economic analysis:[67]

1. generic preference-based HRQoL scales (e.g. EQ-5D)
2. generic preference-based health status scales (e.g. SF-12)
3. disease-specific scales (e.g. OAKHQOL) .

Joint replacement surgery: OA is chronic and progressive. A primary marker of disease progression is treatment escalation to joint replacement.

Care utilisation: Healthcare utilisation by patients with OA of the hip and knee can be extensive, which can have a profound impact on healthcare expenditure and allocation of limited government health resources.[68-70] Care utilisation is measured by the number of care providers visited within a certain time period, including inpatient and ambulatory services (e.g. general practitioner, orthopaedic surgeon, dietician, physiotherapist, rheumatologist).[69, 71, 72]

Treatment satisfaction: Treatment satisfaction is defined as the degree to which patients perceive that the treatment fulfils their health needs.[73] Patient satisfaction is an important indicator of the quality of care provided to patients with OA.[74] Patient-reported outcomes such as treatment satisfaction are used to determine patients' experiences of the disease and can provide information to the physician for facilitating patient-centred care.[74] Treatment satisfaction measures include the treatment satisfaction questionnaire version 1.4 (TSQM-1.4) and the OA treatment satisfaction (ARTS) questionnaire.

Adverse event (AE): AEs are defined as temporary, non-life threatening, unintended responses associated with a medical intervention (surgical procedure or pharmaceutical). AEs generally comprise an increase in disease severity and/or the development of new signs or symptoms. Possible AEs associated with IAGI for OA patients include skin atrophy and depigmentation, fat necrosis, nausea, vomiting, sweating, transient headache, and worsening of pain, stiffness and function.[75, 76]

Serious adverse event (SAE): SAEs are negative experiences associated with a medical intervention that may be life-threatening at the time of occurrence. Examples of SAEs associated with OA may include accelerated OA progression; subchondral insufficiency fracture; complications of osteonecrosis; joint infection; joint effusion; and rapid joint destruction with bone loss resulting in hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events or death.[34, 77] Discontinuation or study withdrawal due to an AE will also be considered an SAE.

5 HTA research questions

The following research questions, covering central HTA domains as designated by the EUnetHTA Core Model (clinical effectiveness and safety; costs; cost-effectiveness and budget impact; and ethical, legal, social and organisational [ELSO] aspects), are addressed for the evaluation of the technology:

- Is IAGI efficacious compared to no treatment or placebo (including oral placebo and sham injection) for patients with primary OA of the hip or knee?
- Is IAGI safe compared to no treatment or placebo (including oral placebo and sham injection) for patients with primary OA of the hip and knee?
- What are the costs associated with IAGI compared to no treatment or placebo (including oral placebo and sham injection) for patients with primary OA of the hip or knee?
- Is IAGI cost-effective compared to no treatment or placebo (including oral placebo and sham injection) for patients with primary OA of the hip or knee?
- What is the budget impact of IAGI compared to no treatment or placebo (including oral placebo and sham injection)?
- Are there ELSO issues related to the use of IAGI for patients with OA of the hip or knee?

6 Effectiveness, efficacy and safety

Summary statement efficacy, effectiveness and safety

Sixteen randomised controlled trials (RCTs) comprising 1,522 patients were evaluated for knee OA, and 4 RCTs with 239 patients were included for hip OA.

For **knee OA**, the evidence suggests that IAGI results in little to no difference in pain at 3 months (SMD -0.04, 95% CI: -0.29 to 0.21, low certainty evidence); however, there may be a small reduction in pain in patients receiving IAGI at 1 month (SMD -0.30, 95% CI: -0.52 to -0.08, with substantial heterogeneity, I^2 = 65.25). IAGI may result in little to no difference in function (MD 0.00, 95% CI: -1.08 to 1.09, low certainty evidence), and likely results in little to no difference in HRQoL (MD 1.80, 95% CI: -2.88 to 6.48, moderate certainty evidence) at 3 months, or at any other timepoints. The evidence suggests IAGI probably results in little to no difference in care utilisation at 3 months (MD -0.19, 95% CI -0.59 to 0.21, moderate certainty of evidence); however, IAGI likely reduces care utilisation up to 1 month (MD -0.43, 95% CI -0.81 to -0.05). There is probably no difference in the rate of AEs (moderate certainty evidence), and a high degree of uncertainty in the rate of SAEs (low certainty evidence) for IAGI compared to sham. No studies reported joint replacement surgery or treatment satisfaction.

For **hip OA**, there is no evidence of a difference between IAGI and sham injection in relation to pain at 3 months (SMD -0.28, 95% CI: -0.76 to 0.20, very low certainty evidence), but the evidence is very uncertain; there is a large difference favouring IAGI at 1 month (SMD -1.60, 95% CI -2.70 to -0.51). No other timepoints were reported. Regarding function, 3-month data were not reported. IAGI may improve function at 1 month (SMD -1.74, 95% CI: -3.08 to -0.41, very low certainty evidence), but the evidence is very uncertain. Data at other timepoints were not reported. Regarding HRQoL, 3-month data were not reported. Evidence suggests HRQoL may be improved with IAGI at 1 month (MD 5.29, 95% CI: -0.10 to 10.68, very low certainty evidence). Data at other timepoints were not reported. There was no evidence of a difference for care utilisation (very low certainty evidence), AEs (very low certainty evidence) and SAEs (very low certainty evidence), noting that the incidence of AEs and SAEs was low in both groups. No studies reported joint replacement surgery or treatment satisfaction.

6.1 Methodology: effectiveness, efficacy and safety

The methods for the clinical evaluation in this HTA were developed with reference to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3)[78] and are presented in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[79] Clinical outcomes for hip and knee OA have been analysed separately.

6.1.1 Databases and search strategy

Systematic literature searches were conducted in 4 biomedical databases – Ovid (Embase, Medline), the Cochrane Library and the INAHTA database. Database searches were conducted to 4 October 2023 for the clinical section. Search strings are presented in ***Appendix 13.2***. Search filters to exclude specific publication types (i.e. editorials, letters to the editor, news articles, conference abstracts) were utilised in all searches. Searches were limited to English, French, German and Italian publications. No date limit was applied. The International Clinical Trials Registry Platform (ICTRP) was searched to identify relevant ongoing clinical trials (***Appendix 13.2.1***, ***Table 44***). Grey literature searches were conducted in HTA and specialist websites (***Appendix 13.3***, ***Table 53***).

6.1.2 Study selection

Results from the systematic literature searches were imported into Rayyan (Rayyan Systems Inc, USA) for study selection.[80] Rayyan allows for blinded title and abstract screening of citations between independent reviewers, and resolution of study inclusion conflicts.[80] Screening was performed to include studies meeting the predefined study selection criteria (***Table 3***). Only studies published in World Health Organization (WHO) Mortality Stratum A countries were included.[81] This limitation aimed to ensure that all included studies have a comparable disease burden and cause of death to Switzerland.[81] Exclusion criteria were based on publication type (e.g. case notes, case reports, opinion pieces).

All search results were screened by title and abstract by 2 independent reviewers. At the completion of title and abstract screening, full-text publications were independently reviewed by each reviewer. Conflicts regarding final study inclusion were settled by a third reviewer. The inclusion and exclusion decisions are detailed in a PRISMA flow chart (***Figure 1***).[79]

Various study designs were considered for inclusion. Systematic reviews and meta-analyses meeting the PICO criteria were sought for inclusion preferentially. Where no up-to-date systematic reviews were identified, the reference lists were checked for further studies to identify any unpublished RCTs. RCT evidence was included in the absence of up-to-date systematic reviews

and meta-analyses. Non-randomised studies of interventions were only sought in the absence of existing RCTs.

Table 3 Study selection criteria

	Inclusion criteria	Exclusion criteria
Population(s)	Adult patients (≥18 years of age) with primary OA of the knee or hip	Secondary OA, post-traumatic OA, combined populations (e.g. hip and knee OA)
Intervention(s)	Intra-articular glucocorticoid injections (i.e. triamcinolone, methylprednisolone, betamethasone acetate, betamethasone sodium phosphate, dexamethasone and dexamethasone sodium phosphate)	Delayed-release formulations
Comparator(s)	• No treatment • Sham injection (e.g. saline injection) • Oral placebo	
Outcome(s)	**Clinical outcomes** • Function – measured using HOOS, KOOS, WOMAC etc. • Pain – measured using NRS and VAS etc. • HRQoL – measured using EQ-5D, SF-12, VR-12 etc. • Joint replacement surgery (i.e. disease progression). • Care utilisation – measured by number of care providers visited within a certain time period (e.g. general practitioner, orthopaedic surgeon, dietician, physiotherapist, rheumatologist) • Treatment satisfaction – measured using ARTS questionnaire or patient-reported satisfaction with treatment etc. • AE • SAE	Inadequate data (e.g. incongruous data reported between figures and text), incomplete reporting, unclear follow-up duration
Design / publication type	**Clinical evidence** • Systematic reviews of RCTs • Primary RCTs, in the absence of up-to-date SRs of RCTs • Non-randomised studies of interventions, in the absence of RCT data	• Single-arm studies • Case reports • Conference abstracts • Letters to the editor • Expert opinions • Editorials • Narrative review articles • Cost-benefit analyses
Language	English, German, Italian, French	All other languages
Country	WHO Mortality Stratum A countries*	non-WHO Mortality Stratum A countries

Abbreviations: **AE**: adverse event; **ARTS**: osteoARthritis Treatment Satisfaction;**EQ-5D**: EuroQol 5-dimension health-related quality of life questionnaire; **HOOS**: Hip dysfunction and Osteoarthritis Outcome Score; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **NRS**: numeric rating scale; **NSAIDs**: non-steroidal anti-inflammatory drugs; **OA**: osteoarthritis; **RCT**: randomised controlled trial; **SAE**: serious adverse event; **SF-12**: 12-Item Short Form Health Survey; **VAS**: visual analogue scale; **VR-12**: Veterans RAND 12 Item Health Survey; **WHO**: World Health Organization; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.
Notes: *WHO Mortality Stratum A countries include Andorra, Australia, Belgium, Brunei, Canada, Croatia, Cuba, Cyprus, Czech Republic [Czechia], Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, the Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, UK and USA.

6.1.3 Assessment of quality of evidence

Different appraisal criteria were used to assess the risk of bias (RoB) of the included evidence base. Critical appraisal was performed independently by 2 reviewers. Any differences between reviewers were settled via consensus and if consensus could not be reached, a third reviewer was consulted. RoB tools used to appraise the included studies depended on the study design. RCTs were evaluated with the Cochrane RoB 2.0 tool.[82]

The overall quality of the evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The 5 domains of the GRADE framework (imprecision, inconsistency, indirectness, RoB, publication bias) were scored (high, moderate, low, very low) according to a decision algorithm developed by Pollock et al.[83] The certainty of evidence supporting an outcome, according to the GRADE approach, is defined as follows:[84]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The GRADEpro guideline development tool was used to construct the summary of findings tables, which feature 6 of the included outcomes (i.e. pain, function, HRQoL, care utilisation, AEs, SAEs).

6.1.4 Data extraction

Data were extracted (at study-arm level) from included publications by a single reviewer using a standardised template adapted according to the design of the included studies. Data checking was performed against the original publication by a second reviewer. Any conflicts were resolved by consensus. If consensus could not be reached, a third independent reviewer was consulted.

Data selected for extraction included:

- **study information:** author, country, publication date, randomisation technique (RCT only), study identifier, enrolment dates, setting (e.g. primary care, secondary care or tertiary hospital), number of centres, study design, follow-up duration, funding source, inclusion and exclusion criteria.

- **demographic information:** number of participants, age, sex, BMI, definition of disease, living arrangement (i.e. partner, family, friends, alone, nursing home), smoking status, comorbidities (i.e. diabetes mellitus type 1 or 2, heart disease, kidney disease, other forms of arthritis, neurological condition, depression, spinal disease, lung disease, hypertension, cancer), severity of OA (as defined by the trial), previous surgery on the afflicted joint (e.g. arthroscopy, meniscectomy), percentage of patients with joint effusion and whether the effusion was removed prior to IAGI, diagnostic criteria (e.g. MRI, X-ray).
- **intervention and comparator:** IAGI details such as dose, frequency of administration, type of steroid administered (i.e. triamcinolone, prednisolone, hydrocortisone, dexamethasone, methylprednisolone, betamethasone, cortisone), IAGI co-administration with local anaesthetic, ultrasound-guidance or landmark guidance, placebo frequency and type (e.g. saline injection, oral formulation), no treatment.
- **outcomes of interest:** number of events per patient and baseline, final or change-from-baseline scores with standard deviation (SD) for any outcome of interest, information on continuous outcome measures used in the included studies (scale and direction of effect) and corresponding timepoints (up to 1 month, 3 months, 6 months, 12 months); AEs, SAEs (per the examples in ***Section 4.4*** or as defined by the RCT authors) and joint replacement surgery information up to the longest reported follow-up timepoint (i.e. can be longer than 12 months).
- **additional noteworthy factors:** limitations or key differences of the study.

6.1.5 Data analysis of efficacy, effectiveness and safety outcomes

6.1.5.1 Meta-analysis of dichotomous outcomes

Dichotomous outcomes were analysed in R Studio statistical software using the meta package.[85] For the dichotomous outcomes of AEs, SAEs and joint replacement surgery, the primary endpoint was longest follow-up. Pairwise meta-analysis was performed for dichotomous data using a random-effects model, where there were sufficient data from the primary studies.[85-88] The inverse-variance method was used to estimate primary study weights.[78] The Mantel–Haenszel (MH) method was used to estimate primary study weights when data were sparse, such as when event rates were low or study sizes were small.[78] Results were reported as risk ratios (RR) with 95% confidence intervals (CI). RR>1 indicated an increased probability of the event occurring in the intervention group relative to the comparator group; RR<1 indicated a reduced probability of the event occurring in the intervention group relative to the comparator group.

Results were described narratively for outcomes reported by a single study or where it was inappropriate to pool trials.

6.1.5.2 Meta-analysis of continuous outcomes

For the continuous outcomes of pain, function, HRQoL, care utilisation and treatment satisfaction, the primary endpoint was analysed at 3 months. The choice of 3 months as the primary timepoint was based on the treatment goals of IAGI in relieving pain and improving function for a chronic disease. Secondary timepoints of up to 1 month, 6 months and 12 months were also assessed. It is worth highlighting that while the 3-month data provide information for efficacy in line with the treatment goals of IAGI, other timepoints provide useful information on the durability of the treatment effect and should not be considered as less clinically relevant than the primary endpoint.

Mixed-effect meta-regression models, incorporating follow-up time as a covariate factor, were used to analyse the continuous outcomes. The mixed-effect model estimated treatment effects for the intervention (IAGI) and comparator (no treatment or placebo) while considering the potential heterogeneity across studies and the variation across different timepoints. The meta-analysis was conducted in R Studio utilising the metafor package with 2-stage analysis multivariate function for longitudinal data (rma.rv).[89] The longitudinal meta-analysis (LMA) takes a first-order heterogeneous autoregressive covariance structure (HAR_1) to account for the within-study longitudinal effect. Within-study covariance was calculated for each study using a method adapted from Horváth (2009).[90] A point estimate (MD and/or SMD) with the corresponding 95% CI was generated for the selected timepoints for each outcome of interest. For SMDs, a difference of 0.2 SD units is considered to be a small clinical effect, 0.5 moderate and 0.8 a large clinical effect.[78, 91]

Various random effects were tested and compared using both HAR_1 and unstructured variance–covariance structure, where model-fitting criteria were used to select the best model. Outcomes reported with multiple measurement scales (e.g. pain, function) were evaluated using SMDs. Each study was included in the analysis once per outcome. Where a study reported multiple scales for the same outcome, scales were selected preferentially based on the hierarchy described in ***Section 4.4***. Continuous outcomes with fewer than 2 studies for any of the timepoints could not be evaluated using LMA. For these outcomes, timepoints with more than 2 studies were meta-analysed individually using pairwise random-effects models, with the primary study weights estimated using the inverse variance method.

6.1.5.3 Assessment of heterogeneity

Heterogeneity of continuous and dichotomous outcomes was assessed statistically using τ^2 and I^2. τ^2 was calculated to quantify the extent of heterogeneity among included studies. I^2 was used to assess the percentage of variability across studies that is due to heterogeneity rather than chance. The significance of I^2 depended on the strength of the evidence for heterogeneity (i.e. τ^2) and the direction and size of the measured effect. These measures are applicable to both univariate meta-analyses and more complex analyses involving mixed-effects models. Specifically, when incorporating timepoint as a covariate, the meta-analysis model accounted for the correlation between timepoints at the individual study level, and then considered their variation from different timepoints and across different studies to derive total heterogeneity. The level of heterogeneity was

interpreted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 6.1). An I^2 of 0–40% is low heterogeneity (i.e. may not be important), 30–60% is moderate, 50–90% is substantial and 75–100% is considerable heterogeneity.[78]

6.1.5.4 Imputation methods for dealing with missing values

Missing values were obtained using formulae detailed in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3).[78] In situations where limited data were available and SD could not be imputed using the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3),[78] it was imputed using the imputation methods described by Braken 1992 in the *R* Studio package 'metagear'.[92, 93]

For studies reporting outcomes graphically, WebPlotDigitizer was used to convert graph points to numerical values.[94]

6.1.5.5 Assessment of small-trial effects

The influence of small-trial effects and their potential association with publication bias could not be evaluated using the method prespecified in the protocol (i.e. Egger's funnel plot analysis) owing to insufficient data. Sensitivity analyses demonstrating the impact of sample size on effect estimates were conducted (see ***Section 6.1.5.6***).

6.1.5.6 Subgroup and sensitivity analyses

In addition to the main analyses, possible effect modifiers were investigated. Subgroup analyses were used to explore subsets of participants or study characteristics. Sensitivity analyses were used to investigate the impact that uncertainty and decisions made during development of the review method had on the effect size of each outcome.

Subgroup and sensitivity analyses were only conducted at the 3-month timepoint (primary endpoint) for clinical outcomes and at the longest follow-up for safety outcomes. Both the subgroup and sensitivity analyses were all pairwise meta-analyses conducted in *R Studio* using the meta package.

Subgroup analyses were conducted using fixed-effects (plural) models. The data included within each subgroup were pooled using random-effects models. The subgroups did not use a common τ^2. Q-tests were performed to determine if differences between subgroups were statistically significant ($p \leq 0.05$).

Sensitivity analyses were conducted using random-effects models. The groups within each discrete analysis did not use a common τ^2. Q-tests were not performed to determine any statistically significant differences between groups within a discrete analysis. Possible sources of uncertainty affecting the results included presence of substantial RoB in the forest plots and imputing SD.[78]

Subgroup analyses were conducted to investigate the impact of patient and intervention characteristics on the results of the meta-analyses as follows:

- comorbidities (diabetes mellitus type 1 or 2, heart disease, kidney disease, other forms of arthritis, neurological condition, depression, spinal disease, lung disease, hypertension, cancer, obesity)
- joint-specific surgical history (previous surgery on affected joint) versus no surgical history
- glucocorticoids administered with local anaesthetic versus no local anaesthetic
- oral placebo versus sham injection
- ultrasound-guided versus landmark-guided IAGI
- severe versus non-severe OA (as defined by the included studies)
- presence of effusion or not
- removal of joint fluid before treatment or not.

Sensitivity analyses were conducted to assess the impact of key assumptions or variations of methodological factors on the clinical results as follows:[34]

- trial size ≥100 per group versus <100 per group
- imputed data (e.g. imputed SDs) versus no imputed data
- high RoB due to missing outcomes versus low RoB due to missing outcomes
- high RoB due to selection bias versus low RoB due to selection bias
- funding (industry versus non industry).

6.1.6 Deviations from the protocol

- Systematic reviews were not included in the clinical evaluation. During the HTA phase it was agreed with FOPH to conduct a de novo clinical evaluation, rather than re-use and/or update existing reviews. This decision was largely informed by the proposed methodology for this HTA (i.e. LMA) and the choice of comparators in the existing reviews. The methodology differed from existing systematic reviews, which conducted independent pairwise analyses at selected timepoints and selected different comparators.
- The GRADE evaluation and subgroup and sensitivity analyses were conducted only at the primary timepoint of 3 months, where data were available. Some outcomes are reported at 1-month in the GRADE tables due to an absence of 3-month data. It was not clearly stated in the protocol that these analyses would be conducted for the primary timepoint only.
- Delayed release IAGI formulations were excluded from the HTA, as these are not used in the Swiss setting. This was not specified in the protocol.

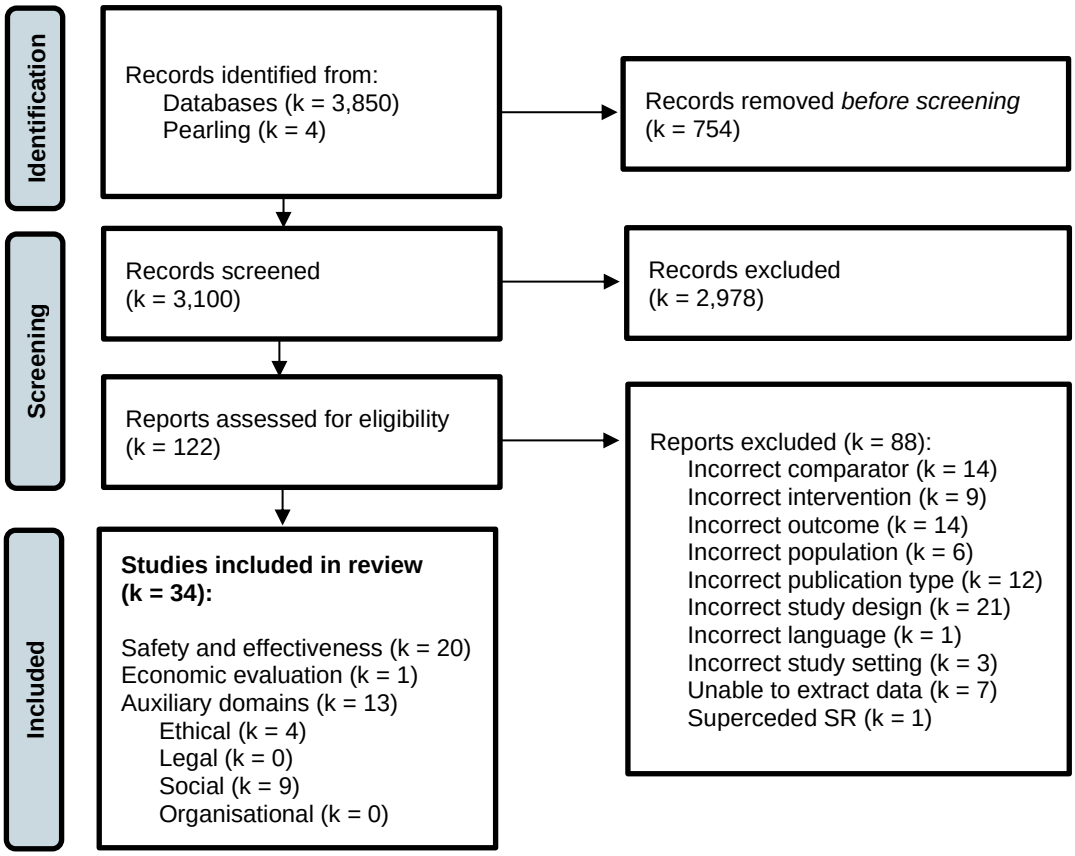
- An additional sensitivity analysis excluding outliers was added. In view of conflicting results from the Swiss study by Tschopp 2023, this was added primarily to determine how robust the results of the meta-analyses were to the presence of outliers.[95]
- When there were insufficient data to conduct an LMA, continuous outcomes were analysed using a pairwise meta-analysis. The analyses were conducted using the meta package in R Studio.[101-103] Outcomes reported with multiple measurement scales (e.g. pain, function) were evaluated using SMDs. Outcomes reported on corresponding measurement scales (e.g. HRQoL) were evaluated using MDs. The meta-analyses were performed using random-effects models, with the inverse-variance method used to estimate between-study variance.
- Small-trial effects were not evaluated due to inadequate data.
- *A priori* subgroup analyses were not conducted on joint-specific surgical history or oral placebo versus sham injection, due to insufficient data.
- *A priori* subgroup analyses were not conducted on the presence of comorbidities or the severity of OA, due to inconsistencies in outcome reporting between included trials.

6.2 Results: effectiveness, efficacy and safety

6.2.1 PRISMA flow diagram

Results of the systematic literature searches are summarised in ***Figure 1***.[96]

Figure 1 PRISMA flowchart for study inclusion



Abbreviations: k: number of publications; **RCT**: randomised controlled trial; **SR**: systematic review.

The systematic review searches retrieved 3,854 records, including 4 via pearling. After removal of duplicates, 3,100 articles were screened by title and abstract, from which 122 were screened by full text and 34 met the inclusion criteria. The included studies comprised 20 RCTs (16 RCTs for knee, 4 for hip), 1 economic evaluation and 13 studies relevant to the ELSO domains. A list of all articles excluded after full-text review is presented in ***Appendix 13.4***.

6.2.2 Characteristics of included studies

6.2.2.1 Knee OA

Sixteen RCTs were included for knee OA, of which 7[95, 97-102] assessed safety and 15[95, 97-99, 101-111] assessed clinical effectiveness (***Table 4***). The included RCTs consisted of single-centre (k = 9), multicentre (k = 4) or unreported (n = 3) studies conducted in Europe (k = 9), Australia (k = 1), Canada (k = 1) or USA (k = 5). Studies were performed from 1980 to 2023. One study fully

conducted in Switzerland was included in the analysis.[95] This study compared the effectiveness of IAGI, hyaluronic acid, platelet rich plasma or placebo on pain among patients with early- to middle-stage knee OA. A major limitation of this study is the small sample size (n = 30 knees per group), which are less accurate than large studies and potentially reported larger effect sizes and wider confident intervals.

Patients were mostly recruited from the outpatient, rheumatology or musculoskeletal units of hospitals. To be eligible for inclusion they must have met the ACR criteria for knee OA based on medical history, physical examination and radiologic, clinical or laboratory findings. Patients with a diagnosis of secondary OA, local or systemic contraindication to the use of intra-articular glucocorticoids, concomitant medical conditions such as generalised pain and local nerve root compression syndromes, gastrointestinal ulcerations and venous thrombosis were excluded. IAGI during the 3 months prior to the study was also grounds for exclusion.

Five studies had a minimum age requirement of 40 years or older.[99, 102, 103, 106, 110] The other studies included patients of age 18 or older. Study sizes ranged from 16 to 486 patients. Patients were predominantly female (2.5–78%) with a mean age range of 55.5 to 70.6 years. The KL grades of patients with knee OA differed across the included studies. Mean duration of OA symptoms experienced by patients ranged from 6 to 104 months. Generally, there were no significant differences in baseline demographics between patients receiving IAGI or sham injection/placebo (***Table 4*** and ***Table 5***).

The most common IAGI agents in the studies were methylprednisolone/methyldprednisolone acetate (k = 7), triamcinolone/triamcinolone acetonide/triamcinolone hexacetonide (k = 6) and cortivazol (k = 1). Common dosage for methylprednisolone acetate was 1 ml of suspension containing 40 mg of methylprednisolone acetate (1 ml/40 mg). Common dosage for triamcinolone was 1 ml/20 mg or 1 ml/40 mg. Sham injections used normal saline (1 ml or 1.5 ml dose), the most common comparator being 1 ml of 0.9% saline. Other comparators were lignocaine, polysorbate, sorbitol solution, benzyl alcohol water and lavage (3 L of cold water).

The most commonly reported outcome for clinical efficacy was pain at 1 month, as measured by visual analogue scale (VAS) (0–20; 0–100) and WOMAC (***Figure 2***). AEs and SAEs were not commonly reported in the included studies.

6.2.2.2 Hip OA

Four studies assessed safety and clinical efficacy in hip OA (***Table 5***).[112-115] The included RCTs consisted of single-centre (k = 3) and multicentre studies (k = 1) conducted in Europe (k = 3) and Canada (k = 1). No study was fully conducted in Switzerland.

Patients were recruited from primary- and secondary-care centres and hospitals. To be eligible for inclusion, patients were required to have a diagnosis of primary hip OA based on ACR criteria or radiological evidence of OA. Minimum pain duration varied across the included trials, ranging from

1 to 6 months. Other reasons for exclusion included presence of comorbid conditions resulting in gross lower limb asymmetry, hip osteonecrosis, presence of local or systemic infection precluding injection, systemic arthritis, inflammatory or neurological disease, allergic reaction to the anaesthetic agent or contact material, and previous intra-articular injection to the index hip.

Sample sizes of the included studies ranged from 52 to 80 patients. Patients were mostly ≥18 years (mean age range 56.9–72.4 years) and female (56–66.2%), with KL and baseline pain scores suggesting moderately painful OA. The duration of illness, prior to enrolment, ranged from approximately 19 to 51 months. Generally, baseline characteristics were similar between patients in the IAGI or sham treatment/placebo groups, suggesting that randomisation was successful.

Methylprednisolone and triamcinolone were the commonly used glucocorticoids administered in the hip OA studies. Common dosages among the included studies were 3 ml/120 mg or 1 ml/40 mg for methylprednisolone acetate, 80 mg for triamcinolone acetonide, or 40 mg triamcinolone hexacetonide with 10 mg bupivacaine. Sham injections used normal saline (1 ml or 2 ml dose). Two studies used saline water with local anaesthetics,[114, 115] while one study used only local anaesthetic (mepivacaine).[113]

The most commonly reported outcome for clinical efficacy was pain at 1 month as measured by VAS (0–20; 0–100) and WOMAC. The most frequently reported safety outcome was withdrawal due to AE or SAE (k = 3) or poor treatment tolerance by patients. Most of the AEs were mild and unrelated to the study intervention.

Table 4 Characteristics of included studies for knee OA

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Baker 2023[103] USA	RCT Double blinded Single-centre	1 month 3 months Single injection	IAGI: 35.5 (6.1) Saline: 31.9 (5.2) IAGI: 55.5 (16.9) Saline: 63.5 (1.9) Overall: 3/31(10%) IAGI: 2 (13%) Saline: 1 (6%)	KL IAGI 1: 0 (0%) 2: 5 (33%) 3: 5 (33%) 4: 5 (33%) Saline 1: 1 (6%) 2: 2 (12%) 3: 3 (19%) 4: 10 (63%)	methylprednisolone acetate 1 ml (40 mg) plus 2 ml lidocaine (1%) (n = 15)	1 ml saline and 2 ml lidocaine (n = 16)	Pain	Government Veterans Affairs Clinical Science Research & Development Career Merit Award (I01 CX001703) a Rehabilitation Research & Development Merit Award (I01 CX003644) and SPiRE Award (I21 RX003157)

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Chao 2010[104] USA	RCT Double blinded Multicentre	1 month 3 months Single injection	NR Overall: 64.3 (11.9) IAGI: 65.3 (11.6) Placebo: 63.2 (12.4) Overall: 2/79 (2.5%) IAGI: 0/34 (0%) Placebo: 2/33 (6%)	NR	Methyprednisolone acetate 1 ml (40 g) plus 2 ml lidocaine (1%) (n = 40)	1 ml 0.9% saline (n = 39)	Pain	Industry Flexion Therapeutics Inc
Conaghan 2018[97] USA	RCT Double blinded Multicentre	3 months 6 months Single injection	IAGI: 30.3 (4.82) Saline: 30.2 (4.69); IAGI: 62.3 (10.08) Saline: 62.4 (8.89); IAGI: 97/161 (60.2%) Saline: 96/162 (59.3%)	KL IAGI 2: 69 (42.9%) 3: 91 (56.5%) 4: 1 (0.6%) Saline 2: 69 (42.6%) 3: 93 (57.4%) 4: 0	Triamcinolone acetonide 40 mg (1 ml) (n = 161)	Saline-solution placebo (5 ml) (n = 162)	Pain Function HRQoL	Flexion Therapeutics Inc

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Dieppe 1980[105] UK	RCT Single blinded NR	1 month Single injection	NR 65 (8.1) NR	NR	20 mg triamcinalone hexacetonide (1 ml), single intra-articular injection (n = 12)	1 ml saline (n = 12)	Pain	Arthritis and Rheumatism Council
Frias 2004[98] Spain	RCT Double blinded Single-centre	1 month 3 months Single injection	NR: Overall: 67 (8) range: 44–85 Overall: 234/299 (78%)	KL Overall: 2: 141 (47) 3: 158 (53)	40 mg triamcinolone acetonide plus lavage (3 L cold [8°C] saline) (n = 237)	Lavage (3 L cold [8°C] saline) (n = 62)	Pain	NR
Friedman 1980[106] USA	RCT Double blinded Single-centre	1 month 2 months Single injection	NR median (range) Placebo:62 (42–77) IAGI: 58 (42 to 75) NR	NR	20 mg triamcinolone hexacetonide (n = 17)	Polysorbate, sorbitol solution, benzyl alcohol and water (n = 17)	Pain	NR

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Gaffney 1995[107] UK	RCT Double blinded Single-centre	1 month Single injection	NR Overall: 67 IAGI: 66 (9.7) Placebo: 68 (8.6) Overall: 60/84 (71%) IAGI: 33 (79%) Placebo: 27 (64%)	NR	20 mg triamcinolone hexacetonide (1 ml) (n = 42)	1 ml 0.9% normal saline (n = 42)	Pain	NR

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Henriksen 2015[99] Denmark	RCT Triple blinded Multicentre	1 month 3 months 6 months Single injection	Overall: 28.9 (3.6) IAGI: 29.0 (3.9) Placebo: 28.9 (3.3) Overall: 63.4 (9.3) IAGI: 61.3 (9.9) Placebo: 65.5 (8.3) Overall: 61/100 (61%) IAGI: 28/50 (56) Placebo: 33/50 (66)	KL Overall: 1: 4 (4) 2: 39 (39) 3: 32 (32) 4: 25 (25) Methylprednisolone acetate: 1: 4 (8) 2: 21 (42) 3: 15 (30) 4: 10 (20) Placebo: 1: 0 2: 18 (36) 3: 17 (34) 4: 15 (30)	40 mg methylprednisolone acetate (1 ml) dissolved in 4 ml of lidocaine hydrochloride (n = 50)	1 ml isotonic saline mixed with 4 ml lidocaine hydrochloride (n = 50)	Pain Function HRQoL	Supported by grant 10-093704 from the Danish Council for Independent Research, Medical Science and by the Oak Foundation, Association of Danish Physiotherapists, Lundbeck Foundation, and Capital Region of Denmark.

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Jones 1996[108] UK	RCT Double blinded Single-centre	1 month 2 months Single injection	NR Overall: 70.6 Overall: 37/59 (63%)	NR	40 mg methyl prednisolone acetate (1 ml) (n = 30)	1 ml 0.9% saline (n = 30)	Pain	NR
Lyons 2005[109] UK	RCT Single blinded NR	1 month 2 months Single injection	NR NR 11/20 (55)	NR	methylprednisolone 80mg (2 ml) and lignocaine 1% (8 ml) (n = 10)	10 ml 1% lignocaine (n = 10)	Pain AE SAE	NR
McAlindon 2017[100] USA	RCT Double blinded Multicentre	24 months Multiple injection (every 12 weeks for 2 years)	IAGI: 30.8 (5.1) Saline: 31.7 (6.6); IAGI: 59.1 (8.3) Saline: 57.2 (7.6) IAGI: 37 (52.9) Saline: 38 (54.3)	KL Triamcinolone: 2: 29 (41.4) 3: 41 (58.6) Saline: 2: 29 (41.4 3: 41 (58.6)	40 mg triamcinolone acetonide (n = 70)	1 ml 0.9% sodium chloride (n = 70)	Pain AE	R01 AR051361 from the National Institute for Arthritis and Musculoskeletal Disorders and Skin Diseases (NIAMS) and UL1TR001064 from the National Center for Advancing Translational Sciences, National Institutes of Health.

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Nielsen 2018[110] Denmark	RCT Double blinded Single-centre	3 months 6 months Single injection	Overall: 29.1 (3.7) Placebo: 29.0 (3.4) IAGI: 29.2 (4.1) Overall: 63.8 (9.0) Placebo: 65.4 (8.3) IAGI: 62.1 (9.4) Overall: 52 (60.5%) Placebo: 30 (66.7%) IAGI: 22 (53.7%)	NR	1 ml methylprednisolone (40 mg/ml) dissolved in 4 ml lidocaine (10 mg/ml) (n = 41)	Placebo and exercise (n = 45)	Pain Function HRQoL	Danish Council for Independent Research (10-093704), Oak Foundation, Lundbeck Foundation, the Capital Region of Denmark
Ravaud 1999[101] France	RCT Double blinded Single-centre	1 month 3 months 6 months Single injection	NR Overall: 65.4 Placebo: 63 (11) IAGI: 67 (12) Overall: 66/98 (67) Placebo: 18/28 (64) IAGI: 18/25(72)	Placebo: 2: 7 (25) 3: 11(39) 4: 10 (36) Cortivazol 2: 8 (32) 3: 10 (40) 4: 7 (28)	3.75 mg cortivazol in 1.5 ml (single injection) (n = 25)	1.5 ml 0.9% normal saline (n = 28)	Pain Function	NR

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Raynauld 2003[102] Canada	RCT Double blinded Single-centre	12 months 24 months Multiple injection (8 injections at 3-month intervals over 21 months	NR Saline: 63.3 (9.0) IAGI: 63.1 (9.1) Overall: 42/68 (68%) Saline:(61) IAGI: (74)	KL Placebo: 2: (67.6) 3: (31.2) IAGI 2: (64.3) 3: (35.3)	40 mg triamcinolone acetonide (1 ml) (n = 33)	1 ml saline (n = 33)	Pain Function AE	NR
Smith 2003[111] Australia	RCT Double blinded NR	1 month 3 months 6 months Single injection	Placebo: 29.8 (5.1) IAGI: 29.3 (4.5) Placebo: 66.3 (11.8) IAGI: 67.3 (9.7) Overall : 27/44 (61.3%) Placebo: 15/18 (83) IAGI: 12/26 (46)	NR	120 mg methylprednisolone acetate following joint lavage (n = 38)	Placebo saline solution (n = 33)	Pain Function AE	National Health and Medical Research Council (Australia) and the Arthritis Foundation of Australia

Author, year; country	Study design; blinding; centres	Follow-up Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention(s) (sample size)	Comparator(s) (sample size)	Outcome(s) (relevant to this HTA)	Funding
Tschopp 2023[95] Switzerland	RCT Double blinded Single-centre	3 months 6 months 12 months Single injection	median BMI (IQR) 25.70 (23.10, 29.80) median age (IQR) 60.00 (54.00, 68.00) Overall: 26 (43.2)	KL Overall: 1: 30 (31.6) 2: 23 (24.2) 3: 42 (44.2) Comparator 1: 8 (32.0) 2: 8 (32.0) 3: 9 (36.0) Intervention: 1: 4 (16.0) 2: 6 (24.0) 3: 15 (60.0)	Single-dose fluoroscopy-guided intra-articular injection under sterile conditions: 1 ml of contrast agent (iopamidol) followed by 1 ml of glucocorticoid (triamcinolone) (n = 30)	1 ml contrast agent only (n = 30)	Pain – NRS, WOMAC Stiffness and Physical function – WOMAC Level of activity – Tegner activity scale AE	Foundation for Research in Rheumatology (Stiftung für Rheumaforschung), Zurich, Switzerland and the Marie-Lou Ringgenberg Foundation, Bern, Switzerland.

Abbreviations: **AE**: adverse event; **BMI**: body mass index; **HRQoL**: health related quality of life; **IAGI**: intra-articular glucocorticoid injection; **IQR**: inter-quartile range; **KL**: Kellgren–Lawrence; **NR**: not reported; **NRS**: numerical rating scale; **RCT**: randomised controlled trial; **SAE**: serious adverse event; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Table 5 Characteristics of included studies for hip OA

Author, year; country	Study design; blinding; centres;	Follow-up; Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention (sample size)	Comparator (sample size)	Outcome	Funding
Atchia 2011[112] UK	RCT Single blind Multicentre	1 month 3 months Single injection	Overall: 29.0 (5.7) Saline: 29.6 (6.5) Standard care/No injection: 28.2 (4.8) IAGI: 27.4 (3.4) Overall: 69 (8) Saline: 70 (10) Standard care/no injection: 68 (7) IAGI: 67 (7) 43/77 (56%) IAGI: 8 Saline: 12 Standard care/no injection: 11	Radiographic grading of severity (Croft) Methylprednisolone acetate 1 or 2: 3 (16) 3 or 4:16 (84) Saline 1 or 2: 3 (16) 3 or 4: 16 (84) Standard care: 1 or 2: 4 (20) 3 or 4: 16 (80)	Methylprednisolone acetate (depomedrone, 3 ml/120 mg) (n = 19)	Normal saline (3 ml) (n = 19) Standard care/no injection (n = 20)	Pain Function AE	Primary author's fellowship funded by Northumbria Healthcare National Health Service Foundation Trust and supported by the UK National Institute for Health and Care Research Biomedical Research Centre for ageing and age-related disease award to the Newcastle upon Tyne Hospitals National Health Service Foundation Trust. Durolane for injection supplied by Q-Med.
Kullenberg 2004[113] UK	RCT Double blinded	1 month 3 months	NR IAGI: 67.3 ± 7.7	NR	80 mg triamcinolone acetonide (n = 40)	anaesthetic (1% mepivacaine) (n = 40)	Pain	NR

Author, year; country	Study design; blinding; centres;	Follow-up; Number of injections	Mean BMI (SD) in kg/m² Mean age in years (SD) % female patients	Disease grade n (%)	Intervention (sample size)	Comparator (sample size)	Outcome	Funding
	Single-centre	Single injection	Local analgesic: 72.7 ± 6.4 NR					
Lambert 2007[114] Canada	RCT Double blinded Single-centre	1 month 2 months Single injection	NR IAGI: 65.6 ± 11 Placebo: 56.9 ± 11 IAGI: 21/31 Placebo: 10/21	KL Triamcinolone hexacetonide 1: 3 (10) 2: 9 (29) 3: 14 (45) 4: 5 (16) Placebo 1: 1 (5) 2: 5 (24) 3: 12 (57) 4: 3 (14)	40 mg triamcinolone haxacetonide + 10 mg bupivacaine (n = 31)	2 ml saline with 10 mg bipuvicaine (n = 21)	Pain Function HRQoL Care utilisation AE	NR
Qvistgaard 2006[115] Denmark	RCT Double blinded Single-centre	1 month 3 months Multiple injection (3	NR IAGI: 69 ± 9(9/23) Saline: 64 ± 11(14/22)	KL Methylprednisolone: 1 to 2: 23 (58) 3 to 4: 17 (42)	1 ml/40 mg methylprednisolone (Depo-medrol) (n = 36)	2 ml saline water with 1 ml of 1% lidocaine (n = 32)	Pain	NR

Author, year; country	Study design; blinding; centres;	Follow-up; Number of injections	Mean BMI (SD) in kg/m^2 Mean age in years (SD) % female patients	Disease grade n (%)	Intervention (sample size)	Comparator (sample size)	Outcome	Funding
		injections at 14-day intervals)	IAGI: 23/32 Saline: 22/36	Saline 1 to 2: 13 (46) 3 to 4: 15 (54)				

Abbreviations: AE: adverse event; **BMI**: body mass index; **HRQoL**: health-related quality of life; **IAGI**: intra-articular glucocorticoid injection; **KL**: Kellgren–Lawrence; **NR**: not reported; **RCT**: randomised controlled trial; **SAE**: serious adverse event; **SD**: standard deviation.

6.2.3 Quality assessment of included studies

The quality of RCTs was evaluated using the Cochrane RoB 2.0 tool[82] for all clinical efficacy outcomes (3-month data or 1-month data in the absence of 3-month data) and safety outcomes (all timepoints). A visual summary of RoB for combined outcomes is displayed in ***Table 6.*** Fourteen RCTs were included in the RoB assessment, all of which reported randomisation methods. All studies aimed to blind participants to the type of injection to minimise performance and detection bias. Three RCTs provided no details regarding how the participants were analysed (domain 2) during follow-up to estimate treatment effects.[95, 98, 104]

Participants were adequately followed-up in 12 RCTs. Two other RCTs had considerable missing participant data, potentially introducing attrition bias.[104, 113] The measurement of outcomes was assessed as low risk across all studies as standardised and validated measurement tools were consistently used. Outcome reporting was considered adequate in 5 RCTs. The remaining studies lacked sufficient information to determine the presence of reporting bias and these were categorised as some concern. In summary, the overall assessment of RoB was low risk in 5 RCTs, some concerns in 7 RCTs, and high RoB in 2 RCTs primarily due to study attrition.

Table 6 Risk of bias summary for clinical outcomes in the RCTs

Study	Outcome	D1	D2	D3	D4	D5	Overall
Knee OA							
Baker 2023	Pain, Function, HRQoL (KOOS)	+	+	+	+	+	+
Chao 2010	Pain (WOMAC)	+	-	X	+	-	X
Conaghan 2018	Pain, Function (WOMAC), HRQoL (KOOS), Utilisation (RES Med)	+	+	+	+	+	+
Frias 2004	Pain (VAS)	+	-	+	+	-	-
Henriksen 2015	Pain, Function, HRQoL (KOOS), AE	+	+	+	+	+	+
McAlindon 2017	AE	+	+	+	+	+	+
Nielsen 2018	Pain, Function, HRQoL (KOOS)	+	+	+	+	+	+
Ravaud 1999	Pain (VAS), Function (Lequesne)	+	+	+	+	-	-
Smith 2003	Pain (WOMAC), Function (Lequesne)	+	+	+	+	-	-
Tschopp 2023	Pain (WOMAC)	+	-	+	+	-	-
Hip OA							
Atchia 2010	AE, SAE	+	+	+	+	-	-
Qvistgaard 2006	Pain (VAS)	+	+	+	+	-	-
Kullenberg 2004	Pain (VAS), Function (Katz)	+	+	X	+	-	X
Lambert 2007	SAE	+	+	+	+	-	-

Abbreviations: **AE**: Adverse event; **HRQoL**: Health-related Quality of Life; **Katz**: Katz Index of Independence in Activities of Daily Living; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **Lequesne**: Lequesne index for knee osteoarthritis; **OA**: osteoarthritis; **RESMed**:

rescue medication; **SAE**: Serious adverse events; **VAS**: Visual Analogue Scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Risk of bias domains:

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

 High risk  Some concern  Low risk

6.2.4 Applicability of included studies to Switzerland

Applicability refers to the generalisability of the included studies to the Swiss context. This involves comparing demographics and clinical characteristics of the included studies to what generally occurs in Swiss practice. Published literature reporting the demographic characteristics of Swiss patients with knee or hip OA who are eligible for IAGI is limited; however, the demographic variables shown in ***Table 7*** are broadly consistent with the PICO criteria for this HTA report.

Table 7 Summary table characterising the Swiss context for the treatment of knee and hip OA

Parameter	Swiss population characteristics	Applicability concern (Yes/No)	Comment
Knee OA			
Demographics	Female gender: 61.8%[116]	Yes	2/16 (12.5%) studies did not report gender distribution. 3/16 (18.75%) had more males than females.
	Mean age: 64.7 years[117]	No	
	Mean BMI (kg/m^2): 27.4 (5.2)[117]	Yes	5/16 (31.25%) studies did not report BMI. Mean range: 27.4 to 35.5
	KL grade: unclear	Yes	Paucity of data on the average KL grade in the Swiss population; 4/16 (25%) studies did not report KL grade.
Intervention †	• Triamcinolone: 84.36% • Betamethasone: 9.28% • Dexamethasone: 3.7% • Methylprednisolone: 1.75% • Methylprednisolone combo: 0.91%	No	
Setting	• Rheumatology and musculoskeletal clinics and hospitals • Outpatient setting	No	
Hip OA			
Demographics	Female gender: 60.2%[116]	No	
	Mean age: 63.6 years[117]	No	
	Mean BMI (kg/m^2): 25.6 (4.8)[117]	Yes	3/4 (75%) studies did not report BMI.
	KL grade: unclear	Yes	Paucity of data on the average KL grade in the Swiss population. One study did not report KL grade.

Parameter	Swiss population characteristics	Applicability concern (Yes/No)	Comment
			One study reported severity based on Croft severity score for hip OA[112].
Intervention †	• Triamcinolone: 82.98% • Betamethasone: 9.67% • Dexamethasone: 3.96% • Methylprednisolone: 1.26% • Methylprednisolone combo: 2.14%	Yes	2/4 studies used higher dosages of triamcinolone and methylprednisolone compared to the recommended dosage in Switzerland.[112, 113] These 2 studies accounted for >25% of the weight in the meta-analysis.
Setting	• Rheumatology and musculoskeletal clinics and hospitals • Outpatient setting	No	

Abbreviations: **BMI**: body mass index; **KL**: Kellgren–Lawrence; **OA**: osteoarthritis.

Notes: † Claims data provided by a large Swiss insurer.

6.2.4.1 Knee OA

The mean age of trial participants (range: 55.5–70.6 years) was similar to the mean age of those in the Swiss population with knee OA (64.7.years), based on the GLAD (Good Life with osteoarthritis in Denmark) Switzerland study.[117] Another study conducted in Switzerland reported a median age of 60.[95] A minimum age requirement of 40 years was part of the inclusion criteria for 5 included studies.[97, 99, 103, 106, 110] OA in females was more prevalent, comprising 61.8% of the patients diagnosed with knee OA, based on Swiss health insurance data. Two of the 16 included studies did not report the gender distribution.[98, 106] Males were more represented in 3 of the included studies, which is not representative of knee OA gender distribution in Switzerland.[103, 104, 111]

Of the 16 included studies, BMI data were reported in 11 studies, revealing a mean BMI range from 27.4 to 35.5 kg/m^2. This corresponds to the overweight and obese category, consistent with the mean BMI of 27 kg/m^2 (SD 5.2) reported in the GLAD Switzerland study.

KL grade was not reported by 25% (4/16) of the studies. There was also inconsistency in the KL grade characteristics of patients included in the studies. One study included patients in all KL grades (0–5), 5 studies included patients with minimal to moderate OA (grade 2–3), 3 studies included patients with minimal to severe OA (grade 1–4), and 2 studies included patients with moderate to severe OA (grade 3 to 4). The study by Tschopp et al, conducted in Switzerland, only included patients with doubtful to moderate OA (KL grade 1–3), introducing uncertainty regarding the representativeness of this study for the OA disease stage of the Swiss population.[95]

The included RCTs were primarily undertaken in single-centre and multicentre sites across North America (USA and Canada) and Europe, with one study contributing data from Australia. One study for knee OA was fully conducted in Switzerland. The European studies are more applicable to the Swiss context, owing to similarities in population and clinical practice.

The glucocorticoids used in the included studies conform with the Spezialitätenliste regarding type and dosage of medication. Triamcinolone (triamcinolone acetonide and triamcinolone hexacetonide) was used by 62.5% (10/16) of studies, with dosages conforming to glucocorticoid preparation in Switzerland. Methylprednisolone was used by 37.5% (6/16) of studies, with one study reporting a higher dosage (120 mg) based on information provided by the preparation Spezialitätenliste in Switzerland.[111] One study reported the use of Cortivazol (3.75 mg).[101] IAGI is performed in hospital and outpatient settings in Switzerland, consistent with the reported treatment setting of patients in the included RCTs.

6.2.4.2 Hip OA

The average mean age of trial participants (range: 55.5–70.6 years) was comparable to the mean age of those in the Swiss population with hip OA (63.6 years), based on the GLAD Switzerland study.[117] The minimum age requirement for inclusion varied among the included studies, with one study requiring at least 18 years old, one study at least 40 and one study at least 50 years old.

Females are generally more at risk of developing OA, comprising 60.2% of the patients diagnosed with hip OA based on Swiss health insurance data. One of the 4 included studies (25%) did not report the gender distribution,[113] while female patients were predominant in 3 of the 4 studies. [112, 114, 115] BMI was not reported by 75% (3/4) of the included studies. Mean BMI was reported in one study and corresponded to the BMI based on the GLAD Switzerland study.[112]

Data on mean KL grade for hip OA of relevance to the Swiss population are lacking. KL grade was not reported by 50% (2/4) of the studies (one study reported the Croft severity score for hip OA in lieu of KL grade). The remaining 2 studies included patients of all KL grades.[114, 115] The lack of Swiss population data makes it difficult to determine whether the included studies based on KL grades are representative of the Swiss population.

The included RCTs were primarily undertaken in single-centre and multicentre sites across Canada and Europe (UK and Denmark). No study was fully conducted in Switzerland. Given the similarity of population and clinical practice, European studies are more relevant in the Swiss context.

The glucocorticoids used in the included studies conform with the Spezialitätenliste regarding the type of medication used. Triamcinolone (2/4; 50%) and methylprednisolone (2/4; 50%) were the commonly reported glucocorticoids used in the included studies. However, higher dosages were used by one study that used triamcinolone[113] and one study that used methylprednisolone.[112] IAGI is performed in hospital and outpatient settings in Switzerland, consistent with the reported treatment settings of patients in the included RCTs.

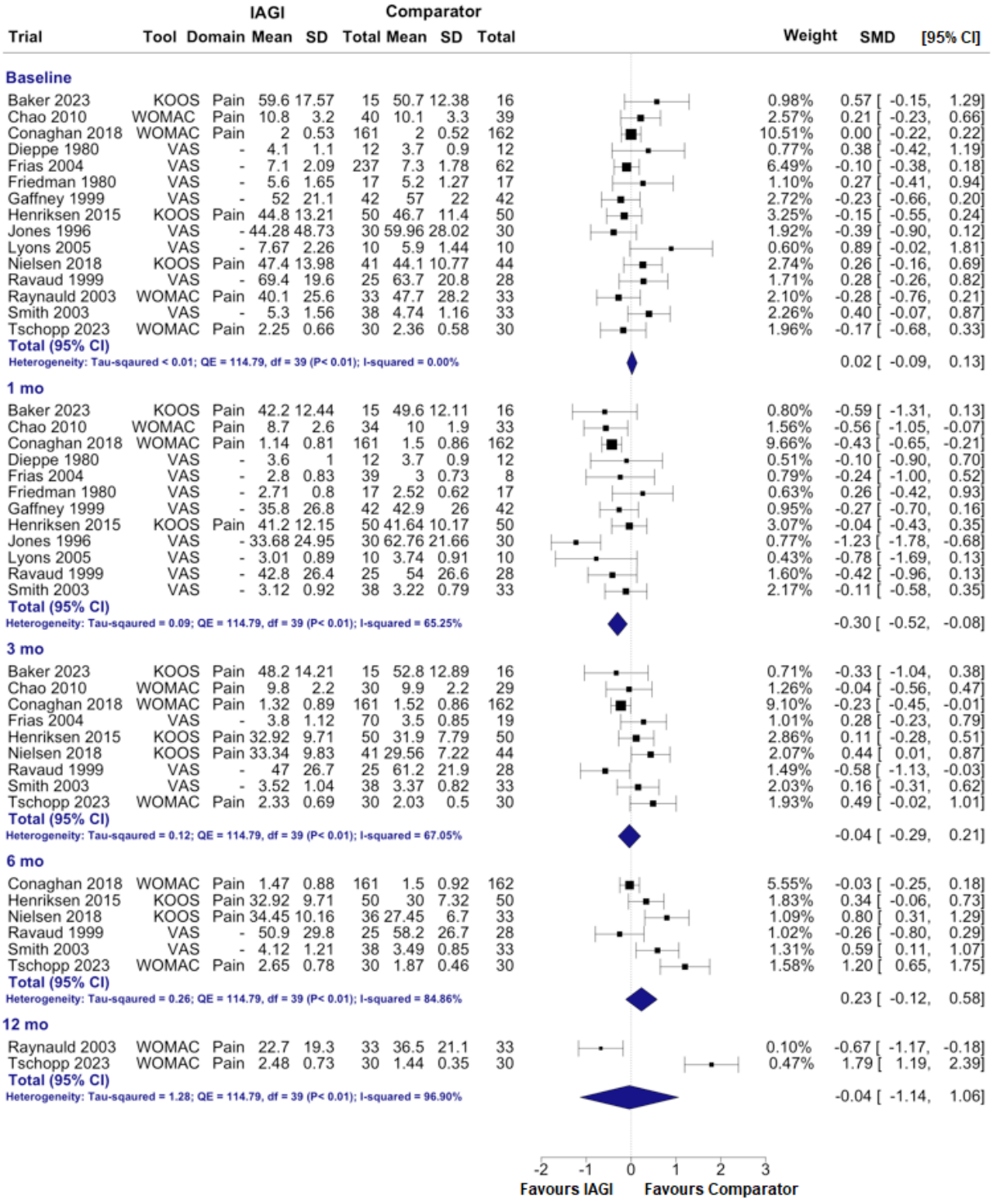
6.2.5 Findings: efficacy

6.2.5.1 Knee OA

6.2.5.1.1 Pain

Nine RCTs provided data comparing pain during IAGI and sham injection for patients with knee OA at 3 months (***Figure 2***).[95, 97-99, 101, 103, 104, 110, 111] The analysis did not reveal a clinically important or statistically significant difference between groups (SMD -0.04, 95% CI: -0.29 to 0.21); substantial heterogeneity was observed (I^2 = 67.05). The overall certainty of evidence was low.

Figure 2 Forest plot indicating standardised mean difference in pain for IAGI compared to sham injection for knee OA



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **SD**: standard deviation; **SMD**: standardised mean difference; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Pain data were reported by 12 studies at 1 month,[97-99, 101, 103-109, 111] 6 studies at 6 months,[95, 97, 99, 101, 110, 111] and 2 studies at 12 months.[95, 102] There was a clinically small reduction in pain intensity favouring IAGI that was statistically significant at 1 month (SMD -0.30, 95% CI: -0.52 to -0.08); substantial heterogeneity was observed (I^2 = 65.25). No clinically or statistically significant differences were observed at other timepoints.

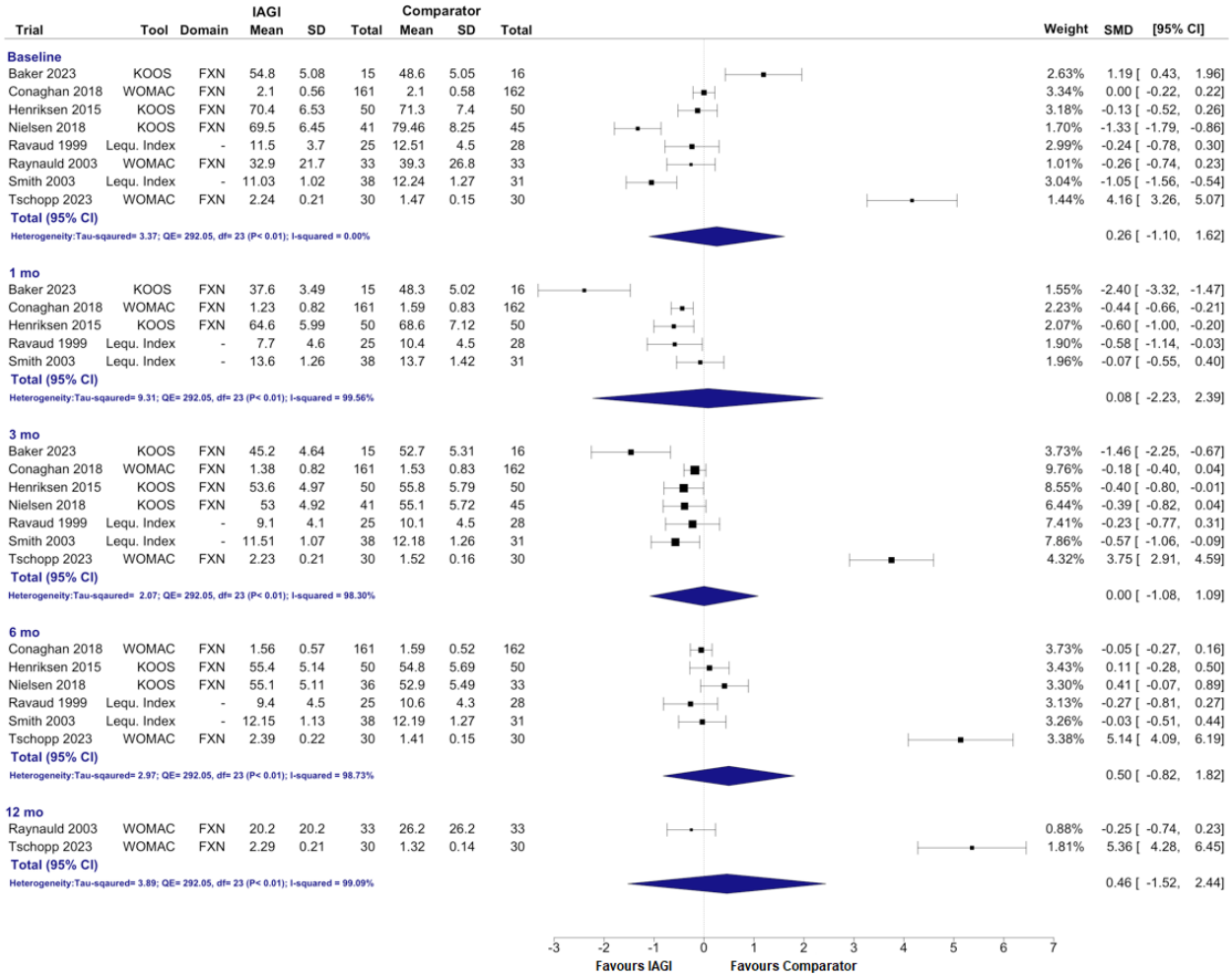
There were no significant subgroup differences detected at 3 months for the use of local anaesthetic (χ^2 = 0.22, degrees of freedom [df] = 1, p = 0.64), use of ultrasound guidance (χ^2 = 3.31, df = 2, p = 0.19) or the aspiration of fluid prior to injection (χ^2 = 0.00, df = 1, p = 0.95) (***Appendix 13.5.1.1***, ***Figure 24***, ***Figure 25***, ***Figure 27***). A significant difference was detected for the presence of joint effusion at 3 months (χ^2 = 8.42, df = 2, p = 0.01), suggesting this factor is a contributor to heterogeneity in the results (***Appendix 13.5.2***, ***Figure 26***). Studies that did not report the presence or absence of joint effusion favoured IAGI, whereas studies that did report the presence of effusion found no significant difference between IAGI and the comparator. Studies that reported no effusion favoured the comparator. These findings are not easily explained clinically, and should be interpreted with caution.

Sensitivity analyses in studies with sample sizes ≤99 and ≥100, sources of funding, whether SDs were imputed, and the removal of outliers in the analysis and risk of selection bias showed no impact on the results of the overall analysis (***Appendix 13.5.2.1***, ***Figure 39***, ***Figure 40***, ***Figure 41***, ***Figure 42***, ***Figure 43***).

6.2.5.1.2 Function

Seven RCTs provided data comparing function during IAGI and sham injection for patients with knee OA at 3 months (***Figure 3***).[95, 97, 99, 101, 103, 110, 111] The analysis found no clinically important or statistically significant difference between groups (MD 0.00, 95% CI: -1.08 to 1.09); heterogeneity was significant (I^2 = 98.30). The overall certainty of the evidence was low.

Figure 3 Forest plot indicating standardised mean difference in function for IAGI compared to sham injection for knee OA



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **SMD**: standardised mean difference; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Function data were reported by 5 studies at 1 month,[97, 99, 101, 103, 111] by 6 studies at 6 months,[95, 97, 99, 101, 110, 111] and 2 studies at 12 months.[95, 102] No statistically significant differences were found between groups at any timepoint. Significant heterogeneity was observed across all timepoints, particularly at 12 months. The heterogeneity observed in relation to Tschopp 2023 is likely due to baseline imbalances in WOMAC function scores (significantly lower in the comparator arm), which carried through in the reported changes in scores across timepoints. As such, Tschopp 2023 is likely to be biasing results in favour of the comparator, noting that removal of this study does not change the null effects observed in the meta-analyses at 3, 6 and 12 months.

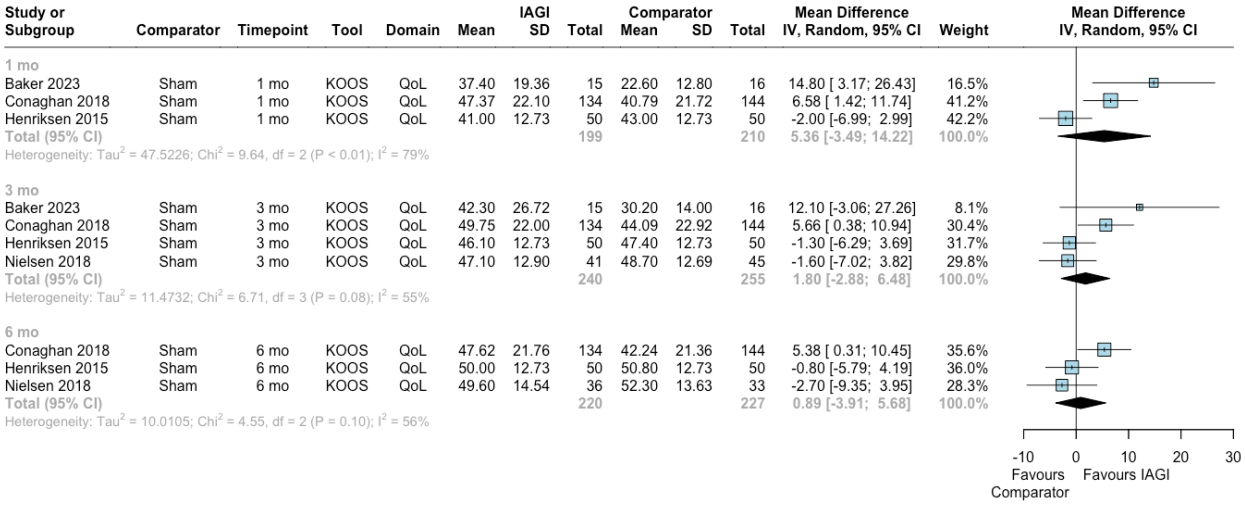
There were no significant subgroup differences at 3 months for the use of local anaesthetic (χ^2 = 1.17, df = 1, p = 0.28), use of guided ultrasound (χ^2 = 0.01, df = 2, p = 0.60), the presence of joint effusion (χ^2 = 1.30, df = 2, p = 0.52) or the aspiration of fluid prior to injection (χ^2 = 0.41, df = 1, p = 0.52) (***Appendix 13.5.1.2***, ***Figure 28***, ***Figure 29***, ***Figure 30***, ***Figure 31***). Sensitivity analyses studies with sample sizes ≤99 and ≥100 and risk of selection bias did not alter the results (***Figure 44***, ***Figure 48***). Sensitivity analysis on sources of funding (government as source of funding) and

imputed SDs favoured IAGI (***Figure 45***, ***Figure 46***). Significant differences that favoured IAGI were observed at 1 month (SMD -0.35 [-0.58 to -0.11]) and 3 months (SMD -0.32 [-0.53 to -0.10]) when outlier data were removed from the analysis (***Figure 47***).

6.2.5.1.3 Health-related quality of life

Four RCTs provided data comparing HRQoL during IAGI and sham injection for patients with knee OA at 3 months (***Figure 4***).[97, 99, 103, 110] Based on a minimal clinically important difference (MCID) of 8.0 points representing 'somewhat' of an improvement in HRQoL,[118] the analysis did not reveal a clinically important or statistically significant difference between groups (MD 1.80, 95% CI: -2.88 to 6.48), and moderate heterogeneity was observed (I^2 = 55). The overall certainty of the evidence was moderate. HRQoL was also not clinically important or statistically significantly different at 1[97, 99, 110] or 6[97, 99, 103] months assessment.

Figure 4 Forest plot indicating mean difference in HRQoL for IAGI compared to sham injection for knee OA



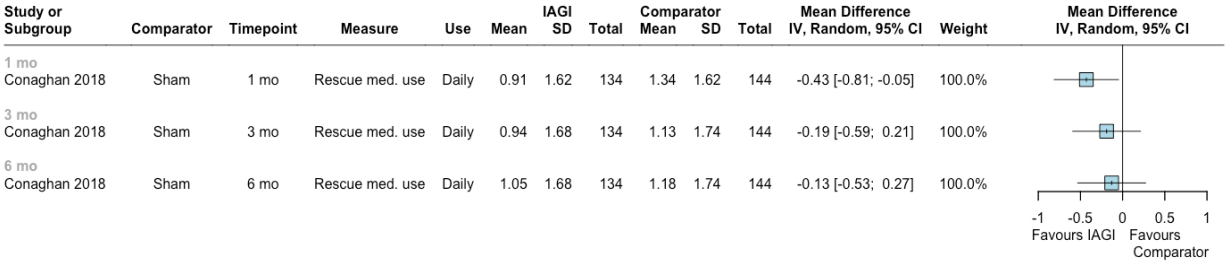
Abbreviations: **CI**: confidence interval; **HRQoL**: health-related quality of life; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **QoL**: quality of life; **SD**: standard deviation.

There were no significant subgroup differences detected at 3 months for the use of local anaesthetic (χ^2 = 3.81, df = 1, p = 0.05). HRQoL was significantly better in patients without guided ultrasound IAGI at 3 months (χ^2 = 6.09, df = 1, p = 0.01). No significant subgroup differences were found for presence of joint effusion (χ^2= 6.09, df = 2, p = 0.05) (***Appendix 13.5.1.3***, ***Figure 32***, ***Figure 33***, ***Figure 34***). A significant difference was detected for the aspiration of fluid prior to injection (χ^2 = 6.09, df = 1, p = 0.01), with studies not reporting joint aspiration favouring IAGI (***Figure 35***). Sensitivity analyses conducted for studies with sample sizes ≤99 and ≥100, and for sources of funding did not alter the results (***Figure 49***, ***Figure 50***).

6.2.5.1.4 Care utilisation

Rescue medication is used as a measure for care utilisation, and was defined as the mean number of daily tablets (500 mg) per week (measured over 24 weeks). One RCT provided data comparing care utilisation during IAGI and sham injection for patients with knee OA at 3 months (***Figure 5***).[97] The analysis did not reveal a significant difference between groups (MD -0.19, 95% CI -0.59 to 0.21). The clinical significance of this result is unclear. The overall certainty of the evidence was moderate.

Figure 5 Forest plot indicating mean difference in care utilisation for IAGI compared to sham injection for knee OA



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **mo**: months; **SD**: standard deviation.

Care utilisation data were reported by one study at 1 month[97] and 6 months[97]. One-month data revealed significantly lower care utilisation usage in the IAGI group (MD -0.43, 95% CI: -0.81 to -0.05); however, the clinical significance of this result is unclear.

Subgroup and sensitivity analyses were not conducted due to only a single study reporting care utilisation data.

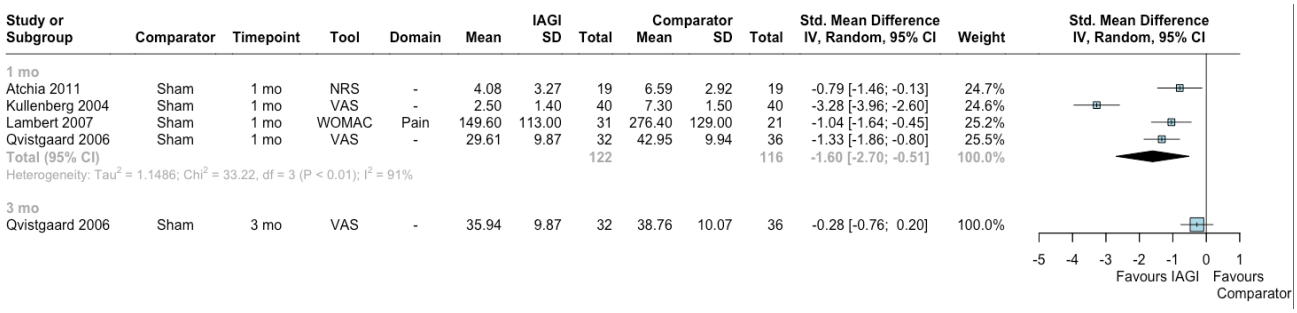
6.2.5.2 Hip OA

Subgroup and sensitivity analyses for hip OA were not performed for any outcomes, due to limited information reported in the included studies.

6.2.5.2.1 Pain

One RCT provided data comparing pain during IAGI and sham injection for patients with hip OA at 3 months (***Figure 6***).[115] The study reported a clinically small difference between groups, which was not statistically significant (SMD -0.28, 95% CI: -0.76 to 0.20). The overall certainty of the evidence was very low.

Figure 6 Forest plot indicating standardised mean difference in pain for IAGI compared to sham injection for hip OA



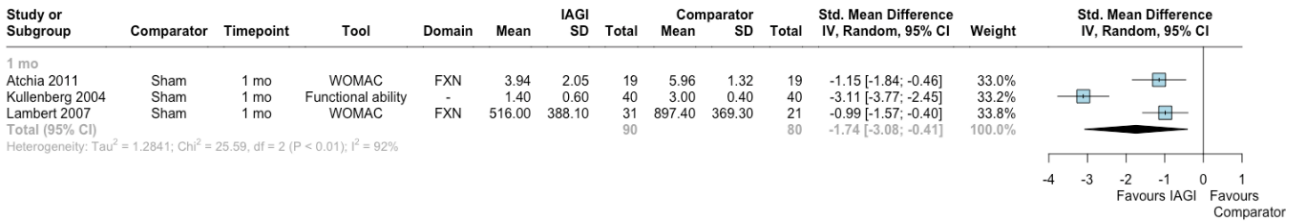
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **mo**: months; **NRS**: numerical rating scale; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Pain data at 1 month were reported by 4 studies.[112-115] There was a large reduction in pain intensity favouring IAGI that was clinically important and statistically significant at 1 month (SMD -1.60, 95% CI: -2.70 to -0.51), with significant heterogeneity observed (I^2 = 91).

6.2.5.2.2 Function

Three RCTs provided data comparing function during IAGI and sham injection for patients with hip OA at 1 month (***Figure 7***).[112-114] The analysis revealed a large difference between groups favouring IAGI that was clinically important and statistically significant (SMD -1.74, 95% CI: -3.08 to -0.41). Significant heterogeneity was observed (I^2 = 92). The overall certainty of the evidence was very low. Three-month data were not available for this outcome.

Figure 7 Forest plot indicating standardised mean difference in function for IAGI compared to sham injection for hip OA

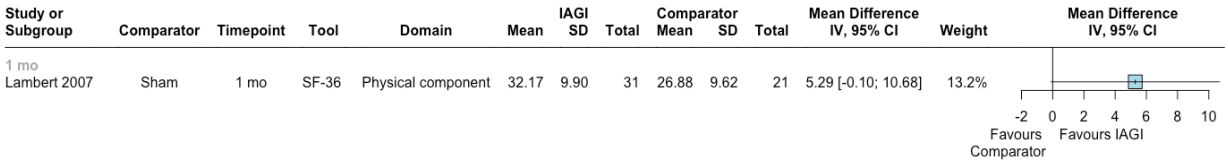


Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

6.2.5.2.3 Health-related quality of life

One study provided HRQoL data comparing IAGI and sham injection for patients with hip OA at 1 month (***Figure 8***).[114] Based on an MCID of 2.0 points,[119] the results showed a clinically important improvement favouring IAGI, noting this difference was not statistically significant (MD 5.29, 95% CI: -0.10 to 10.68). The overall certainty of the evidence was very low. Three-month data were not reported.

Figure 8 Forest plot indicating mean difference in HRQoL for IAGI compared to sham injection for hip OA

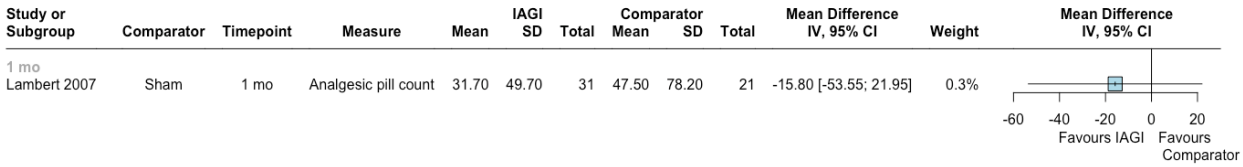


Abbreviations: **CI**: confidence interval; **HRQoL**: health-related quality of life; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **mo**: months; **SD**: standard deviation; **SF-36**: 36-Item Short Form Health Survey.

6.2.5.2.4 Care utilisation

One study provided care utilisation data comparing IAGI and sham injection for patients with hip OA at 1 month (***Figure 9***).[114] For this analysis, care utilisation was measured as the number of analgesic pills taken per patient 1 month after treatment. The result showed no statistically significant difference between groups (MD -15.80, 95% CI: -53.55 to 21.95). The clinical significance of this result is unclear. The overall certainty of the evidence was very low.

Figure 9 Forest plot indicating mean difference in care utilisation for IAGI compared to sham injection for hip OA



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **mo**: months; **SD**: standard deviation.

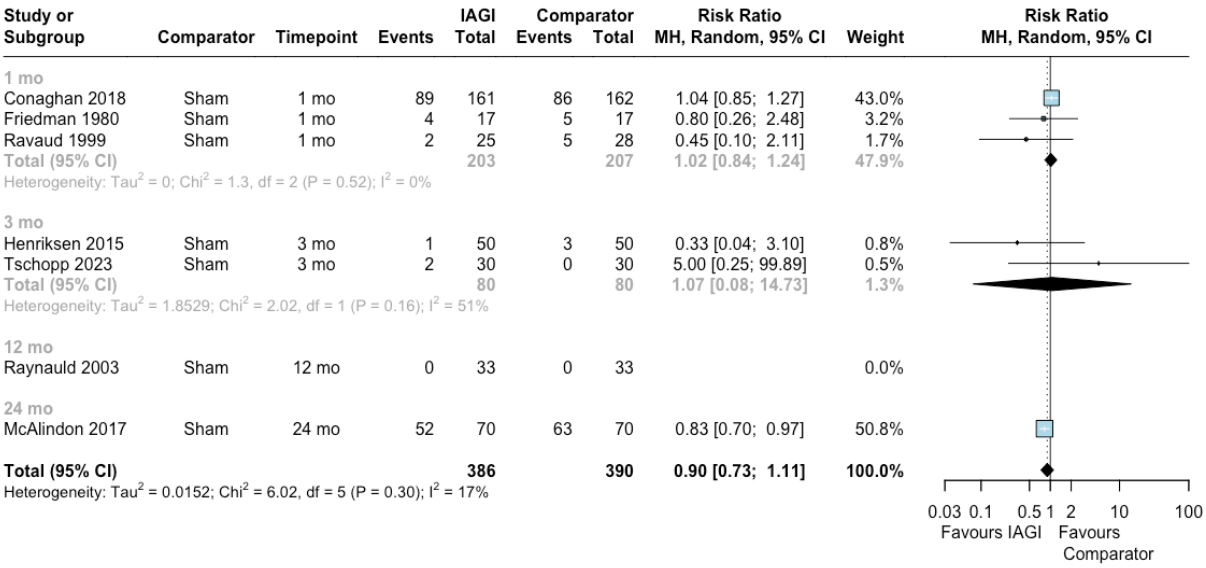
6.2.6 Findings: safety

6.2.6.1 Knee OA

6.2.6.1.1 Adverse events

Seven RCTs provided data comparing AEs during IAGI and sham injection for patients with knee OA up to 24 months (***Figure 10***).[95, 97, 99-102, 106] The analysis did not reveal a statistically significant difference between treatment groups (RR 0.90, 95% CI: 0.73 to 1.11), and no significant heterogeneity was observed ($I^2 = 17$). The overall certainty of the evidence was moderate. AE data were often not reported or not clearly defined.

Figure 10 Forest plot indicating risk ratio for AEs for IAGI compared to sham injection for knee OA up to 24 months

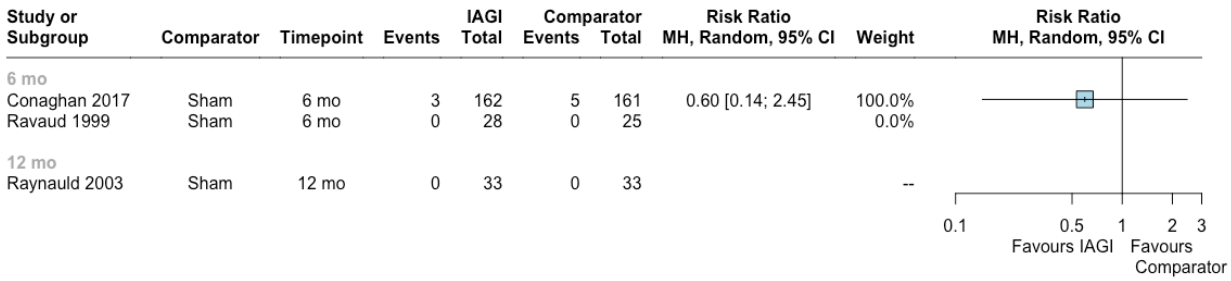


Abbreviations: AEs: adverse events**.CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

6.2.6.1.2 Serious adverse events

SAE data were reported by two studies at 6 months,[97, 101] and one study at 12 months (***Figure 11***).[102] There was no statistically significant difference in the number of SAEs between groups at all timepoints (RR 0.60, 95% CI: 0.14 to 2.45), noting that the incidence of events was low. The overall certainty of the evidence was low. The SAEs reported by Conaghan 2017 were not described, but it was noted that none were considered to be related to the study agents.

Figure 11 Forest plot indicating risk ratio for SAEs for IAGI compared to sham injection for knee OA



Abbreviations: CI: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months; **SAEs**: serious adverse events.

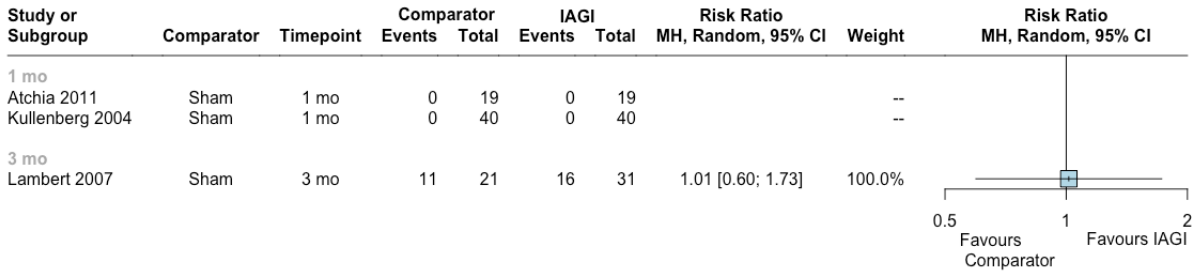
6.2.6.2 Hip OA

6.2.6.2.1 Adverse events

One RCT provided data comparing AEs during IAGI and sham injection for patients with hip OA at 3 months (***Figure 12***).[114] The analysis did not reveal a significant difference in the number of AEs between groups (RR 1.01, 95% CI: 0.60 to 1.73). The overall certainty of the evidence was very low.

AE data were reported by two studies at 1 month, with no events reported in either group.[112, 113] Most AEs reported by Lambert 2017 were either mild and/or considered unrelated to the treatments.

Figure 12 Forest plot indicating risk ratio for AEs for IAGI compared to sham injection for hip OA

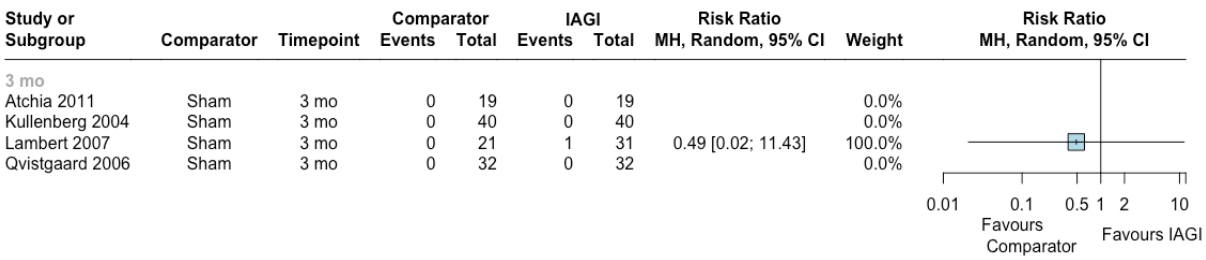


Abbreviations: **AE:** adverse events**; CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

6.2.6.2.2 Serious adverse events

SAE data were reported in four studies at 3 months (***Figure 13***).[112-115] There was no significant difference in the number of SAEs between groups (RR 0.49, CI: 0.02 to 11.43). The overall certainty of the evidence was very low. The single SAE reported by Lambert 2017 was a case of deep vein thrombosis, which occurred in an IAGI patient 3 months after injection.

Figure 13 Forest plot indicating risk ratio for SAEs for IAGI compared to sham injection for hip OA



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months; **SAEs:** serious adverse events.

6.2.7 GRADE Summary of findings

Following the GRADE approach, a list of prioritised clinical outcomes is reported in the summary of findings tables. For all such tables, the risk and the associated 95% CI in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (plus associated 95% CI). Clinical outcomes were primarily assessed at 3 months; however, due to limited hip OA outcome data for function, quality of life (QoL) and care utilisation these were assessed at 1 month (***Table 8, Table 9***). This is important to note, as other outcomes at later timepoints showed reduced treatments effects, as reported in ***Section 6.2.5.1*** and ***Section 6.2.5.2***.

The certainty of evidence supporting an outcome, according to the GRADE approach, is defined as follows:[84]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 8 GRADE summary of findings table: IAGI for knee OA

Outcome	Anticipated absolute effect (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo/sham	Risk with IAGI			
Pain (3 months; measured using SMDs; lower values favour IAGI)	-	SMD 0.04 SDs lower (0.29 lower to 0.21 higher)	-	871 (9 RCTs)	⊕⊕◯◯ Low[a,b,h]
Function (3 months; measured using SMDs; lower values favour IAGI)	-	SMD 0.00 SDs lower (1.08 lower to 1.09 higher)	-	722 (7 RCTs)	⊕⊕◯◯ Low[b,c,h]
Health-related quality of life (3 months; measured using KOOS QoL scale 0–100; higher values favour IAGI)	45 points	MD 1.80 points higher (2.88 lower to 6.48 higher)	-	495 (4 RCTs)	⊕⊕⊕◯ Moderate[d]
Care utilisation (3 months; measured using mean number of daily tablets [500 mg] per week; lower values favour IAGI)*	1.13 analgesic tablets	MD 0.19 tablets lower (0.59 lower to 0.21 higher)	-	278 (1 RCT)	⊕⊕⊕◯ Moderate[e]
Adverse events (longest follow-up; range 1–24 months)	415 per 1,000	374 per 1,000 (303 to 461)	RR 0.90 (0.73 to 1.11)	776 (7 RCTs)	⊕⊕⊕◯ Moderate[f]
Serious adverse events (longest follow-up; 6 months)	31 per 1,000	19 per 1,000 (4 to 76)	RR 0.60 (0.14 to 2.45)	323 (1 RCT)[i]	⊕⊕◯◯ Low[g,j]

Abbreviations: **CI**: confidence interval; **BMI:** Body Mass Index; **IAGI**: intra-articular glucocorticoid injection; **KOOS QoL**: Knee Injury and Osteoarthritis Outcome Score quality of life scale; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: risk ratio; **SD**: standard deviation; **SMD**: standardised mean difference.

Notes:

* mean number of daily rescue medication tablets (500 mg) per week.

a. BMI of participants in 4 studies was not reported and in 3 studies the BMI was obese, whereas the Swiss population BMI was 27.4.

b. Substantial heterogeneity was present.

c. BMI of participants in 3 studies was not reported and in 2 studies the BMI was obese, whereas the Swiss population BMI is 27.4.

d. BMI of participants in 1 study was not reported and in 2 studies the BMI was obese. BMI in the Swiss population is 27.4

e. BMI of the single study was an average of 30.2 (i.e. obese) whereas Swiss population BMI is 27.4.

f. BMI of 4 studies was not reported and in 2 studies the BMI was obese, whereas Swiss population BMI is 27.4.

g. BMI of the single study was an average of 30.2 (i.e. obese) whereas Swiss population BMI is 27.4.

h. A difference of 0.2 SD is considered small, 0.5 is moderate and 0.8 is large.

i. Data were reported from 3 RCTs; however, as 2 RCTs reported no events, only the results from 1 RCT could be analysed as a RR.

j. Downgraded due to imprecision owing to low event rates and wide CIs.

Table 9 GRADE summary of findings table: IAGI for hip OA

Outcome	Anticipated absolute effect (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo/sham	Risk with IAGI			
Pain (3 months; measured using VAS scale; 0–100; lower values favour IAGI)	38.76 points	MD 2.82 points lower (21.42 lower to 15.78 higher)	-	68 (1RCT)	⨁◯◯◯ Very low[a,b,j]
Function (1 month; measured using SMDs; lower values favour IAGI)	-	SMD 1.74 SD lower (3.08 lower to 0.41 lower)	-	170 (3 RCTs)	⨁◯◯◯ Very low[c,d,e,f,i]
Health-related quality of life (1 month; measured using SF-36, physical component scale; 0–100; higher values favour IAGI)	26.88 points	MD 5.29 points higher (0.10 lower to 10.68 higher)	-	52 (1 RCT)	⨁◯◯◯ Very low[g,h]
Care utilisation (1 month, measured using analgesic tablet count per patient after 1 month; lower values favour IAGI)*	47.5 analgesic tablets	MD 15.8 analgesic tablets fewer (53.55 fewer to 21.95 more)	-	52 (1 RCT)	⨁◯◯◯ Very low[g,h]
Adverse events (3 months)†	516 per 1,000	521 per 1,000 (310 to 893)	1.01 (0.60 to 1.73)	52 (1 RCT)	⨁◯◯◯ Very low[g,h]
Serious adverse events (3 months)†	32 per 1,000	16 per 1,000 (1 to 369)	0.49 (0.02 to 11.43)	52 (1 RCT)	⨁◯◯◯ Very low[g,h]

Abbreviations: **CI**: confidence interval; **BMI**: Body Mass Index; **IAGI**: intra-articular glucocorticoid injection; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: risk ratio; **SD**: standard deviation; **SF-36**: short-form 36; **SMD**: standardised mean difference; **VAS**: visual analogue scale.

Notes:

* mean number of daily rescue medication tablets (500 mg) per week.

† SAEs were reported by 4 RCTs, but only 1 study had event data; the other 3 studies reported 0 events in both treatment arms, which did not contribute to the RR, but these are included to provide evidence for the limited safety risks associated with IAGI and placebo.

a. BMI not reported.

b. small sample size of 68 total participants.

c. Kullenberg has high study attrition and was rated as high RoB

d. High heterogeneity (92% I^2).

e. BMI not reported in 2/3 studies; sex not reported in 1/3 studies.

f. Sample size only 170 participants.

g. BMI not reported.

h. Sample size only 52 participants.

i. Generally, a difference of 0.2 SD is considered small, 0.5 is moderate, and 0.8 is large.

j. ***Figure 6*** reports SMDs owing to the numerous measurement scales reported at 1 month; however, as there was only 1 RCT reported at 3 months, the MD from the study is reported in this table instead of the SMD reported in ***Figure 6***.

7 Costs, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

Compared to placebo, IAGI was shown to result in significant improvements in pain in the short-term for both hip and knee OA. Effects beyond 1 month were found to be uncertain, with no significant differences observed. Given the observed short-term improvements in pain, economic modelling was conducted to explore the cost utility of a single IAGI in the management of knee OA as an exemplar case. The analysis examined IAGI as an adjunct to standard care compared to standard care alone. Expected per patient costs for the delivery of a single IAGI injection were estimated for both knee and hip OA.

To assess the economic benefit of IAGI, reported outcomes were translated into a preference-based utility measure, allowing the incremental quality-adjusted life years (QALYs) gained to be estimated. While HRQoL data collected using the disease-specific KOOS-QoL measure were reported in the clinical evidence review, generic preference-based health utility index HRQoL data are required for the economic evaluation. EQ-5D utility scores for IAGI and standard-care cohorts were predicted from weighted WOMAC pain and function scores up to 6 months post-injection among knee OA patients. A mean expected incremental QALY gain of 0.013 (95% CI: -0.019 to 0.044) over 6 months was estimated. Differences in KOOS-QoL HRQoL outcomes were not statistically significant at any timepoints.

The incremental cost-effectiveness ratio (ICER) for a single IAGI injection, relative to standard care, was estimated to be CHF12,456 per QALY gained. Probabilistic sensitivity analysis (PSA) showed the probability of IAGI being cost effective relative to standard care alone exceeded 50% beyond a willingness-to-pay (WTP) threshold of approximately CHF13,000. At hypothetical WTP thresholds of CHF50,000 and CHF100,000, IAGI demonstrated 71.9% and 75.0% probabilities of cost-effectiveness, respectively. Around 22.0% of iterations fell in the fourth quadrant of the cost-effectiveness plane, where IAGI is dominated (i.e. is more expensive and less effective than standard care). This highlights uncertainty in the effectiveness of IAGI in improving patient HRQoL. Incremental per patient costs were estimated at CHF157.10 for knee OA and CHF182.80 for hip OA.

Only one cost-effectiveness study meeting the PICO criteria for knee OA was identified. This study from the New Zealand healthcare payer perspective assessed the cost-utility of IAGI as an adjunct to core treatment compared to core treatment alone, finding IAGI to be a cost-effective adjunctive therapy. Despite differences in the modelling methodologies between the current HTA and the New Zealand study, the overall findings appear to be in broad alignment. However, probabilistic analysis performed for the present evaluation highlighted uncertainty in the treatment benefit attributed to IAGI, whereas the existing study indicated confidence that IAGI was associated with a positive treatment effect.

The current utilisation of IAGI among Swiss patients diagnosed with primary OA of the knee or hip was estimated using data provided by a large Swiss insurer and extrapolated to the total Swiss population. Estimated IAGI injection figures were extrapolated to predict the future budget impact. The analysis considered the expected per patient cost for IAGI and possible cost offsets from reduced use of standard-care pain relief medications. The net financial impact of IAGI for knee OA was estimated at CHF0.832 million in 2025, increasing to CHF0.97 million in 2029. For hip OA, the net financial impact was estimated at CHF0.52 million in 2025, increasing to CHF0.57 million in 2029.

7.1 Methodology: review of economic literature

7.1.1 Search strategy and study selection

The systematic literature searches outlined in ***Section 6.1*** were used to identify studies reporting on economic outcomes of IAGI for OA of the hip and knee. The population, intervention and comparator criteria outlined in ***Table 3*** (***Section 6.1.2***) also guided the selection of relevant economic evidence. Relevant outcomes included:

- direct medical costs of the technology and associated services
- incremental costs
- incremental effectiveness – incremental QALYs or incremental effect expressed using another relevant unit of health outcome
- cost-effectiveness/cost utility – expressed as ICER
- total costs to the Swiss healthcare payer.

Eligible studies included full economic evaluations with cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), cost analyses, other economic analyses (e.g. cost-consequence analysis or cost-minimisation analysis), or budget impact analyses. The economic search string and search results are summarised in ***Appendix 13.2.2***. Database searches were conducted to 16 October 2023 for the economics section.

7.1.2 Assessment of evidence quality

Each cost-effectiveness study was assessed against the applicability checklist items outlined in the NICE appraisal checklist to appraise the study's applicability to the evaluation context.[120] The NICE checklist considers the applicability of each study in terms of the following: population studied, interventions included, healthcare system of use, analysis perspective, discounting of future costs and outcomes, and outcome measures used.

Studies were judged as directly applicable, partially applicable or not applicable to the HTA key questions. For directly and partially applicable studies, initial assessments against the study limitations checklist items were made and studies were rated as having minor limitations, potentially serious limitations or very serious limitations.[120] Only Swiss-specific evaluations were judged as directly applicable. The results of included assessments were described narratively.

More-informed critical assessments of the clinical evidence used in any directly or partially applicable studies were made in comparison with results of the clinical evidence review performed as part of the current HTA.

7.1.3 Methodology for data extraction, analysis and synthesis of health economic data

Data pertaining to the following domains were extracted from studies meeting the PICO criteria: country, perspective, type of analysis, population, intervention, comparator, outcome measure used, conflicts of interest, analysis methods, model used (if relevant), time horizon, discount rate, key sources of evidence (for efficacy inputs), currency and costing year, results (incremental cost), incremental effectiveness (ICER), uncertainty analysis (type and key drivers), and additional comments (e.g. author conclusions). Data were extracted by one reviewer and checked by a second. A more detailed assessment of specific aspects of the modelling and input variables was subsequently undertaken to better inform a comparison between this study and the current HTA.

Results of the included studies (i.e. those that met the PICO criteria) were synthesised narratively. Extracted incremental costs and ICERs were converted to 2024 Swiss francs (CHF) by using annual average foreign exchange rates for the reported costing year (or publication year if the costing year was not reported) and inflated to 2024 values (applying a healthcare goods-specific consumer price index).[121, 122] Both the original and converted incremental costs and ICERs are reported.

7.2 Results: review of economic literature

7.2.1 Search results

A PRISMA flowchart summarising the overall systematic literature search is included in ***Section 6.2.1***. Only one cost-effectiveness study meeting the PICO criteria for knee OA was identified. No studies assessing the cost-effectiveness of IAGI relative to standard care for patients with hip OA were identified. Data extraction and an assessment of the applicability and study limitations were undertaken for the single included study. Extraction, applicability appraisal and study limitations templates are available (***Appendix 13.6***, ***Table 54*** to ***Table 57***).

7.2.2 Study characteristics and quality assessment of included studies

The included study was conducted from the perspective of the New Zealand healthcare sector, and assessed the cost-effectiveness of IAGI as an adjunct to core treatment compared to core

treatment alone in patients with knee OA.[123] Core treatment included patient education, land-based exercise and weight management. The cost-effectiveness of other adjunct treatments was also assessed, including but not limited to IAGI, aquatic-based exercise, heat therapy and NSAIDs. The selection of adjunctive treatments was based on a clinical practice guideline from the Royal Australian College of General Practitioners.[1] Evidence of treatment effectiveness was obtained from a systematic review that informed the clinical practice guideline. Costs of these treatments were calculated by applying local reference prices to estimated resource use. A computer simulation model was employed over a lifetime horizon to estimate the cost-effectiveness of each adjunctive treatment at different WTP thresholds (i.e. 1, 2 and 3 times the gross domestic product per capita). AEs considered in the study included vascular events, heart failure and upper gastrointestinal complications.

IAGI was found to be cost-effective at all WTP thresholds. The incremental cost of IAGI relative to core treatments alone was NZD564 (90% uncertainty interval [UI]: 380–739) (CHF409; 90% UI: 275–535) and the incremental effectiveness of IAGI relative to core treatments alone was 0.023 QALYs (90% UI: 0.004–0.043). The relevant ICER was not reported; however, using the reported incremental costs and QALYs an ICER of NZD24,532 (CHF17,774) can be calculated. The study suggested that implementing high-value, low-cost adjunct interventions for knee OA—in addition to recommended core treatments—could lead to substantial health gains at a low cost to the health system in New Zealand.

The study was judged as partly applicable to the research question (***Appendix 13.6.2***, ***Table 56***). Conducted within a New Zealand healthcare setting, the model cohort was representative of the New Zealand adult population age ≥35 years. Individuals could begin the simulation with existing OA or develop incident OA over the simulation period. The overall methodological study quality was assessed as having minor limitations, since the study met all of the checklist criteria (***Appendix 13.6.2***, ***Table 57***).

7.3 Methodology: economic evaluation

The available published economic evidence was judged to be insufficient to answer the research questions posed in this HTA. De novo economic modelling was undertaken to estimate the cost utility of IAGI relative to standard care (without IAGI) from the perspective of the Swiss healthcare payer. A large volume of RCT evidence for knee OA was identified, including a Swiss RCT.[95] Less evidence was found for hip OA. A reference case for knee OA was therefore developed as an exemplar case and a summary of the evaluation undertaken is provided in ***Table 10***.

A health economic analysis plan was drafted and peer-reviewed as part of the HTA process.

Table 10 Summary of the economic evaluation undertaken for IAGI vs standard care for knee OA

Population	Patients ≥18 years of age with knee OA (as an exemplar case)
Intervention	IAGI (provided as an adjunct to standard care)
Comparator	Standard care without IAGI
Perspective on costs	Swiss healthcare payer
Perspective on outcomes	Personal health of person receiving the intervention
Type of analysis	CUA
Time horizon	6 months
Source of effectiveness inputs	Systemic review and meta-analysis
Measuring and valuing health effects	WOMAC pain and function scores were mapped into preference-based utility scores using the GLM equation presented by Bilbao 2020.[124] QALYs gained were then calculated.
Evidence of resource use and costs	Systematic review and meta-analysis (resource utilisation), expert opinion, Spezialitätenliste, TARMED
Discount rate	NA, given short time horizon
Sensitivity analyses	Parameter uncertainty explored using one-way DSA and PSA

Abbreviations: **CUA**: cost-utility analysis; **DSA**: deterministic sensitivity analysis; **GLM**: generalised linear model; **IAGI**: intra-articular glucocorticoid injection; **NA**: not applicable; **OA**: osteoarthritis; **PSA**: probabilistic sensitivity analysis; **QALY**: quality-adjusted life year; **WOMAC**: Western Ontario and McMaster Universities Arthritis index.

7.3.1 Population

Patients ≥18 years of age with knee OA were selected as the exemplar case. The target population was previously described (***Section 4.1***)

7.3.2 Intervention and comparator

The intervention (IAGI) was described in ***Section 4.2***. The comparator for the economic evaluation was defined as standard care without IAGI. It was assumed that IAGI is used as an adjunct to standard care. This reflects the comparison drawn in the existing economic evaluation, which assessed the cost-effectiveness of IAGI as an adjunct to core treatment.[123] Where the intervention of interest is an adjunctive therapy, placebo comparison data may be appropriate for trial-based economic studies.[125]

7.3.3 Outcome

Health outcomes were measured in QALYs lived as described in the following section. The outcome of the economic evaluation is reported as ICER. The costs and outcomes were not discounted given the short time horizon.

7.3.4 Perspective

The analysis was conducted from a Swiss healthcare payer perspective, being the relevant perspective for the decision-maker. Direct medical costs for services covered by mandatory health insurance (OKP) were included, irrespective of the actual payer (e.g. health insurers, other social insurance, the government, cantons, communities or patients). Non-medical and indirect costs (e.g.

travel costs, informal care or productivity losses) were not considered. Costs were reported in Swiss francs (CHF) for a common costing year of 2024.

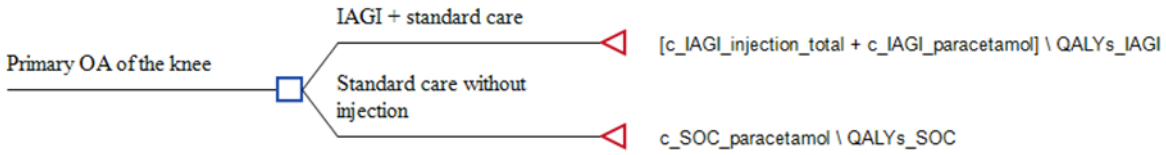
7.3.5 Model conceptualisation

IAGI is used as a non-surgical option for treating OA symptoms, with a primary aim to provide short-term improvement in pain, function and HRQoL.[126-128] In particular, IAGI is used in patients who cannot tolerate long-term therapy with paracetamol and NSAIDs, those for whom drugs are no longer effective, those who are contraindicated for surgical interventions, and those who want to delay or avoid surgical treatment.[35, 126, 127]

The single cost-effectiveness study identified employed a state-transition microsimulation model to simulate the disease course of knee OA in the New Zealand adult population age ≥35 years over a lifetime horizon.[123] However, the included RCTs lacked clinical evidence on the efficacy of IAGI in delaying or avoiding surgical intervention. Most were limited to reporting on short-term pain and/or function outcomes, with a limited number also reporting HRQoL data. As such, the economic evaluation focused on the effectiveness of IAGI in reducing short-term pain and improving short-term function and HRQoL. The model did not extend to modelling the delay or avoidance of surgical intervention.

An ICER for IAGI versus standard care was calculated using estimated base case treatment costs and estimated QALYs over 6 months. Analyses were performed using TreeAge Pro (***Figure 14***).[129]

Figure 14 Modelling approach used to estimate the incremental cost-effectiveness ratio of IAGI vs standard care



Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis; **QALY**: quality-adjusted life years; **SOC**: standard care.

7.3.6 Time horizon

A lifetime horizon is generally specified as being the most appropriate time horizon, given that OA is a chronic disease.[130] However, Hiligsmann 2014 also highlight that clinical studies of OA are often too short to fully assess all relevant outcomes and that modelling beyond trial duration requires several assumptions.[130] This limitation was evident following a preliminary review of the RCT evidence included in this HTA. A short-term time horizon of 6 months was used for the present economic evaluation, with a focus on evaluating the incremental costs and benefits of IAGI on short-term pain, function and HRQoL outcomes.

7.3.7 Treatment effect

Clinical data evaluating the efficacy of IAGI in relation to placebo or no treatment were used to inform the estimates of incremental benefit for the economic evaluation.

The clinical evidence review reported no significant differences in HRQoL, based on data collected using the disease-specific KOOS-QoL measure (***Section 6.2.5***, ***Figure 4***). For economic evaluations, however, generic preference-based health utility index HRQoL data are required. No studies included in the clinical evidence review reported HRQoL using a generic, preference-based health utility index. Estimation of QALYs requires HRQoL data on a preference-based utility scale.

Four studies pertaining to OA of the knee reported HRQoL data.[97, 99, 103, 110] All these studies used the QoL domain of the KOOS tool—a disease-specific, non-preference-based measure that captures knee-related QoL. One study pertaining to OA of the hip reported HRQoL data using the SF-36—a generic, non-preference-based measure.[114]

A mapping algorithm was required to translate the reported outcomes into a preference-based utility measure. Translation to a preference-based utility scale was performed for knee OA as the exemplar case. Additional uncertainty introduced via the use of a mapping algorithm is an inherent limitation.

The Health Economics Research Centre (HERC) provides an online database of studies mapping to the EQ-5D. The current version (9.0) is based on updated systematic literature searches conducted in January 2023 and was last updated in December 2023.[131] Studies conducting statistical mapping to predict EQ-5D utilities from any source instrument were included in the database if the estimated algorithms were reported in sufficient detail to allow other researchers to use them. This tool was used to identify a relevant mapping algorithm for the present economic evaluation.

Six studies mapping from WOMAC to the EQ-5D were included in version 9.0 of the HERC online database (***Table 11***).[131] No studies mapping from KOOS were included. External scoping searches identified one study mapping from KOOS to the EQ-5D.[132] It was impossible to determine if this study was purposefully excluded from the database or missed; however, the study was conducted in a younger population of patients undergoing anterior cruciate ligament surgery. WOMAC mapping studies conducted in older OA populations were prioritised for this HTA.

Table 11 Identified studies mapping from WOMAC to the EQ-5D utility index

Study ID	Disease or patient group	Observations in the sample	EQ-5D version	Used in current HTA
Ayala 2021[133]	Hip or knee OA	716	EQ-5D-5L (Spanish tariff)	No
Barton 2008[134]	Knee pain	348	EQ-5D	No
Bilbao 2020[124]	Hip or knee OA	748	EQ-5D-5L (Spanish tariff)	Yes, the preferred GLM model was used
Price 2019[135]	Knee replacement for arthritis	978	EQ-5D	No
Wailoo 2014[136]	Hip or knee OA	7,072	EQ-5D-3 (UK tariff)	No
Xie 2010[137]	Knee OA	258	EQ-5D	No

Abbreviations: **EQ-5D**: EuroQol 5-dimension health-related quality of life questionnaire; **GLM**: generalised linear model; **HTA**: health technology assessment; **OA**: osteoarthritis.
Source: Data extracted from version 9.0 of the HERC mapping database.[131]

The preferred generalised linear model (GLM) model reported by Bilbao 2020 was used to predict EQ-5D utilities at baseline and at 1-, 3- and 6-month follow-up.[124]

$$Predicted\ EQ-5D\ utility = 0.9516 + 0.0034 \times \frac{Pain^2}{100} - 0.0044 \times \frac{Pain^3}{10{,}000} - 0.0062 \times Function - 0.0042 \times \frac{Pain \cdot Function}{100}$$

This mapping algorithm was developed based on observations in patients with hip or knee OA. Patients were recruited from 6 hospitals and 21 primary care centres across 3 regions of Spain.[124] The baseline sample had a mean age of 69.8 years and 61.9% were female. Limitations of the algorithm are that mapping is based on EQ-5D-5L utilities valued using the Spanish tariff. Despite also being a Western European country, preference-based utilities valued from Spanish preferences may not reflect Swiss population preferences.

QALYs gained over 6 months were estimated for IAGI and standard care arms using the following equation:

$$QALYs_{gained} = (utility_{1\ month} - utility_{basline}) \times \left(\frac{1}{12}\right) + (utility_{3\ month} - utility_{basline}) \times \left(\frac{2}{12}\right) + (utility_{6\ month} - utility_{basline}) \times \left(\frac{3}{12}\right)$$

7.3.8 Accounting for uncertainty

Parameter uncertainty was explored using one-way deterministic sensitivity analysis (DSA) and PSA. Consistency between the ranges used in DSAs and the distributions used in PSAs was maintained. A summary of the uncertainty ranges and distributions assigned to each model input is provided in ***Appendix 13.6.4, Table 59***. Reporting focused on describing how uncertainty in the model inputs affects the economic findings. There is no accepted WTP threshold in Switzerland.

Using cost-effectiveness acceptability curves (CEACs) produced via PSAs, the probability of cost-effectiveness is expressed as a function of WTP.

7.4 Results: costs and cost-effectiveness

7.4.1 Cost analysis

Questions about what types and amounts of resources are used when delivering the intervention or comparator, and how much these cost to deliver, were addressed. Healthcare resources associated with IAGI and standard care components potentially affected by the use of IAGI were identified, measured and valued.

7.4.1.1 IAGI costs

IAGI is performed in an outpatient setting. Unit costs for outpatient IAGI procedures were informed by TARMED, and the Spezialitätenliste for drug costs (or expert advice for drugs not included on the list).

TARMED positions listed in ***Table 12*** relate to intra-articular injections of the knee or hip.

Table 12 TARMED positions for intra-articular injection of the knee or hip

Resource	TARMED code	Comments	Tax points (AL + TL)	Price (CHF)
Joint puncture – knee	24.0130	Joint puncture (including ganglion, joint cyst), shoulder, elbow, knee, upper ankle joint OSG	64.43	56.79
Joint puncture – hip	24.0140	Joint puncture (including ganglion, joint cyst), sacroiliac joint, hip, carpal and tarsal joints, lower ankle USG	72.03	61.95

Abbreviations: **AL**: medical service; **CHF**: Swiss franc; **TL**: technical performance;
Notes: Tax points were valued using the mean 2024 cantonal tax point values (TPV: 0.88; simple average TPV across cantons, as reported by New Index).

Additional TARMED positions and Spezialitätenliste items may be co-claimed with the above-listed positions. These items are discussed below.

7.4.1.1.1 Glucocorticoid medication costs

Anatomical Therapeutic Chemical (ATC) code H02AB is used for glucocorticoids for systemic use. ATC code H02BX is for combined preparations (e.g. glucocorticoid combined with a local anaesthetic).[138] Glucocorticoid preparations available in Switzerland include the preparations listed in ***Appendix 13.6.3***, ***Table 58***.

Claims data from a large Swiss insurer were requested to quantify the relative use of each preparation for IAGI in Switzerland (***Table 13***).

Table 13 Relative use of glucocorticoid preparations for intra-articular injection by diagnosis category

Active Substance	Knee OA	Hip OA	Both knee and hip OA
Triamcinolone (%)	84.36	82.98	90.20
Betamethasone (%)	9.28	9.67	8.07
Dexamethasone (%)	3.70	3.96	1.44
Methylprednisolone (%)	1.75	1.26	0.00
Methylprednisolone combinations (%)	0.91	2.14	0.29

Abbreviations: **OA**: osteoarthritis.
Source: Data provided by a large Swiss insurer

Given the large representation of triamcinolone in Swiss practice, costs for this preparation were used to estimate the average per patient costs for IAGI. The Swiss RCT specified a 1 mL dose of triamcinolone (Triamcort® Depot),[95] while a local clinical expert identified Keracort® 40 mg as a typical material cost associated with IAGI.

The typical dosage of triamcinolone acetonide is 40 mg.[39, 139] This is consistent with more recently published clinical trials, which have administered 40 mg doses of triamcinolone acetonide.[97, 98, 102] Older studies administered 20 mg doses of triamcinolone hexacetonide.[105-107] Costs for 40 mg/mL preparations (Kenacort® 40 mg/ml or Triamcort® Depot 40 mg/ml) were used in the average per-patient cost estimations. Estimated costs for the glucocorticoid, at the per-patient level, are shown in ***Table 14***.

Table 14 Estimated average per-patient glucocorticoid costs for a single IAGI

Preparation	Cost per pack (CHF)	Cost per 1mL of 40 mg/mL	Quantity (mL)	Cost per IAGI (CHF)
Kenacort® 40 mg/ml	18.75 (1 ml ampoule of 40 mg/ml suspension)	18.75	1	18.75
Triamcort® Depot 40 mg/ml	17.25 (1 ml ampoule of 40 mg/ml crystal suspension)	17.25	1	17.25
	242.2 (25 1 ml ampoules of 40 mg/ml crystal suspension)	9.69	1	9.69
Average cost per patient				**15.23**[A]

Abbreviations: **CHF**: Swiss francs; **IAGI**: intra-articular glucocorticoid injection.
Notes:
A: Simple average cost across the 3 preparations

7.4.1.1.2 Additional co-claimed procedures

Additional services considered part of the IAGI procedure include a physician visit, diagnostic joint arthrocentesis, image guidance and anaesthesia use. Clinical advice is that fluid is removed and analysed for crystals to detect pseudogout prior to knee injections.

Swiss clinicians were consulted for their expert opinion on the percentage of IAGI performed alongside a diagnostic joint arthrocentesis, the percentage with which anaesthesia would be

administered, and the percentage with which imaging guidance (ultrasound, fluoroscopy) would be used. These expert inputs are summarised in ***Table 15***.

Table 15 Expert input on proportion of patients receiving additional services alongside intra-articular injection

Service	Expert inputs, knee	Expert inputs, hip
Diagnostic joint arthrocentesis	100%, 80%, 90% Average = 90%	100%, 70%, 20% Average = 63.3%
Image guidance	50%, 50%, 30%* Average = 43.3%	80%, 100%, 100% Average = 93.3%
Anaesthesia	50%, 80%, 0% Average = 43.3%	100%, 80%, 0% Average = 60%

Notes:
* expert additionally noted 60% would be ultrasound 'prepared'.
Response 'always' imputed as 100%; response 'none' imputed as 0%.

Table 16 provides an overview of additional TARMED positions and medications associated with IAGI included in the cost analysis.

Table 16 Key TARMED positions and medications associated with intra-articular injections

Resource	Code	Tax points (AL + TL)	Cost per unit (CHF)	Comments
TARMED Services				
Physician visit	00.0010	18.61	16.40	Consultation, first 5 minutes
	+00.0020	18.61	16.40	Consultation, every additional 5 minutes (patient age 6–75 years)
	+00.0030	9.31	8.21	Consultation, last 5 minutes
Arthrocentesis	NA	NA	NA	Expert advice states there is no specific code for arthrocentesis (existing positions do not differentiate diagnostic vs therapeutic interventions)
Ultrasound	39.3700	97.46	85.90	Expert advice states that, while some practitioners may use fluoroscopy, ultrasound is more common
	or 39.3710	151.41	133.46	
Fluoroscopy	39.1110	108.02	95.21	
Local anaesthesia	00.1190	7.90	6.96	Local anaesthesia by injection into skin/subcutis/mucous membrane; other localisations up to 20 cm²
Medications				
Lidocaine	NA	NA	1.00 per 2 ml	Costing per expert advice
Carbostesine	NA	NA	6.05 per 5 ml	Costing per expert advice. One third of experts suggest lidocaine may be mixed with carbostesine (a preparation of bupivacaine)

Abbreviations: **AL**: medical service; **CHF**: Swiss franc; **NA**: not applicable; **TL**: technical performance.
Note: Tax points were valued using the mean 2024 cantonal tax point values (TPV: 0.88; simple average TPV across cantons, as reported by New Index).

7.4.1.1.3 Summary of total costs for IAGI

A summary of the expected per-patient cost per IAGI injection of the knee is provided in ***Table 17***.

Table 17 Summary of costs for IAGI of the knee

Resource	Code or preparation	Tax points per unit[A]	Price per unit (CHF)	Units	Proportion of patients using	Expected per patient cost (CHF)
TARMED services						
Joint puncture	24.0130	64.43	56.79	1	0.57 (0.50 to 0.70)[B]	32.37
Physician time	00.0010	18.61	16.40	1	1.00	16.40
	+ 00.0020	18.61	16.40	2.5 (1 to 4) [C]	1.00	41.00
	+ 00.0030	9.31	8.21	1	1.00	8.21
Ultrasound	39.3700 or 39.37100	97.46 or 151.41	109.68[D]	1	0.43 (0.30 to 0.50)	47.16
Local anaesthesia administration	00.1190	7.90	6.96	1	0.25[E]	1.71
Medication costs						
Triamcinalone	Kenacort® 40 mg/ml or Triamcort® Depot 40 mg/ml	NA	15.23	1	1.00	15.23
Local anaesthesia	Lidocaine	NA	1.00 per 2 ml	1–2 units	0.43 (0.00 to 0.80)	0.65
Cost per IAGI						
Expected per patient cost						162.72

Abbreviations: **CHF**: Swiss francs; **IAGI**: intra-articular glucocorticoid injection.
Notes:
A: Tax points valued using the mean 2024 cantonal tax point values (TPV: 0.88; simple average TPV across cantons, as reported by New Index).
B: If an ultrasound position (39.3700 or 39.3710) is claimed, the joint puncture item (24.0130) is not applicable. Calculated as 1.00 minus the proportion of patients using ultrasound.
C: 15- to 30-minute consultation (average 22.5-minute consultation used in base case).
D: Ultrasound price per unit calculated as simple average of TARMED positions 39.3700 and 39.3710.
E: If an ultrasound position (39.3700 or 39.3710) is claimed, the local anaesthesia by injection item (00.1190) is not applicable. Therefore, proportion of patients using this TARMED position was calculated as the proportion of patients receiving anaesthesia multiplied by the proportion of patients not using ultrasound.

Table 18 provides a summary of the expected per-patient cost per IAGI injection of the hip.

Table 18 Summary of costs for IAGI of the hip

Resource	Code or preparation	Tax points per unit[A]	Price per unit (CHF)	Units	Proportion of patients using	Expected per patient cost (CHF)
TARMED services						
Joint puncture	24.0140	72.03	61.95	1	0.07 (0.00 to 0.20)[B]	4.44
Physician time	00.0010	18.61	16.40	1	1.00	16.40
	+ 00.0020	18.61	16.40	2.5 (1 to 4)[C]	1.00	41.00
	+ 00.0030	9.31	8.21	1	1.00	8.21
Ultrasound	39.3700 or 39.3710	97.46 or 151.41	109.68[D]	1	0.93 (0.80 to 1.00)	102.00
Local anaesthesia administration	00.1190	7.90	6.96	1	0.04[E]	0.29
Medication costs						
Triamcinalone	Kenacort® 40 mg/ml or Triamcort® Depot 40 mg/ml	NA	15.23	1	1.00	15.23
Local anaesthesia	Lidocaine	NA	1.00 per 2 ml	1–2 units	0.60 (0.00 to 1.00)	0.90
Cost per IAGI						
Expected per patient cost						188.48

Abbreviations: **CHF**: Swiss francs; **IAGI**: intra-articular glucocorticoid injection.
Notes:
A: Tax points valued using the mean 2024 cantonal tax point values (TPV: 0.88; simple average TPV across cantons, as reported by New Index).
B: If an ultrasound position (39.3700 or 39.3710) is claimed, the joint puncture item (24.0140) is not applicable. Calculated as 1.00 minus the proportion of patients using ultrasound.
C: 15- to 30-minute consultation (average 22.5-minute consultation used in base case).
D: Ultrasound price per unit calculated as simple average of TARMED positions 39.3700 and 39.3710.
E: If an ultrasound position (39.3700 or 39.3710) is claimed, the local anaesthesia by injection item (00.1190) is not applicable. Therefore, proportion of patients using this TARMED position was calculated as the proportion of patients receiving anaesthesia multiplied by the proportion of patients not using ultrasound.

7.4.1.2 Standard care costs

Standard care costs considered were limited to the costs for concomitant pain relief medications.

Costs for physician visits associated with patient education, physiotherapy-led exercise programs and any other components of standard care (e.g. insoles) were excluded from the cost analysis, given no data on the impact of IAGI on their use were identified in the clinical review. If incurred, these costs would apply across both treatment arms and are not expected to be impacted by the use of IAGI.

The clinical evaluation (***Section 6***) provided data on whether the use of IAGI affected the amount of pain relief medication required, based on included RCT evidence. The results and associated costings are summarised below for knee and hip OA in turn.

7.4.1.2.1 Knee OA

The meta-analysis presented in ***Section 6.2.5.1*** reported a significant difference in rescue medication use in favour of IAGI at 1 month and no significant differences at 3 or 6 months (***Figure 5).*** These findings were based on data reported in a single RCT.[97]

Conaghan 2018 recorded rescue medication use as the mean (± standard error [SE]) number of daily rescue medication tablets (500 mg) per week, up to 24 weeks follow-up.[97] In the trial, analgesic medications for index-knee pain were withheld, with the exception of acetaminophen or paracetamol (≤3,000 mg/day; 500 mg tablets provided as rescue treatment).

For the cost analysis, data for daily rescue medication use per week were extracted using WebPlotDigitizer.[140] These data were used to estimate total tablets consumed per week and added to calculate the cumulative number of tablets consumed over 6 months. A small cost offset (CHF5.63) associated with IAGI use was derived (***Table 19***).

Table 19 Calculated rescue medication use over 6 months for knee OA

Treatment arm	Tablets consumed over 6 months	Cost per tablet (CHF)	Total cost over 6 months (CHF)
IAGI	174.16 (SE: 4.90)	0.14	24.38 (95% CI: 23.03 to 25.75)
Placebo	214.35 (SE: 4.90)	0.14	30.00 (95% CI: 28.65 to 31.37)
Incremental			-5.63 (95% CI: -7.54 to -3.74)

Abbreviations: **CHF**: Swiss franc; **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **SE**: standard error.
Note: Cost (CHF) per 500 mg tablet calculated as the average cost/tablet across all 500 mg tablet packs listed on the Spezialitätenliste (as of January 2024).[141]

7.4.1.2.2 Hip OA

The meta-analysis presented in ***Section 6.2.5.2*** reported no significant differences in rescue medication utilisation at 1 month (***Figure 9***). These findings were based on data reported in a single RCT.[114]

Lambert 2007 reported rescue medication use as a monthly pill count at 1- and 2-month follow-up.[114] In the trial, medications were monitored using a medication log, with intake of analgesics assessed by pill count. Patients were asked to maintain a constant NSAID dosage throughout the trial.

In the cost analysis, costs for rescue medication were calculated by adding the reported monthly medication use to calculate cumulative use over 2 months. The type of medication the pill count referenced was not reported in the study. It was conservatively assumed that pill count reflected paracetamol use. The resulting incremental costs suggest uncertainty as to whether IAGI is associated with any cost offsets over 2 months (***Table 20***).

Table 20 Calculated rescue medication use over 2 months for hip OA

Treatment arm	Tablets consumed over 2 months	Cost per tablet (CHF)	Total cost over 2 months (CHF)
IAGI	67.2 (SE: 13.8)	0.14	9.43 (95% CI: 5.67 to 13.14)
Placebo	107.8 (SE: 27.1)	0.14	15.14 (95% CI: 7.83 to 22.50)
Incremental cost			-5.71 (95% CI: -13.95 to 2.46)

Abbreviations: **CHF**: Swiss franc; **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **SE**: standard error.
Note: Cost (CHF) per 500 mg tablet calculated as the average cost/tablet across all 500 mg tablet packs listed on the Spezialitätenliste (as of January 2024).[141]

7.4.1.3 Adverse event costs

No AE costs were included in the cost analysis, as no significant difference in rates was found in the trials, with included studies suggesting IAGI are safe (***Section 6.2.6***).

7.4.1.4 Joint replacement costs

Clinical evidence for the impact of IAGI on progression to joint replacement is limited. Indeed, none of the included studies reported total joint replacement surgery rates as an outcome measure. A narrative summary of the potential economic impacts of delaying knee replacement surgery is provided as an adjunct to the results of the cost-effectiveness analysis. Nevertheless, no link between IAGI and delayed total knee arthroscopy (TKA) could be established in this HTA.

7.4.2 Modelled health outcomes

In this section, the translation of clinical data into an estimate of incremental benefit in terms of QALYs lived, is described.

7.4.2.1 Pooled WOMAC domain scores

Studies reporting WOMAC pain and function scores were identified from the studies included in the clinical evidence review (***Section 6***). Both pain and function WOMAC scores were reported by 4 studies included in the clinical evidence review. One study in which multiple injections were provided over the follow-up period was not further considered for modelling because the modelling sought to capture QALY benefits per injection.[102]

Poor reporting of WOMAC scores across studies assessing the benefits of physical therapies for knee OA has previously been documented, resulting in uncertainty in the interpretation of individual trial results.[142] Studies reporting WOMAC scores included in this review suffered from this same limitation. A summary of the assumptions needed to standardise the reported WOMAC pain and function scores is included in ***Table 21***. For one study, it was impossible to make a reliable assumption about the reporting of WOMAC scores, so this study was not further considered for the modelling.[95]

Table 21 Reported and adjusted WOMAC pain and function scores at baseline

Study ID	Mean reported pain score (SD)	Mean reported function score (SD)	Mean adjusted pain score 0–20 (SD)	Mean adjusted function score 0–68 (SD)	Comments
Conaghan 2018[97]	IAGI: 2.0 (0.52) Placebo: 2.0 (0.52)	IAGI: 2.1 (0.58) Placebo: 2.1 (0.51)	IAGI: 10.0 (2.60) Placebo: 10.0 (2.60)	IAGI: 35.7 (9.86) Placebo: 35.7 (8.67)	Study implies mean (SD) scores reported on a 0–4 scale.
Smith 2003[111]	IAGI: 10.3 (3.2) Placebo: 9.2 (2.2)	IAGI: 34.6 (11.6) Placebo: 31.0 (8.1)	IAGI: 10.3 (3.20) Placebo: 9.2 (2.2)	IAGI: 34.63 (11.6) Placebo: 31.0 (8.1)	Baseline values suggest reporting using standard Likert score range.
Tschopp 2023[95]	IAGI: 2.25 (1.00–3.50) [A] Placebo: 2.0 (1.50–3.50) [A]	IAGI: 2.05 [0.90–3.72] [A] Placebo: 1.40 [0.70–2.30] [A]	NE	NE	Impossible to determine score range used for reporting. Study authors contacted for clarity without success.

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **NE**: not estimable; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.
Notes:
A: data reported as median [IQR]

WOMAC pain and function scores for IAGI and standard care (placebo) cohorts were adjusted to the 0–20 and 0–68 score ranges, respectively, if required. Pooled mean WOMAC pain and function scores were then calculated using the inverse variance weighting method. The included studies reported WOMAC scores at baseline and at 1-, 3- and 6-month follow-up.[97, 111] ***Table 22*** summarises the derived total weighted mean scores.

Table 22 Pooled WOMAC pain and function scores

Intervention, WOMAC domain (score range)	Baseline	1 month	3 months	6 months
IAGI				
WOMAC pain (0–20)	10.15 (0.17)	6.03 (0.27)	7.02 (0.38)	7.78 (0.43)
WOMAC function (0–68)	35.22 (0.53)	23.01 (1.54)	25.94 (1.95)	28.51 (1.83)
Standard care				
WOMAC pain (0–20)	9.57 (0.40)	7.54 (0.02)	7.30 (0.15)	7.32 (0.10)
WOMAC function (0–68)	33.12 (2.34)	27.75 (0.59)	25.54 (0.36)	26.13 (0.87)

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.
Notes: Data from Conaghan 2018 and Smith 2003 were pooled.[97, 111] Results reported as weighted mean with standard deviation (SD).

7.4.2.1.1 Representativeness of studies included in economic analysis

To determine if the pooled WOMAC estimates generated from Conaghan 2018 and Smith 2003 that informed the model were representative of the clinical review estimates (***Section 6.2***) z-tests were performed on SMD effect estimates (see ***Appendix 13.6.5***).

The majority of the post-hoc-generated pooled WOMAC SMD effect estimates for pain and function were representative of the pooled estimates generated for the clinical review. Despite most estimates being representative, some of the post-hoc-generated summary measures were either an overestimation (i.e. pain at 1 month, function at 1 month, function at 3 months) of the IAGI treatment effect or an underestimation (i.e. pain at 6 months) of the placebo effect, relative to the clinical review. The combined impact that the overestimation of the IAGI treatment effect and underestimation of the placebo-effect may have had on the translated utilities and QALYs gained estimates is unknown. Therefore, it is imperative that the output of the CUA be interpreted with caution. The complete comparison between the pooled estimates is detailed in ***Appendix 13.6.5, Table 60***.

7.4.2.1.2 Applicability of studies included in economic analysis

A comparison between the health economics model population and the Swiss population, as defined in ***Section 6.2.4***, was made to assess the applicability of the studies included in the economic modelling to the Swiss context.

Overall, the model population is broadly consistent with the Swiss population and healthcare context (***Table 23***). The demographics (age, gender, BMI) of the 2 populations are comparable. The medical settings in which the model population received IAGI (or placebo) were comparable to the Swiss context. The studies informing the model population took place in both inpatient and outpatient healthcare settings, in jurisdictions considered to be WHO Mortality Stratum A. Triamcinolone acetate 40 mg was the main form of IAGI used among the model population, with it being the glucocorticoid used in the larger of the 2 studies (Conaghan 2018).[97] This is consistent with the Swiss context, in which triamcinolone is the most common glucocorticoid used. Methylprednisolone acetate (120 mg) was administered in the second study (Smith 2003).[111] This was not representative of the dose (20 to 80 mg) recommended for use in a large joint such as knees in Switzerland (***Table 39***). In the Swiss context only 1.8% of the population received methylprednisolone acetate for knee OA, substantially less than the 18% in the model population. It is unclear if these differences could have had any significant impact on the economic findings. A conclusion on the applicability of the KL grade reported in the model population to the Swiss context could not be drawn due to a lack of appropriate evidence.

Table 23 Applicability of the model population to the Swiss healthcare context for knee OA

Parameter		Swiss population characteristics	Conaghan 2018[97] patient characteristics	Smith 2003[111] patient characteristics	Model population †	
					Patient characteristics	Applicability to Switzerland
Sample size		NA	323	71	394	NA
Demographics	Female (n)	61.8% (NR)	59.75% (193)	38.03% (27)	55.84% (220)	Yes
	Age (mean [SD], years)	64.7 (NR)	62.35 (9.49)	66.84 (10.68)	63.16 (9.85)	Yes
	BMI (mean [SD], kg/m^2)	27.4 (5.2)	30.25 (4.75)	29.53 (4.76)	30.12 (4.75)	Yes
	KL grade (%, [n])	Unclear	1 = 0% (0) 2 = 42.72% (138) 3 = 56.97% (184) 4 = 0.31% (1)	NR	Unable to combine	Unclear
Intervention (%, large joint dose)		• Triamcinolone (84.36%, 20 to 40 mg) • Betamethasone (9.28%, 1 ml) • Dexamethasone (3.70%, 4 to 6 mg) • Methylprednisolone (1.75%, 20 to 80 mg) • Methylprednisolone combination ‡ (0.91%, NR)	Triamcinolone acetonide (100%, 40 mg)	Methylprednisolone acetate (100%, 120 mg)	• Triamcinolone acetonide (82%, 40 mg) • Methylprednisolone acetate (18%, 120 mg)	• Triamcinolone acetonide: Yes • Methylprednisolone acetate: No
Medical setting		• Inpatient • Outpatient	Outpatient	Inpatient	• Inpatient • Outpatient	Yes

Parameter	Swiss population characteristics	Conaghan 2018[97] patient characteristics	Smith 2003[111] patient characteristics	Model population †	
				Patient characteristics	Applicability to Switzerland
Location	Switzerland	• USA • Canada • Australia • New Zealand • Hong Kong (China) • European Union	Australia	• USA • Canada • Australia • New Zealand • Hong Kong (China) • European Union	Yes

Abbreviations: **BMI**: body mass index; **kg/m²**: kilograms per metres squared; **KL**: Kellgren–Lawrence; **mg**: milligrams; **ml**: millilitres; **n**: not reported; **NA:** not applicable; **NR**: not reported; **OA**: osteoarthritis; **SD**: standard deviation; **USA**: Untied States of America.

Notes:

† Combined population of Conaghan 2018 and Smith 2003.[97, 111]

‡ Combination of methylprednisolone acetate and lidocaine (Depo Medrol® Lidocaine)

7.4.2.2 Predicted preference-based utility scores

EQ-5D utility scores for IAGI and standard care cohorts at baseline and 1-, 3- and 6-month follow-up were predicted from the pooled WOMAC domain scores using the preferred GLM model presented by Bilbao 2020 (***Section 7.3.7***). EQ-5D-5L utility index scores for IAGI and standard care at each timepoint are summarised in ***Table 24***.

Table 24 Predicted EQ-5D-5L utility index scores at baseline and 1-, 3- and 6-month follow-up

Intervention	Baseline	1 month	3 months	6 months
IAGI	0.55 (0.01)	0.72 (0.02)	0.68 (0.02)	0.65 (0.02)
Standard care	0.58 (0.03)	0.66 (0.01)	0.69 (0.004)	0.68 (0.01)

Abbreviations: **EQ-5D-5L**: EuroQoL5-dimension questionnaire, 5-level version; **IAGI**: intra-articular glucocorticoid injection.

7.4.2.3 Estimated QALYs gained

QALYs gained over 6 months were estimated for the IAGI and standard care arms using the relevant equation presented in ***Section 7.3.7***. Results are provided in ***Table 25***.

Table 25 Estimated incremental QALYs gained at 6-month follow-up

Intervention	QALYs gained (6 months)	Incremental QALYs gained
IAGI	0.061 (0.007)	0.013 (0.016)
Standard care	0.048 (0.014)	

Abbreviations: IAGI: intra-articular glucocorticoid injection; **QALY**: quality-adjusted life year.

7.4.3 Cost-effectiveness outcomes

7.4.3.1 ICER

The base case ICER is presented in ***Table 26***. The ICER captures the incremental cost per additional QALY gained.

Table 26 Base case incremental-cost effectiveness ratio

	Cost (CHF)	Incremental cost (CHF)	Effectiveness (QALYs gained)	Incremental effectiveness	ICER (CHF per QALY)
IAGI	187.11	157.10	0.061	0.013	12,456
Standard care	30.01		0.048		

Abbreviations: CHF: Swiss franc; **IAGI**: intra-articular glucocorticoid injection; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year.

The base case ICER for IAGI versus standard care was estimated to be CHF12,456 per QALY gained. The incremental cost, which reflects the additional costs for IAGI (relative to no injections), as well as differences in consumption of pain relief medication across arms, was estimated to be CHF157.10. This included an incremental cost of CHF162.72 for IAGI and an incremental cost of CHF-5.63 (i.e. a small cost saving) for paracetamol consumption. IAGI was found to be more

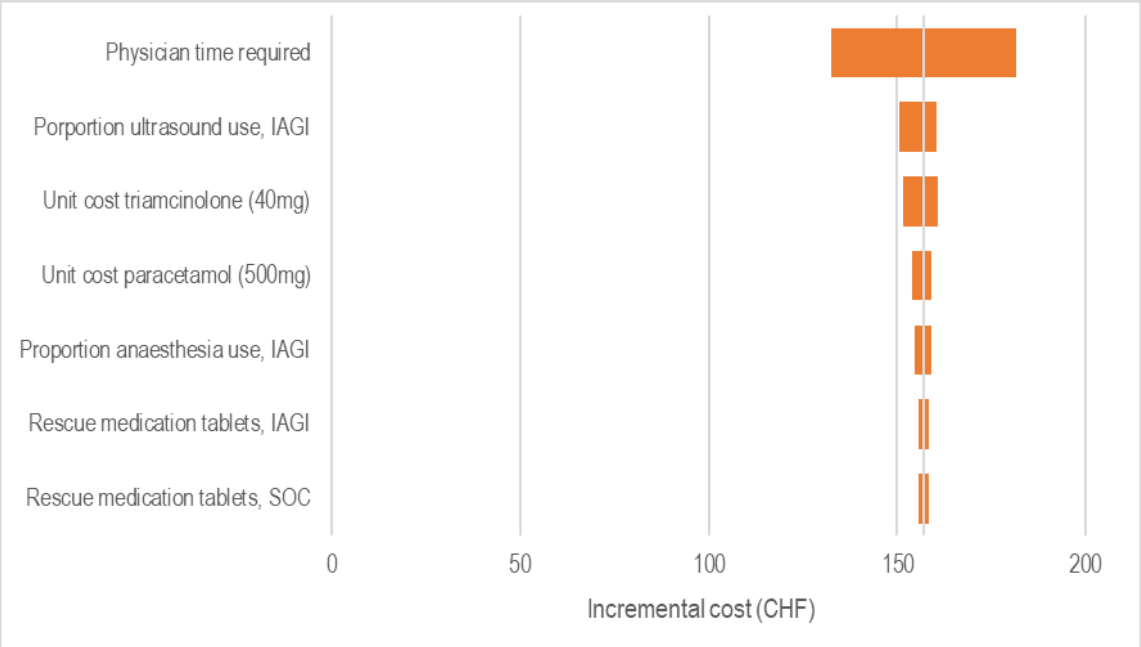
effective than standard care alone (incremental QALYs gained of 0.013 over 6 months) although sensitivity analysis showed this to be highly uncertain.

7.4.3.2 Uncertainty analysis

7.4.3.2.1 Univariate sensitivity analysis

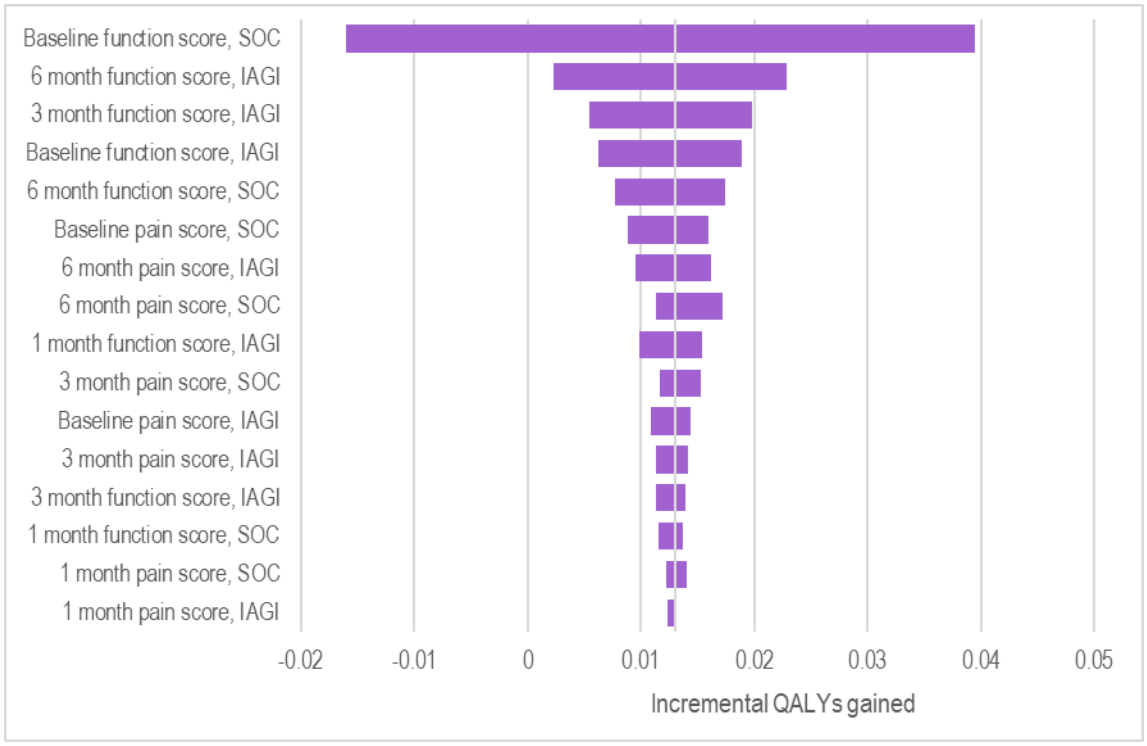
DSA results were presented visually using tornado diagrams. Tornado diagrams against incremental cost (***Figure 15***), incremental QALYs gained (***Figure 16***) and the ICER (***Figure 17***) are presented.

Figure 15 Tornado diagram against incremental costs for IAGI vs standard care



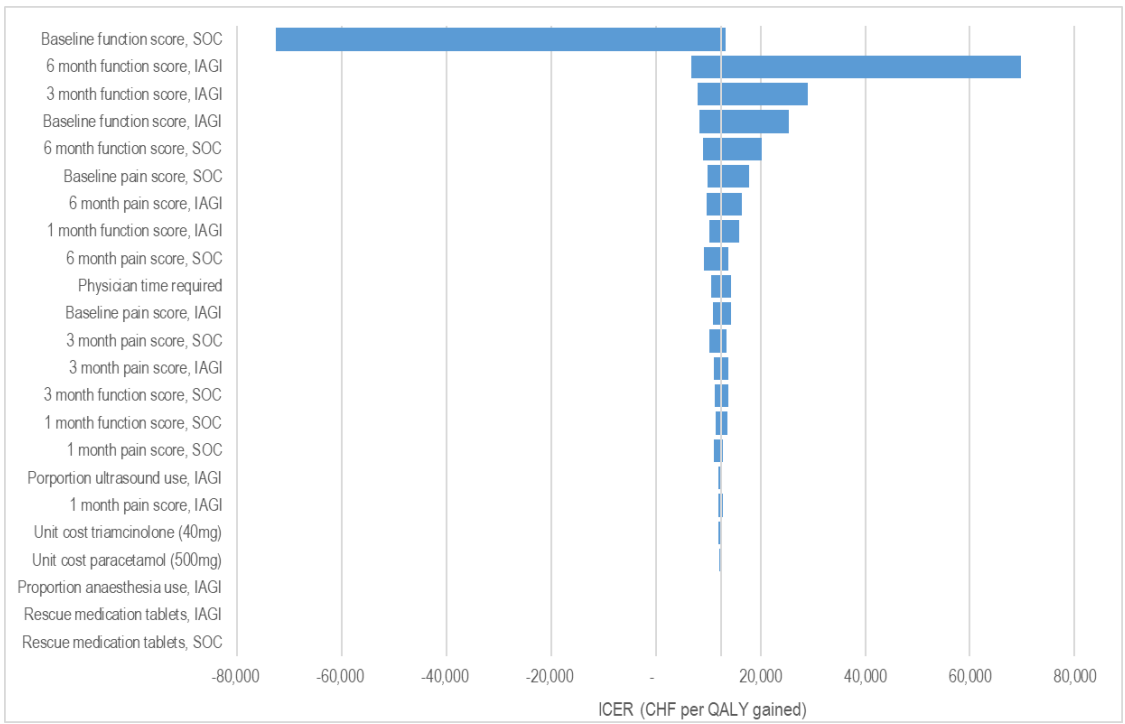
Abbreviations: **CHF**: Swiss franc; **IAGI**: intra-articular glucocorticoid injection; **SOC**: standard of care.

Figure 16 Tornado diagram against incremental QALYs gained for IAGI vs standard care



Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **QALY**: quality-adjusted life year; **SOC**: standard of care.

Figure 17 Tornado diagram against the ICER for IAGI vs standard care



Abbreviations: **CHF**: Swiss franc; **IAGI**: intra-articular glucocorticoid injection; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **SOC**: standard of care.

Notes:

Negative ICER: The results fall in the north-west quadrant of the cost-effectiveness plane (i.e. IAGI is more costly and less effective than standard care). These ICERs reflect situations in which IAGI is dominated by standard care.

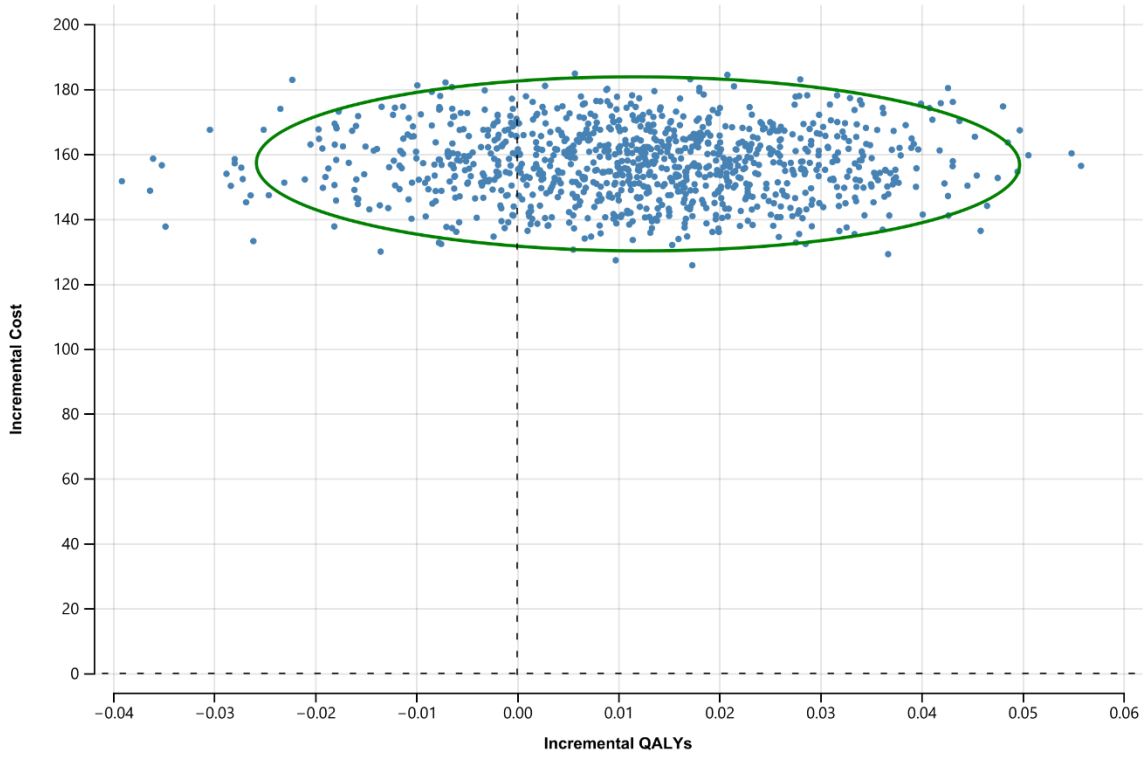
Univariate sensitivity analysis demonstrated the pooled WOMAC domain scores—in particular, the baseline WOMAC function score in the standard-care arm and the 6-month function score in the IAGI arm—to be the most important drivers of the ICER (***Figure 17***). In univariate sensitivity analysis, the baseline WOMAC function score in the standard-care arm was the only variable to invert the expected incremental QALYs gained from positive (favouring IAGI) to negative (favouring standard care; ***Figure 16***). When expected incremental QALYs gained are negative, IAGI is dominated by standard care.

The largest driver of incremental costs was the expected time required by physicians to administer IAGI (***Figure 15***). The impact of uncertainty in incremental costs was small compared to the impact of uncertainty on the incremental effectiveness side of the ICER equation. Expected incremental costs remained positive, at between CHF132 and CHF182 across all DSA scenarios.

7.4.3.2.2 Probabilistic sensitivity analysis

PSA captures the joint uncertainty across model parameters, giving decision-makers information on the overall certainty of the economic outcomes. Incremental cost-effect pairs from the PSA simulations were presented on the cost-effectiveness plane and a 95% confidence ellipse was drawn (***Figure 18***). A CEAC was also produced (***Figure 19***).

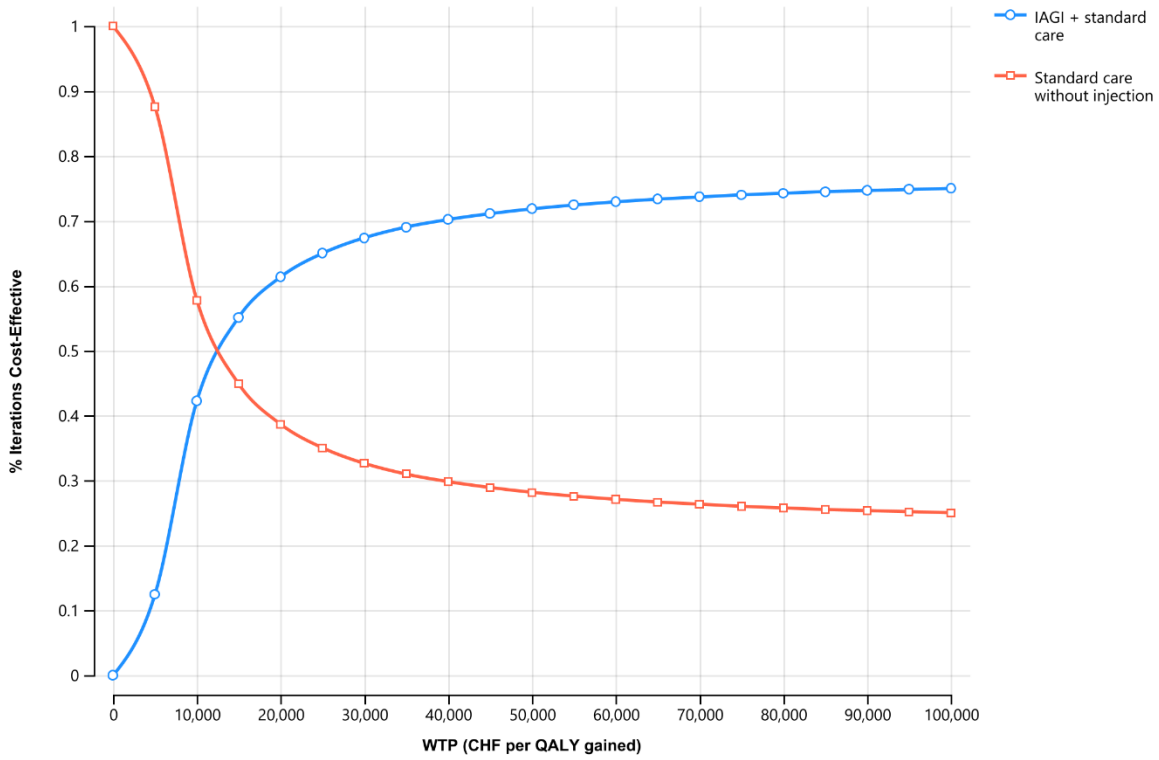
Figure 18 Scatter plot of incremental cost-effect pairs on the cost-effectiveness plane for IAG vs standard care



Abbreviations: **QALY**: quality-adjusted life year.

It is evident from the scatter plot that IAGI, when provided as an adjunct to standard care, is more expensive than standard care alone. Mean expected incremental cost is CHF 157.09 (95% CI 136.74 to 177.35). The scatter plot further suggests uncertainty around the clinical benefits of IAGI, with an expected mean incremental QALY of 0.013 (95% CI -0.019 to 0.044), meaning the incremental benefit ranges from favouring IAGI to favouring standard care alone. Overall, around 22.0% of iterations fall in the fourth quadrant of the cost-effectiveness plane, where IAGI is dominated (i.e. is more expensive and less effective than standard care).

Figure 19 Cost-effectiveness acceptability curve for IAGI vs standard care



Abbreviations: **CHF**: Swiss franc; **IAGI**: intra-articular glucocorticoid injection; **QALY**: quality-adjusted life year; **WTP**: willingness-to-pay.

The CEAC suggests a higher probability that IAGI is cost effective relative to standard care alone beyond a WTP threshold of approximately CHF13,000. At a hypothetical WTP of CHF50,000, IAGI demonstrated a 71.9% probability of being cost effective. At a hypothetical WTP of CHF100,000, this probability increased slightly to 75.0%.

7.4.4 Other considerations

7.4.4.1 Frequency and duration of therapy

The economic analysis estimated the cost utility associated with a single IAGI in the management of knee OA. In contrast, the published economic evaluation assumed continued use of IAGI at a rate of 4 injections/year to maintain treatment effect.[123] The exact duration of time over which patients were modelled to receive IAGI in the evaluation was unclear.

To provide context on utilisation patterns of IAGI in Switzerland, Swiss clinicians were consulted for their expert opinion regarding how frequently (on average) patients with OA of the knee or hip are likely to receive IAGI, and for how long (on average) patients would be likely to continue to receive IAGI to manage their OA. A summary of clinician responses is provided in ***Table 27***.

Table 27 Clinician feedback regarding frequency of IAGI injections and duration of treatment in Switzerland

Question	Responses	Comments
OA of the knee		
How frequently, on average, are patients with OA of the knee likely to receive IAGI?	Maximum of 3–4/year if reduction in pain Up to 3/year 1–2/year	Dependent on whether a reduction in pain is achieved
For how long, on average, are patients likely to continue to receive IAGI to manage their knee OA?	Up to 2 years 3 years 5–8 years	Patients with knee OA may have a longer conservative treatment period. Patients eligible for surgery will most likely have a knee replacement within 2 years in Switzerland.
OA of the hip		
How frequently, on average, are patients with OA of the hip likely to receive IAGI?	Maximum of 3–4/year if reduction in pain 1/year <1/year	Dependent on whether a reduction in pain is achieved
For how long, on average, are patients likely to continue to receive IAGI to manage their hip OA?	Patients likely to get hip replacement if repeat injections needed 2 years 2–4 years	In Switzerland, access to hip surgery is fast. Patients with a continuous need for injections are likely to have a hip joint replacement. In rare cases, young patients or those ineligible for surgery will receive repeat injections.

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.

Swiss health insurer data were also analysed to assess the frequency of IAGI and the duration of IAGI management. Annual frequency of use figures for patients with a diagnosis of knee or hip OA included in the dataset are summarised in ***Table 28*** and ***Table 29***, respectively. Duration of use data are summarised in ***Table 30***.

Table 28 Frequency of IAGI among patients with knee OA, health insurer data

Statistical measures	2018	2019	2020	2021	2022	2023
Mean	1.57	1.69	1.70	1.53	1.64	1.52
25th percentile	1.00	1.00	1.00	1.00	1.00	1.00
Median	1.00	1.00	1.00	1.00	1.00	1.00
75th percentile	2.00	2.00	2.00	2.00	2.00	2.00
90th percentile	3.00	3.00	3.00	3.00	3.00	3.00

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.

Table 29 Frequency of IAGI among patients with hip OA, health insurer data

Statistical measures	2018	2019	2020	2021	2022	2023
Mean	1.32	1.66	1.56	1.53	1.54	1.57
25th percentile	1.00	1.00	1.00	1.00	1.00	1.00
Median	1.00	1.00	1.00	1.00	1.00	1.00
75th percentile	1.25	2.00	2.00	2.00	2.00	2.00
90th percentile	2.00	3.00	3.00	2.70	3.00	2.60

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.

Table 30 Duration of IAGI use among patients with OA of the knee or hip, health insurer data

Diagnosis category	Mean (years)	Median (IQR) (years)	90th percentile (years)
Knee OA	0.71	0.09 (0, 0.87)	2.62
Hip OA	0.60	0.07 (0, 0.67)	2.08

Abbreviations: **IQR**: interquartile range; **OA**: osteoarthritis.

Analyses provided by a large Swiss insurer indicate that at the higher end (90th percentile) of IAGI users for knee OA, patients receive 3 IAGI annually (2018–2023; ***Table 28***) and for hip OA 2–3 IAGI annually (2018–2023; ***Table 29***). This appears to align with clinical expert opinion, which indicated patients may receive 1–2 IAGI/year up to a maximum of 3–4 IAGI/year for knee OA and <1 IAGI/year up to a maximum of 3–4 IAGI/year for hip OA, depending on whether a reduction in pain is achieved (***Table 27***). The clinical evidence review demonstrated reductions in pain at 1 month after IAGI that do not persist at longer timepoints, suggesting repeat injections may be needed to maintain treatment effect (as modelled for knee OA patients in Wilson 2020).[123] Importantly, no serious safety concerns attributed to IAGI use were identified in the clinical evidence review.

Similarly, the duration of IAGI use observed in the Swiss insurer dataset appears to fall within expectations, with the 90th percentile figures (2.62 years for knee; 2.08 years for hip; (***Table 30***) falling within the ranges expressed in the clinical expert opinion (***Table 27***).

7.5 Budget impact

7.5.1 Methodology for budget impact analysis

7.5.1.1 Justification and selection of data sources

The current budget impact of IAGI was derived using the estimated per patient cost per injection (***Section 7.4.1***). These estimates were combined with the calculated annual numbers of IAGI injections to estimate the expect cost of IAGI for management of primary OA of the knee or hip to the Swiss healthcare payer.

The total number of patients with primary OA of the knee or hip that received at least one IAGI service, and the total number of IAGI services provided to patients with primary OA of the knee or hip, were provided by a large Swiss insurer annually over the period 2018–2023. Patients with primary OA of the knee or hip were identified according to relevant ICD-10-GM codes (hip: M16.0, M16.1, M16.9; knee: M17.0, M17.1, M17.9). IAGI services were identified as claims made for TARMED position 24.0130 or 24.0140 in combination with glucocorticoid medication in the same benefit case. Estimates provided by the insurer were then extrapolated to the entire Swiss population. Data from the insurer also provided background demographic information on patients receiving IAGI in Switzerland. Expected IAGI figures were extrapolated over 5 years (2025–2029) to predict the future budget impact of the service.

No scenario modelling was undertaken to explore the potential budget impact of limitation or disinvestment on use in Switzerland.

A summary of the data sources applied in the utilisation and financial impact estimates is provided in ***Table 31***.

Table 31 Data sources applied in the utilisation and financial impact estimates for IAGI use in Switzerland

Data	Source	Justification
Patients with OA of the hip or knee receiving at least one IAGI service	Data from one large insurer, extrapolated to total Swiss population (2018–2023).	Patients with primary OA of the knee, hip, or knee + hip were identified according to relevant ICD-10-GM codes (hip: M16.0, M16.1, M16.9; knee: M17.0, M17.1, M17.9). Those with at least one IAGI service (TARMED position 24.0130 or 24.0140 in combination with a glucocorticoid medication) were selected. These figures were extrapolated to the Swiss population using the ratio of Swiss population: persons insured by the insurer.
IAGI services provided to patients with primary OA of the knee or hip	Data from one large insurer	Analysis of insurance data on the frequency of IAGI injection per patient per year (***Table 28*** and ***Table 29***).
Cost per IAGI injection	Expected average per patient injection costs calculated as part of the cost analysis.	Expected average per patient costs per injection were calculated as part of the cost analysis. Results for knee and hip injections were previously reported in ***Table 17*** and ***Table 18***, respectively.

Data	Source	Justification
Cost offsets	Expected average per patient cost offsets from reduced paracetamol use. Calculated based on data presented by Conaghan 2018 (knee) and Lambert 2007 (hip).[97, 114]	Expected average per patient cost offsets (per injection) due to reduced pain relief medication consumption were calculated as part of the cost analysis. Results for knee and hip injections were previously reported in ***Table 19*** and ***Table 20***, respectively. Uncertainty was explored in sensitivity analysis.

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **ICD-10-GM**: International Classification of Diagnoses, 10th revision, German medication; **OA**: osteoarthritis.

7.5.1.2 Background data

Table 32 summarises the derived number of patients in Switzerland with primary OA of the knee or hip that received at least one IAGI, as estimated using data from a large insurer, extrapolated to the total Swiss population. The total number of IAGI services provided to patients with primary OA of the knee or hip between 2018 and 2023—again as estimated using data from a large insurer extrapolated to the total Swiss population—are also summarised (***Table 32***).

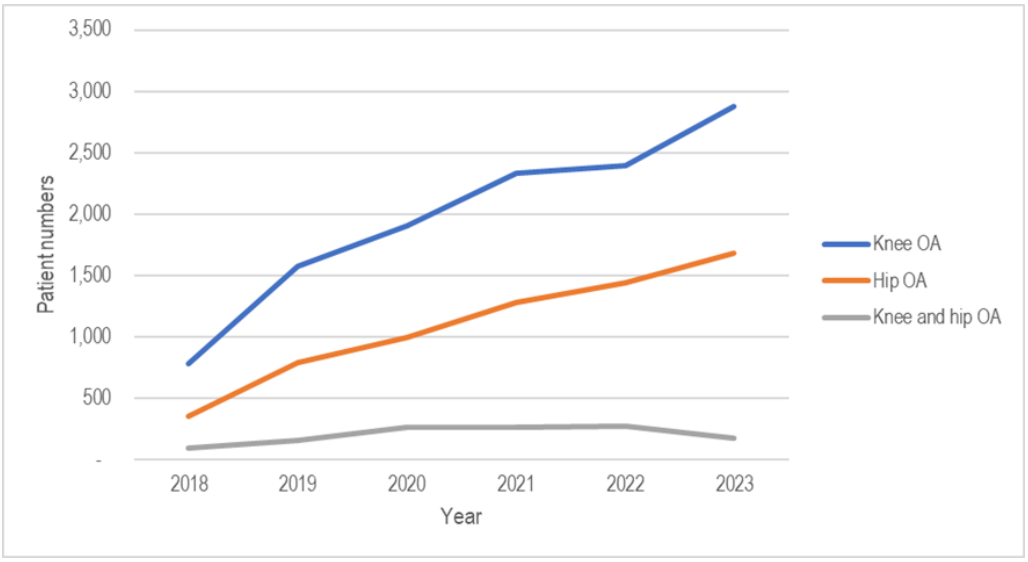
Table 32 Estimated patient and IAGI service numbers across Switzerland, 2018–2023

Description	2018	2019	2020	2021	2022	2023
Patient numbers						
Patients with OA of the knee receiving at least one IAGI	784	1,574	1,903	2,330	2,397	2,878
Patients with OA of the hip receiving at least one IAGI	358	793	992	1,282	1,439	1,687
Patients with OA of the hip + knee receiving at least one IAGI	99	154	268	270	275	177
Injection numbers						
Total knee IAGI services provided to patients with primary OA	1,342	2,839	3,520	3,829	4,197	4,563
Total hip IAGI services provided to patients with primary OA	499	1,410	1,708	2,136	2,339	2,749

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.
Source: Patient and injection numbers derived from claims data from a large Swiss insurer, extrapolated to the entire Swiss population.

Total knee and hip IAGI patient numbers from 2018 to 2023 for Switzerland are displayed visually in ***Figure 20***.

Figure 20 Estimated IAGI service numbers over the period 2018–2023



Abbreviations: **IAGI**: intra-articular glucocorticoid injection.
Source: Patient numbers derived from claims data from a large Swiss insurer, extrapolated to the entire Swiss population.

Figure 20 suggests a step annual growth in the number of patients receiving IAGI. However, uncertainties in the underlying data were identified in relation to:

- accuracy of the growth rate suggested; concerns that growth observed in the dataset was partly an artifact of increasing completeness of ICD-10 diagnosis data
- completeness of IAGI service number estimates; concerns of incomplete diagnosis data
- injections performed using ultrasound would only incur TARMED costs for positions 39.110, 39.3700 or 39.3710 (identification of injections using only TARMED positions 24.0130 and 24.0140 may have overlooked some injections).

Accordingly, additional data and expert input were sought to inform estimates of IAGI utilisation and expected growth, as detailed below.

7.5.1.2.1 Growth rate

Expert clinical advice indicates the use of IAGI is expected to remain relatively stable. One expert noted IAGI is an old treatment and there are no foreseen changes in treatment guidelines. However, experts acknowledged demographic changes may drive an overall increase in injection numbers. Potential for a slight increase in the use of ultrasound-guided IAGI was noted by one expert; another noted observing a decreasing number of injections per patient per year.

Overall, expert clinical advice confirmed that the growth observed in the insurance dataset is unlikely to reflect trends in IAGI use.

Two growth rate estimates—whose patterns were identified as most likely by clinical experts—were employed for the extrapolations:

- Predicted growth in prevalent knee OA and hip OA patient numbers reported in the 2021 Global Burden of Disease study for Western Europe: compound annual growth rate (CAGR) between 2020 to 2050 of 0.7% and 0.9% p.a. for knee OA and hip OA, respectively.[143] Note this closely reflects Swiss adult (≥18 years) population growth (CAGR between 2018 to 2022 of 0.8% p.a.).
- Observed growth in the number of primary TKA and total hip arthroplasty procedures for primary OA reported by the Swiss National Hip & Knee Joint Registry (2023 report): CAGRs between 2018 to 2022 of 6.1% p.a. for TKA and 3.5% p.a. for THA.[116]

For the base case, average estimates of annual growth (weighted by expert responses; 4.3% p.a. for knee, 2.6% p.a. for hip) were used. The alternate sources were used interchangeably to inform the lower and upper bounds for sensitivity analysis.

7.5.1.2.2 Patient numbers

Patients diagnosed with knee and hip OA were distributed based on the relative number of knee/hip patients in the rest of the cohort. This adjustment was made to the 2023 Swiss patient numbers derived from the insurance dataset (***Table 33).***

Table 33 Derived number of patients receiving IAGI for knee OA or hip OA, 2023

	Extrapolated from insurance data	Extrapolated for insurance data, with adjustment
Patients with OA of the knee receiving at least one IAGI	2,878	2,989[A]
Patients with OA of the hip receiving at least one IAGI	1,687	1,752[B]
Patients with OA of the hip + knee receiving at least one IAGI	177	0

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.
Notes:
A: Calculated as 2,878+(177*(2,878/(2,878+1,687)))
B: Calculated as 1,687+(177*(1,687/(2,878+1,687)))
Source: Patient numbers derived from claims data from a large Swiss insurer, extrapolated to the entire Swiss population.

Expert clinical advice variably expressed concerns that patient numbers extrapolated from the insurance dataset may underestimate the true number of patients receiving IAGI across Switzerland (one expert indicated the estimates may be reasonable; one felt they may be underestimated; a third felt they may be underestimated for knee OA [~20%] but overestimated for hip [~10%]).

Estimates derived directly from the insurance dataset were used in the base case. In sensitivity analysis, they were increased by 20% for knee OA and varied ±10% for hip OA.

7.5.1.2.3 Injections per patient

Expert opinion regarding the frequency of use of IAGI injections suggests patients may receive anywhere from 1–4 injections per year, depending on whether a reduction in pain is achieved.

Analysis of insurance data indicates an average annual use of 1.52–1.70 injections for knee OA patients and 1.32–1.66 for hip OA patients (***Table 28*** and ***Table 29***). Expert opinion agrees the utilisation estimates for knee OA (1.52–1.70 per patient) may be reasonable. For hip OA, one expert felt utilisation may be overestimated (more likely 1–1.2 per patient); 2 experts agreed they were reasonable.

For the base case, average estimates from the insurance dataset (1.61 for knee OA; 1.53 for hip OA) were used to estimate the total number of IAGI per year. In sensitivity analysis, estimates were varied across the ranges reported in the insurance dataset. For hip OA, scenario analysis applying a utilisation rate of 1.1 (average of 1–1.2) per patient per year was also undertaken.

7.5.1.2.4 Alternate estimate for knee OA

A crude estimate of the number of patients expected to use IAGI annually was made by multiplying the number of incident cases per year by expert estimates of utilisation.

Incident case numbers were derived from Obermüller 2024, a retrospective analysis of German health claims data.[144] This study found yearly incidence proportions to remain quite stable over time. In this same study, longitudinal analysis of patients first diagnosed in 2015 indicated that 62.4% of incident knee OA patients were prescribed any of the guideline-recommended analgesic prescription medications during follow-up. The proportion who received glucocorticoids specifically was not reported.

Expert clinical advice indicates that, of knee OA patients who are prescribed pain relief medication, 5–15% (weighted average: 10.8%) may be prescribed IAGI.

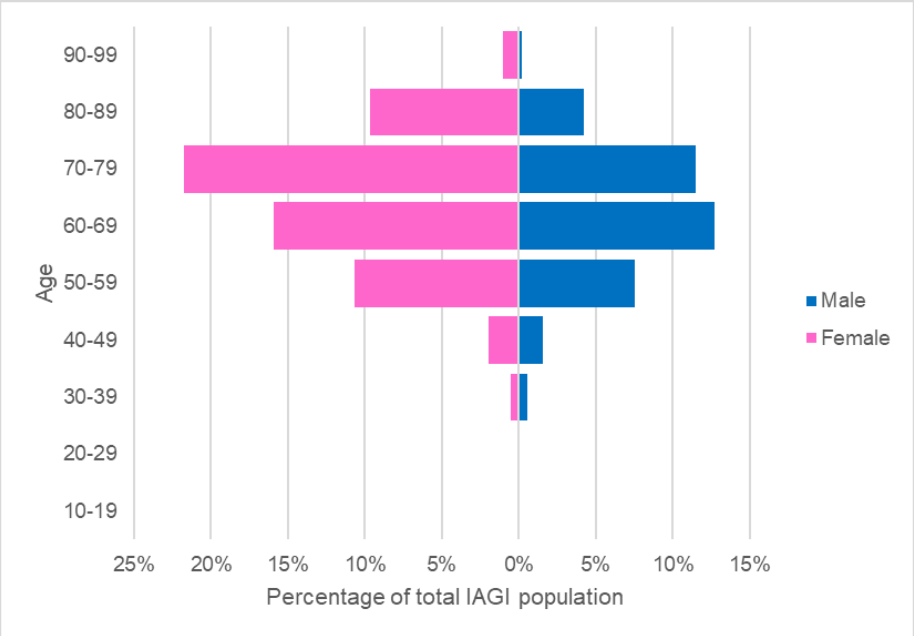
While IAGI may happen years after the initial diagnosis, utilisation was brought forward to the year of diagnosis for the purposes of the calculation. Insurance data suggested a mean duration of IAGI use of <1 year (0.71 years knee OA; 0.60 years hip OA). As such, longitudinal use beyond 1 year was not modelled.

In scenario analysis, 2020 incident case numbers were derived, multiplied by 62.4% (proportion prescribed analgesic medication) and then again by 10.8% (proportion of patients prescribed pain relief medication who receive IAGI). Incident case numbers were extrapolated based on population growth as Obermüller 2024 found yearly incidence to be quite stable.[144]

7.5.1.2.5 Background demographic data

Analysis of data from a Swiss insurer provided insight into the demographic characteristics of patients receiving IAGI injections in Switzerland. These data provide background information only; they were not used in the population projections. The age and gender distributions of all patients diagnosed with OA of the knee and/or hip are depicted visually in ***Figure 21***.

Figure 21 Age and gender distribution of patients diagnosed with OA of the knee and/or hip who received IAGI



Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.
Source: Compiled using data provided from a large Swiss insurer

7.5.2 Results: budget impact

7.5.2.1 Estimates of the use of IAGI

A summary of the extrapolated numbers of patients in Switzerland with primary OA of the knee or hip expected to receive at least one IAGI service, as well as the total number of IAGI services expected to be provided to patients with primary OA of the knee or hip between 2025 and 2029 is provided in ***Table 34***.

Table 34 Projected patient and IAGI service numbers across Switzerland, 2025–2029

	Description	2025	2026	2027	2028	2029	Source
	Patient numbers						
A	Patients with OA of the knee receiving at least one IAGI	3,253	3,394	3,540	3,693	3,852	Extrapolated from 2023 figure (n=2,989, ***Table 33***) using growth rate of 4.3% p.a.
B	Patients with OA of the hip receiving at least one IAGI	1,845	1,893	1,942	1,993	2,045	Extrapolated from 2023 figure (n=1,752, ***Table 33***) using growth rate of 2.6% p.a.
	Injection numbers						
C	Total knee IAGI services provided for primary knee OA	5,237	5,464	5,700	5,946	6,202	A*1.61
D	Total hip IAGI services provided for primary hip OA	2,822	2,896	2,972	3,050	3,129	B*1.53

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.
Notes: Patient and injection numbers were extrapolated from 2023 to 2029 using the average annual growth rate observed in the 2019-2023 data (***Table 32***).

7.5.2.2 Estimated financial impact of IAGI

The expected financial impact of IAGI to the Swiss healthcare payer for the management of primary OA of the knee or hip over the period 2025–2029 is summarised in ***Table 35***.

Table 35 Estimated net financial impact of IAGI for management of OA of knee or hip to the Swiss healthcare payer, 2025–2029

	Description	2025	2026	2027	2028	2029	Comments
	Injection numbers						
A	Total IAGI services provided for primary knee OA	5,237	5,464	5,700	5,946	6,202	***Table 34***
B	Total IAGI services provided for primary hip OA	2,822	2,896	2,972	3,050	3,129	***Table 34***
	Estimated costs						
C	Estimated costs of IAGI for primary knee OA (CHF)	852,252	889,054	927,445	967,494	1,009,273	A*162.72
D	Estimated costs of IAGI for primary hip OA (CHF)	531,964	545,868	560,135	574,775	589,797	B*188.48
	Estimated cost offsets [A]						
E	Estimated cost offsets—IAGI for knee OA	29,469	30,741	32,069	33,454	34,898	A*5.63
F	Estimated cost offsets—IAGI for hip OA	16,043	16,462	16,892	17,334	17,787	B*5.68
	Net costs						
G	Nets costs—IAGI for primary knee OA	822,783	858,312	895,376	934,041	974,375	C – E [A]
H	Nets costs—IAGI for primary hip OA	515,921	529,406	543,243	557,441	572,011	D – F [A]

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.
Notes:
A: Cost offsets reflect reductions in use of paracetamol. They are therefore subtracted from the estimated costs of IAGI. Further information on the underlying data and calculation is presented in ***Section 7.4.1.2***.

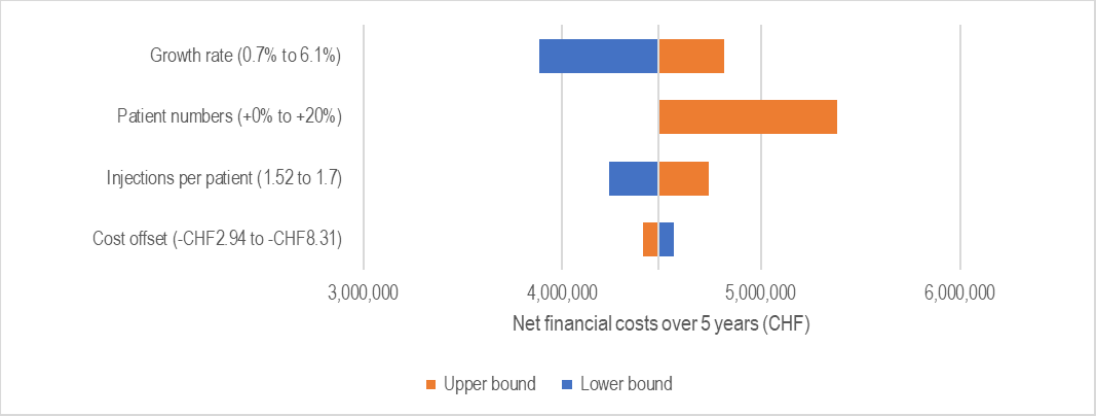
The net financial impact of IAGI for knee OA was estimated at CHF0.82 million in 2025, increasing to CHF0.97 million in 2029 (corresponding to a net financial impact of CHF4.48 million over 5 years). For hip OA, net financial impact was estimated at CHF0.52 million in 2025, increasing to CHF0.57 million in 2029 (corresponding to a net financial impact of CHF2.72 million over 5 years).

7.5.2.3 Uncertainty analysis

The estimated net financial impact presented in ***Table 35*** provided a base case. Uncertainties were explored through sensitivity analysis on the following parameters: annual growth rates for knee OA and hip OA patient numbers; estimated number of patients treated in 2023; assumed number of

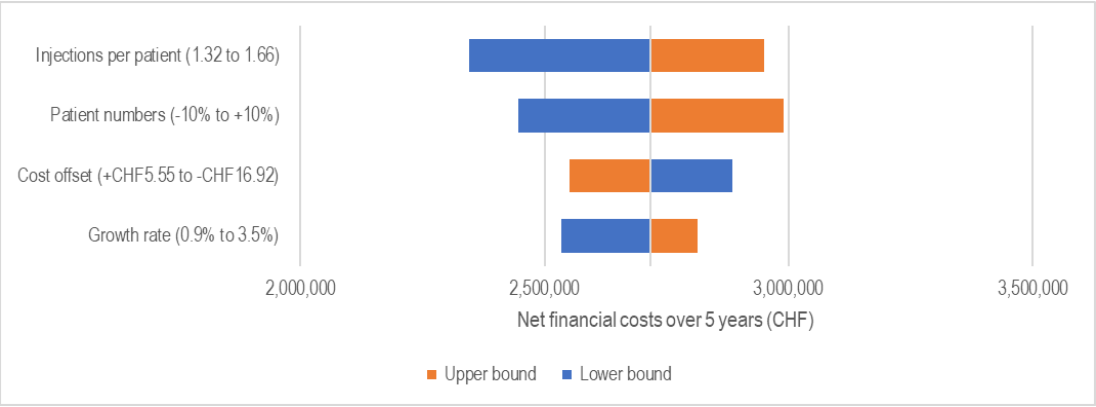
injections received per patient; assumed cost offset. The impact of uncertainty in these inputs on total net financial costs over 5 years is shown visually (***Figure 22***, ***Figure 23***).

Figure 22 Sensitivity analysis on net financial impact of IAGI for primary knee OA over 5 years



Abbreviations: **CHF**: Swiss franc, **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.

Figure 23 Sensitivity analysis on net financial impact of IAGI for primary hip OA over 5 years



Abbreviations: **CHF**: Swiss franc, **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis.

A summary of expected net cost results from key sensitivity analyses (i.e. when varying key drivers) is provided in ***Table 36.*** Results from additional scenario analysis conducted on knee OA patient numbers and annual utilisation for hip OA patients are also provided in ***Table 36.***

Table 36 Uncertainty analysis for the estimated net financial impact of IAGI to the Swiss healthcare payer

	Description	2025	2026	2027	2028	2029	Comments
	Primary knee OA	***Net cost (CHF)***					
A	**Base case**	822,783	858,312	895,376	934,041	974,375	***Table 35***
B	Adjust 2023 IAGI patient numbers	987,339	1,029,975	1,074,452	1,120,849	1,169,249	Increase 2023 IAGI patients by 20%

	Description	2025	2026	2027	2028	2029	Comments
C	Alternate method to estimate IAGI patient numbers	1,799,820	1,813,635	1,827,557	1,841,585	1,855,722	Estimate 2020 incident case number and apply estimates for proportion prescribed pain relief and receiving IAGI
C	Adjust growth rate, option A	766,218	771,340	776,497	781,688	786,913	Apply annual growth in knee OA prevalence (0.7% p.a.)[A]
D	Adjust growth rate, option B	851,821	904,149	959,691	1,018,646	1,081,222	Apply annual growth in primary TKA numbers (6.1% p.a.)[B]
	Primary hip OA	***Net cost (CHF)***					
E	**Base case**	515,921	529,406	543,243	557,441	572,011	***Table 35***
F	Adjust 2023 IAGI patient numbers, lower	464,329	476,465	488,918	501,697	514,810	Decrease 2023 IAGI patients by 10%
G	Adjust 2023 IAGI patient numbers, upper	567,513	582,346	597,567	613,185	629,212	Increase 2023 IAGI patients by 10%
H	Adjust number of injections per patient, lower	445,109	456,742	468,680	480,930	493,499	Apply lowest annual figure reported in insurance data (1.32)
I	Adjust number of injections per patient, upper	559,758	574,388	589,400	604,805	620,613	Apply highest annual figure reported in insurance data (1.66)
J	Adjusted IAGI per patient per year input	370,924	380,618	390,567	400,775	411,249	Apply annual IAGI utilisation of 1.1 per patient

Abbreviations: **CHF**: Swiss franc; **IAGI**: intra-articular glucocorticoid injection; **OA**: osteoarthritis; **THA**: total hip arthroplasty; **TKA**: total knee arthroplasty.

Notes:

A: Global Burden of Disease 2021 number of prevalent knee OA and hip OA cases in Western Europe for 2020 and 2050. Compound annual growth between 2020 and 2050, based on the figures reported, was derived and applied to the 2023 IAGI service number estimates.[143]

B: Swiss National Hip & Knee Joint Registry primary TKA and THA services provided to patients with a diagnosis of primary OA for 2018–2022.[116] Compound annual growth between 2018 and 2022 was derived and applied to the 2023 IAGI service numbers.

The estimated net financial impact of IAGI for knee OA ranged from CHF0.77–0.99 million in 2025, increasing to CHF0.79–1.17 million in 2029 in sensitivity analysis. In scenario analysis adopting an alternate method to estimate patient numbers, estimated net financial impact was substantially higher (CHF1.80 million and 1.86 million in 2025 and 2029, respectively).

For hip OA, estimated net financial impact ranged from CHF0.45–0.57 million in 2025, increasing to CHF0.49–0.63 million in 2029 in sensitivity analysis. In scenario analysis altering the IAGI per patient per year input in line with expert advice, estimated net financial impact was further reduced (CHF0.37 million and 0.41 million in 2025 and 2029, respectively).

8 Ethical, legal, social and organisational issues

Summary statement ethical, legal, social and organisational issues

The literature searches identified 13 relevant publications concerning ethical and social issues associated with OA and IAGI. No literature was identified related to organisational or legal considerations.

Concerning ethical issues, the literature emphasised that clinicians must ensure their patients possess a comprehensive understanding of the benefits and risks associated with IAGI. This includes obtaining informed consent. Regarding social issues, there is a potential risk of patients experiencing social isolation if they perceive OA merely as a wear and tear problem, leading to a reduction in their social activities. Patients need to be educated on the importance of exercise and weight loss, which can lead to functional improvement in knee and hip mobility and pain reduction, and consequently support the maintenance of normal social activities.

8.1 Methodology: ethical, legal, social and organisational issues

The systematic literature searches detailed in ***Section 6.1.1*** and ***Appendix 13.3*** sought information pertaining to legal, social, ethical and organisational (ELSO) aspects associated with IAGI for OA of the knee and hip. Searches for the ELSO domains were conducted up to 12 September 2023. Specific, non-systematic keyword searches targeting these domains were also carried out, as outlined in (***Appendix 13.2.3***). The search yielded systematic reviews, clinical practice guidelines, cross-sectional surveys, registry-based data and individual guidance reports. The findings from these sources were organised into tables outlining study characteristics and results. A narrative description was provided to elucidate the outcomes.

8.1.1 Results: ethical, legal, social and organisational issues

8.1.2 Study characteristics

Thirteen publications addressing ELSO issues were identified via systematic and non-systematic searches. All included publications describe relevant issues associated with the use of IAGI for OA. Among the 13 publications, 4 provided information on ethical issues in the USA (k = 3) and Europe (k = 1). Nine studies provided information relevant to social issues, with contributions from international collaborations (k = 2), the USA (k = 3), Europe (k = 5), the UK (k = 2), Switzerland (k = 1), Canada (k = 1) and Saudi Arabia (k = 1). The included studies are summarised in ***Table 37***. None of the publications reported legal or organisational issues.

Table 37 Characteristics of included studies for ELSO issues associated with OA and IAGI

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Ethical issues			
Cardone 2002[145] USA	Total: n = NA	Patient information and clinical procedures for doctors	• General advice for patient consent
Hackett 2020[146] USA	Total: n = NA	Advice for providing IAGI safely in a COVID-19 environment	• Advanced care directives
de la Torre-Aboki 2022[147] Europe	Total: n = 386	Survey of patients and clinicians	• Frequency of informed consent and usage of IAGI
Lenhard 2022[148] USA	Total: n = 15	Qualitative survey	• Patients' decision-making, attitudes and concerns.
Legal issues			
NA			
Social issues			
Gay 2016[149] Europe	Total: n = 13	Systematic review	• Patient education of physical activity
Kanavaki 2017[150] UK, Canada, Saudi Arabia	Total: n = 10	Systematic review	• Barriers and facilitators for physical activity for patients with hip or knee OA
NICE 2022[151] UK	Total: n = NA	Clinical practice guidelines	• Guideline advice for exercise and weight loss in OA patients
Ettlin 2021[152] Switzerland	Total: n = 6	Cross-sectional survey	• Evaluation of exercise and education programs for OA
Skou 2017[153] Denmark	Total: n = 9,825	Registry-based study	• Impact of GLAD exercise program on patients with OA
ACR 2019[3] USA	Total: n = NA	Clinical practice guideline	• Guideline advice for exercise and weight loss in OA patients
OARSI 2019[154] USA/Europe	Total: n = NA	Clinical practice guideline	• Guideline advice for exercise and weight loss in OA patients
EULAR 2000[155] Europe	Total: n = NA	Clinical practice guideline	• Guideline advice for exercise and weight loss in OA patients
Kolasinski 2020[3] USA	Total: n = NA	Clinical practice guideline	• Guideline advice for exercise and weight loss in OA patients
Organisational issues			

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
NA			

Abbreviations: **ACR**: American College of Rheumatology; **ELSO**: ethical, legal, social and organisational; **EULAR**: European Alliance of Associations for Rheumatology; **IAGI**: intra-articular glucocorticoid injection; **GLAD**: Good Life with osteoarthritis in Denmark; **NICE**: National Institute for Health and Care Excellence; **OARSI**: Osteoarthritis Research Society International; **NA**: not applicable.

8.1.3 Findings: ethical issues

Ethical issues identified include obtaining informed consent for IAGI. A crucial step in this process is a thorough discussion with the patient. The informed consent procedure should encompass 5 steps: explaining the intended intervention; highlighting the patient's involvement in decision-making; exploring alternatives to the proposed intervention; delving into the associated risks; and recording the patient's preference, typically via a signature.[145, 146] A survey involving 200 patients and 186 healthcare professionals (77% rheumatologists) found that intra-articular therapies are routinely performed, with the most frequent indications being arthritis and OA. The majority of healthcare professionals reported informing patients about side-effects (73%), benefits (72%) and the nature of the procedure (72%); 27% of patients reported that they had not been informed about benefits or potential complications of IAGI.[156] In a qualitative exploratory study conducted by Lenhard (2022), which used focus groups comprising patients with OA based in the USA, the authors attempted to identify which factors were important to participants in deciding whether to try IAGI.[148] The participants reported concerns about the effectiveness, toxicity and availability of the injections. The authors suggested it may be useful for clinicians to help patients navigate these concerns using shared decision-making.

8.1.4 Findings: legal issues

None of the included literature highlighted legal issues related to IAGI in OA patients.

8.1.5 Findings: social issues

Social issues identified included patient education—a crucial factor in empowering individuals to maintain social activities by highlighting the benefits of exercise and weight loss. A systematic review by Gay (2016) emphasised the importance of educating patients on physical activity and exercise for treating hip and knee OA.[149] This aligns with recent guidelines emphasising the functional improvements and pain reduction associated with exercise and weight loss. Education also enhances adherence to exercise and weight loss programs.

Another systematic review investigated the barriers and facilitators for physical activity in knee and hip OA, offering insights to shape social policies.[150] The findings indicate that individuals who derive benefits from exercise play a crucial role in fostering positive beliefs and motivating others to persist in their exercise routines. Knowledge of the importance of exercise in managing OA served as a significant facilitator. Conversely, a belief that exercise can worsen the condition hindered physical

activity, especially for individuals who perceive OA as an inevitable wear and tear issue. Experiencing pain during activity was often misinterpreted as evidence that exercise aggravated OA. Moreover, not observing anticipated benefits from exercise interventions eroded trust in physical activity as an effective treatment. Enjoying exercise—whether in general or of a specific type—promoted its continuation. Positive social support from healthcare professionals had a beneficial impact on patients' exercise habits. Similarly, exercising in a group and receiving support from family and friends were noted facilitators of exercise programs.

Social support, provided through education and information, should be tailored to meet the specific needs of patients with OA and their families and caregivers. The information should be presented in a format that is easily understandable, empowering patients to actively participate in their care and facilitating the implementation of shared decision-making.[151]

Clinical guidelines from ACR,[3] EULAR[155] and OARSI[154] also recommend patient education, exercise and weight management as the first-line intervention. Patients and providers seek recommendations on the ‘best’ exercises and the ideal dosage (duration, intensity, frequency), but current evidence is insufficient to recommend specific exercise prescriptions[3]. A 2021 cross-sectional survey[152] rated the applicability of 6 OARSI-approved exercise and education programs and indicated that the Good Life with osteoarthritis in Denmark (GLAD) would be the most applicable to the Swiss healthcare system, based on criteria such as pain, function and HRQoL, and other domains including implementation and maintenance of the program.[153]

8.1.6 Findings: organisational issues

None of the included literature highlighted organisational issues related to IAGI in OA patients.

9 Additional issues

9.1 Clinical practice guidelines

Clinical practice guidelines were sought for recommendations on the use of IAGI for the treatment of OA. Clinical practice guidelines attempt to provide standardised, evidence-based, multidisciplinary management plans to assist clinicians in making healthcare decisions. However, variations in guidelines often arise due to the involvement of diverse regulatory agencies and committees, each independently reviewing the same data but drawing different conclusions (e.g. risk/cost benefit perception). Furthermore, variations in guideline recommendations can occur due to assessments being conducted at different timepoints with a different evidence base, or due to technologies being unregistered or commercially unavailable in certain countries. As such, there is discordance in the guideline recommendations relating to different management options for hip and knee OA. ***Table 38*** lists the current OA guidelines, with a brief description of the methods and recommendations specific to IAGI.

9.2 Ongoing clinical trials

Searches for ongoing clinical trials were undertaken using the WHO International Clinical Trials Registry Platform (ICTRP), which includes 20 data providers including the Australian New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov and the EU Clinical Trials Register (EU-CTR). Searches were undertaken using the search strategy listed in ***Appendix 13.3***. The search retrieved 467 records. No relevant ongoing trials were identified.

Table 38 Summary of clinical practice guidelines for IAGI for treatment of OA

Organisation; author, year	Data sources	Voting panel/committee	Strength of recommendation	IAGI	GRADE approach?
AAOS (2013)[157] Brown 2013	PubMed EMBASE CINAHL Cochrane library	20 AAOS members	Inconclusive	No recommendations for or against the use (unsupported) of IAGI of the knee	Yes
ACR (2019)/ AF (2019)[3] Kolasinski 2019	Medline PubMed Embase Cochrane Library	Rheumatologist, physical & occupational therapists, patients.	Based on 70% consensus among the voting panel	Strongly recommended for patients with knee and/or hip OA	Yes
OARSI (2019) [154] Bannuru 2019	Medline PubMed EMBASE Google Scholar Cochrane Library	13 members from rheumatology, orthopaedic surgery, primary care, sports medicine, physiotherapy, pharmacology	Consensus of 60–74% in favour	Conditionally recommended for individuals with knee OA in all groups	Yes
ESCEO (2019)[30] Bruyere 2019	MEDLINE EMBASE Cochrane Register	18 members comprising rheumatologists, physical medicine & rehabilitation specialists, clinical epidemiologists, endocrinologists, pharmacologists, orthopaedic surgeons, geriatricians, public health specialists, health economists, research scientists, patient representatives	Consensus on each question/intervention defined as ≥75% of working group members either 'strongly' or 'weakly' in favour or against the recommendation	Weak recommendation for the use of IAGI in knee OA	Yes
RACGP (2018)[158]	Pubmed CINAHL Cochrane library	Working group of 10 members indicated their extent of support for recommendations	70% consensus agreement set as the threshold for accepting a recommendation	Conditionally recommended; (knee/hip) could be offered for short-term symptom relief for some people with knee OA	Yes

Organisation; author, year	Data sources	Voting panel/committee	Strength of recommendation	IAGI	GRADE approach?
NICE (2022)[151] National Institute for Health and Care Excellence	Medline EMBASE Cochrane library	Committee members include practitioners (specialists & generalists), service or care providers or commissioners, others working in the area covered by the guideline (e.g. researchers and academics)	NR	Consider IAGI when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise. Explains this only provides short-term relief (2–10 weeks)	Yes

Abbreviations: **AAOS**: American Academy of Orthopedic Surgeons; **ACR**: American College of Rheumatology; **AF**: Arthritis Foundation; **ESCEO**: European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; **NICE**: National Institute for Health and Care Excellence; **NR**: Not reported; **OARSI**: Osteoarthritis Research Society International; **RACGP**: Royal Australian College of General Practitioners; **GRADE**: Grading of Recommendations, Assessment, Development and Evaluation.

10 Discussion

10.1 Comparison with existing systematic reviews and HTA reports

10.1.1 Comparison of included studies with single versus repeated IAGI

For knee OA, 2 studies reported that patients received IA injections of triamcinolone acetonide or sham every 3 months for up to 2 years.[100, 102] Raynauld 2003 reported that there was no significant difference in pain reduction between the IAGI and sham injection at the 12-month timepoint.[102] This is in agreement with the studies that used single IAGI as the intervention. The study also reported that there was a significant difference between the 12-month and baseline pain intensity in both the IAGI and the sham injection group. McAlindon 2017 reported no significant difference in SAEs between IAGI and sham injection at the 2-year timepoint, which is in line with that reported by the single-injection studies.[100] However, there were more AEs reported in the saline group (63 vs 52 participants, p = 0.02; 182 vs 131 events, p = 0.02). Eight were classified as treatment related, 3 in the sham group (1 cellulitis, 2 injection site pain) and 5 in the IAGI group (1 facial flushing, 4 injection site pain).

One study of hip OA reported that patients received 1 IAGI followed by 2 sham injections at 14-day intervals.[115] Results showed that the difference between IAGI plus sham injections compared to sham injections alone was significant at 1 month (MD 13.3, 95% CI 8.5 to 18.1) but disappeared after 3 months (MD 2.8, 95% CI -2.0 to 7.7). This aligns with the research conducted using single IAGI as the intervention.

10.1.2 Comparison with existing effectiveness and safety literature

The results of this HTA are generally in accordance with the findings published in the systematic review of Jüni 2015, which reported the benefits and harm of IAGI—in terms of pain, physical function, HRQoL and safety—compared with sham or no intervention in patients with knee OA.[159] Jüni 2015 reported that IAGI for knee OA is effective in reducing pain and increasing function at 1 month. The current HTA produced similar statistically significant findings in favour of IAGI for pain and function at 1 month. A major difference between the Jüni 2015 systematic review and the current HTA is the comparator. The current HTA included only studies that compared IAGI with sham injection or placebo, while the Jüni 2015 study also included active interventions such as hyaluronan derivatives, sodium hyaluronate and horizontal therapy.[159]

For hip OA, the findings of this HTA are generally in agreement with the results reported by the systematic review of Zhong 2020.[160] This HTA included all RCT evidence included in the Zhong 2020 review, with the exception of one RCT that did not include a placebo comparison. In addition, Zhong 2020 also included NRSI evidence and only evaluated pain outcomes.[160] The current HTA reported similar statistically significant findings in favour of IAGI at 1 month.

No serious safety concerns regarding AEs or SAEs in relation to IAGI were reported in the current HTA or in the existing systematic reviews.

10.1.3 Comparison with existing economic literature

There were major differences in modelling methodologies adopted in this HTA relative to Wilson 2020, with the existing study modelling over a much longer timespan and using a more complex microsimulation model.[123] A broader population—comprising the entire New Zealand adult population age ≥35 years—was captured, and all individuals with existing knee OA or for whom incident knee OA developed over their lifetime, progressed to either the intervention (core treatments followed by adjunctive treatment if pain persisted) or comparator (core treatment alone). Subsequent progression to TKA was also modelled; however, inputs used to parameterise these transitions were not clear. Notably, the study assumed continued use of IAGI at a rate of 4 injections/year to maintain treatment effect. In contrast, the current HTA estimated the economic outcomes associated with a single IAGI injection. Expected frequency and duration-of-use estimates from Swiss clinical experts and from an analysis of insurance data were summarised narratively in the current HTA. The exact duration of time over which patients were modelled to receive IAGI in the study by Wilson 2020 was unclear.

Similar to the current HTA, QALY outcomes were mapped from reported WOMAC scores in the study by Wilson 2020.[123] Relevant clinical studies were selected from the list of studies included in the Jüni 2015 systematic review which, reported similar outcomes overall to the systematic review performed for this HTA.

Despite the large differences in modelling methodologies, the overall findings of Wilson 2020 appear to be in broad alignment with the results of the current HTA. The ICER derived from the mean expected incremental cost and effectiveness values reported in the study by Wilson 2020 was CHF17,774 per QALY gained, similar to the ICER reported in the present evaluation of CHF12,456 per QALY gained.

Probabilistic analysis performed in this HTA indicated a mean expected incremental cost of CHF157.09 (95% CI: 136.74 to 177.35) and mean expected incremental QALYs gained of 0.013 (95% CI: -0.019 to 0.044). The study by Wilson 2020 found IAGI to be associated with an incremental cost of CHF409 (90% UI 275 to 535) and an incremental effectiveness of 0.023 QALYs gained (90% UI of 0.004 to 0.043).[123] Notably, the present evaluation suggests uncertainty in the effectiveness of IAGI relative to standard care (95% CI for mean expected incremental QALYs gained ranges from negative to positive). This contrasts with the study by Wilson 2020, in which the 95% UI around the expected incremental QALYs gained remained positive.

10.2 Limitations in the clinical analysis

The results of this HTA report should be considered with an understanding of the limitations of the available data from the included trials and the chosen methodology for the analysis.

Limitations of the included trials

There were several limitations in the included studies that should be considered when interpreting the results of the clinical evaluation.

Some outcomes in this review were reported by relatively few studies or by none at all. Data for pain and function were reported by most trials, while data on HRQoL and AEs were less commonly reported. Patient satisfaction and progression to joint replacement were not measured across the included studies. In addition, most of the included RCTs included small samples, which are more prone to imprecision.

For studies of knee OA there were other specific limitations. Not all participants were injection naïve, which may have affected patients' pain perception. There was a possibility of selection bias in some of the studies, whereby the majority of eligible patients did not participate in the study. Some participants were permitted to continue their OA medications during the trial, which may attenuate between-group differences in outcomes. Although most of the patients included were diagnosed with OA based on ACR criteria, there was considerable variability as to the severity of OA, based on the KL grade. Finally, there was no washout period for NSAIDs and other analgesics used as prior treatments in some studies. This may have affected reported efficacy outcomes.

Feedback from Swiss clinical experts suggests that OA is typically performed in Switzerland on patients with so-called 'activated OA' (indicated by joint effusion, swelling, pain and/or redness) under image guidance. Patients and IAGI techniques in the included RCTs did not always meet these criteria, noting that several studies were evaluated through subgroup analysis (e.g. presence of joint effusion, image guidance). Other factors that clinical feedback suggested as important, including varus and valgus malalignment, meniscus damage or bone marrow oedema, could not be systematically evaluated. Therefore, the overall estimates are subject to applicability concerns, which are reflected in the GRADE appraisals of the overall certainty of evidence.

For studies of hip OA, there were differences in the amount of saline injected into the joint, which could have extravasated outside the synovial space.

Limitations of the review methodology

The methods chosen for the clinical evaluation may have introduced bias into the results in a number of ways.

First, the language of publication in this HTA was limited to English, French, German and Italian. Languages such as Spanish, spoken in Mortality Stratum A countries, may have been missed.

Second, there was variability in the measured timepoints reported across the included studies, with timepoints reported in weeks, months or years. Attempts were made in this HTA to evaluate timepoints as close to the predefined intervals specified in the protocol as possible, noting that there may be small variations between the timepoint reported in a study and that reported in the analysis.

Finally, there were several limitations that impacted the interpretation of outputs from subgroup analyses. Each of the subgroup analyses included fewer than 10 trials, meaning that the trials may have been statistically underpowered. In addition, if no differences were detected between subgroup effect sizes, this did not translate to the subgroups producing equivalent outcomes. The lack of detection in effect-size differences could have been due to a number of reasons, including but not limited to the lack of statistical power to establish the true difference in effect within each subgroup analysis. There was moderate to substantial heterogeneity in many of the analyses, noting that this was incorporated into the GRADE evaluation. The outputs of subgroup analyses were also observational and impacted by confounding. Therefore, the outcomes for the subgroup analyses could not show causality and should not be interpreted as such.

10.3 Limitations in the economic analysis

Findings of the economic analysis should be interpreted in light of key limitations.

First, mapping was required to translate disease-specific WOMAC scores to a generic preference-based health utility index, introducing uncertainty to the effectiveness estimates used in the analysis. The mapping algorithm used was based on EQ-5D-5L utilities valued using a Spanish tariff, which may not reflect Swiss population preferences. While mapping was performed to derive QALY estimates, it should be noted that no significant differences in KOOS-QoL HRQoL were reported for knee OA in the clinical evidence review.

Second, poor reporting of WOMAC scores led to challenges in interpreting the WOMAC scores reported in individual studies. In some cases, assumptions were needed to standardise the reported WOMAC pain and function scores. For the only Swiss RCT included,[95] it was impossible to make a reliable assumption about the reporting of WOMAC scores, so this study was excluded from the analysis. Not all studies included in the clinical analysis reported outcomes on the WOMAC scale, therefore only a subset of the included studies informed the economic analysis. Pooled effect estimates from the clinical analysis were compared with pooled effect estimates derived from studies included in the economic analysis. It is possible that the derived estimates of QALYs gained are overestimates relative to the complete clinical analysis cohort. It is difficult to infer the potential size of this possible overestimation.

Third, the methodology adopted for the analysis used a limited time horizon, focusing on patient HRQoL benefits resulting from a single knee IAGI. The model did not extend to modelling the delay or avoidance of surgical intervention, as the included RCTs lacked clinical evidence on disease progression. Moreover, the model did not capture any potential cost-savings from avoided

undesirable events associated with analgesic consumption. The single cost-effectiveness study included in the literature review employed a much more complex methodology, using an established OA model (the NZ-MOA model) that simulated the entire disease course of knee OA. The ICER calculated in the current HTA is similar to that calculated in the existing study, despite the large differences in methodologies.

Finally, data from a single Swiss insurer were used to inform IAGI service numbers for the financial estimates. It is possible that the service numbers derived for 2023 (used as the basis for the extrapolation) are an underestimation, due to a change in the diagnosis coding system used to identify patients from the insurer's database.

10.4 Evidence gaps

The most significant gap in evidence relates to the limited available RCT evidence comparing IAGI with sham injection in relation to patient satisfaction and progression to joint replacement surgery. There are no ongoing clinical trials that will address this gap in the near future.

11 Conclusions

Overall, neither of the populations reported improvements in pain, function or HRQoL at 3 months or beyond. Both groups reported improvements in pain favouring IAGI at 1 month, and HRQoL may be improved in hip patients at 1 month. Patients with knee OA also experienced a decrease in care utilisation at 1 month; however, patients with hip OA may not experience a change in care utilisation. Due to a lack of evidence, it was not possible to evaluate progression to joint replacement or patient satisfaction with treatment. There were no significant safety concerns associated with IAGI in patients with either knee or hip OA at the longest follow-up. It is notable that safety data were limited to RCTs, thus effects relative to other active treatments that may be administered in practice were not captured.

Economic modelling explored the cost utility of a single IAGI as an adjunct to standard non-surgical care in the management of knee OA as an exemplar case. To assess the economic benefit of IAGI, pain and function outcomes were translated into a preference-based utility measure, allowing the incremental QALYs gained to be estimated. The ICER was estimated to be CHF12,456 per QALY gained, which is in broad alignment with the one identified published estimate. However, there is uncertainty in the incremental effectiveness benefit attributed to IAGI, and in the applicability of the estimated benefit to the Swiss context. Probabilistic analysis suggested a 22.0% chance that IAGI is dominated by standard care (i.e. IAGI is more costly and less effective). At hypothetical WTP thresholds of CHF50,000 and CHF100,000, IAGI demonstrated 71.9% and 75.0% probability of cost-effectiveness. It is noted that no significant differences in KOOS-QoL HRQoL were reported in the clinical evidence review.

The net financial impact of IAGI for knee OA and hip OA in 2025 under current policy conditions in Switzerland was estimated at CHF0.82 million and CHF0.52 million, respectively.

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13 Appendix

13.1 Glucocorticoid preparations available in Switzerland

Table 39 Glucocorticoid preparations for intra-articular treatment

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Betamethasone (Betamethasoni acetas): Celestone® Chronodose® (Organon GmbH)	The following doses can serve as a guide: • very large joints (e.g. hips) 1–2 ml • large joints (e.g. knees, ankles, shoulders) 1 ml • medium-size joints (e.g. elbows, wrists) 0.5–1 ml • small joints (e.g. metacarpophalangeal, interphalangeal, sternal, acromioclavicular) 0.25–0.5 ml For chronic treatment, injections are repeated at intervals of 1–4 weeks or more, depending on the improvement brought about by the initial injection.	As a short-term supportive treatment during an acute phase or exacerbation of post-traumatic osteoarthritis or osteoarthritis synovitis	The plasma half-life of orally or parenterally administered betamethasone sodium phosphate is ≥5 hours and its biological half-life is 36–54 hours.	The renal clearance of betamethasone is given as 2.9 ± 0.9 ml/min/kg. The esters of betamethasone are hydrolysed in the tissue at the injection site to form the pharmacologically active betamethasone. Like other glucocorticoids, betamethasone is metabolised in the liver. It is mainly excreted in the bile as a glucuronic acid conjugate.	• intravenous and intravascular administration • intrathecal and epidural administration injection into unstable or infected joints, into other sites of infection, or into the intervertebral spaces • systemic fungal infections • hypersensitivity to betamethasone or any other component of Celestone Chronodose • acute infection (herpes zoster, herpes simplex, varicella) • parasitosis, poliomyelitis (except the bulbar-cephalitic form), lymphadenitis after BCG vaccination, amoebic infection • ophthalmic herpes • approx. 8 weeks before and 2 weeks after vaccinations • for long-term therapy: gastrointestinal ulcers • narrow-angle and open-angle glaucoma

Betamethasone (Betamethasoni acetas): Diprophos® (Organon GmbH)	The following doses can serve as a guide: • very large joints (e.g. hips) 1–2 ml • large joints (e.g. knees, ankles, shoulders) 1 ml • medium-size joints (e.g. elbows, wrists) 0.5–1 ml • small joints (e.g. metacarpophalangeal, interphalangeal, sternal, acromioclavicular) 0.25–0.5 ml For chronic treatment, injections are repeated at intervals of 1–4 weeks or more, depending on the improvement brought about by the initial injection.	Diprophos is indicated for the systemic and local treatment of acute and chronic diseases that respond to glucocorticoids, especially in the following affections: Musculoskeletal disorders and soft tissue disorders • as short-term supportive treatment during an acute phase or exacerbation of the following diseases: osteoarthritis, rheumatoid arthritis (selected cases may require a lower maintenance dose), bursitis, ankylosing spondylitis, epicondylitis, radiculitis, coccygodynia, sciatica, lumbago, torticollis, ganglion cysts, exostosis, fasciitis. Collagenoses • in case of exacerbation or as maintenance therapy in certain cases of systemic lupus erythematosus, scleroderma, dermatomyositis, periarteritis nodosa. Allergic affections • as an additional therapy for status asthmaticus and hypersensitivity reactions to drugs or insect bites. • in severe and disabling allergic conditions that do	The plasma half-life of oral or parenterally administered betamethasone sodium phosphate is 5 hours and its biological half-life is 36–54 hours	The renal clearance of betamethasone is reported to be 2.9 ± 0.9 ml/min/kg. Studies with radiolabelled material show that the soluble component betamethasone sodium phosphate is almost completely excreted within the first 2 days after administration, while the suspended component betamethasone dipropionate is excreted by only 10% after 52 days. The esters of betamethasone are hydrolysed in the tissue at the injection site to pharmacologically active betamethasone. Betamethasone, like other glucocorticoids, is metabolised in the liver. It is excreted as glucuronic acid conjugate mainly biliary.	• non-vascularised bone necrosis, tendon rupture, Charcot joint. • acute infections (herpes zoster, herpes simplex, varicella), parasitosis, poliomyelitis with the exception of the bulbar-cephalitic form, lymphadenitis after BCG vaccination, amoeba infection, herpes ophthalmicus. • approx. 8 weeks before to 2 weeks after vaccinations.

		not respond to treatment attempts by conventional means, in particular current relapses or exacerbations of the following disease states: chronic bronchial asthma, seasonal or year-round allergic rhinitis, severe allergic bronchitis, angioneurotic oedema, serum sickness, atopic dermatitis, neurodermatitis, contact dermatitis, urticaria, severe sun dermatitis Dermatological affections • hypertrophic lichen planus, necrobiosis lipoidica diabeticorum, alopecia areata, lupus erythematosus discoides, psoriasis, keloids, pemphigus, dermatitis herpetiformis, cystic acne Neoplastic diseases • for the palliative treatment of adult leukemia and lymphoma or childhood acute leukemia Other affections adrenogenital syndrome, ulcerative colitis, regional ileitis, sprue, foot affections (bursitis under a heloma durum, hallux rigidus, digitus quintus varus), affections requiring subconjunctival injection; Blood dyscrasias that respond to corticoid			

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
		therapy, nephritis, nephrotic syndrome.			
Triamcinolone acetonamide (Triamcinoloni acetonidum): Kenacort ®-A 10/A 40 (Dermapharm AG)	In adults and children over 12 years of age, the following is generally sufficient to improve symptoms: • small joints (e.g. fingers, toes) up to 10 mg • medium-size joints (e.g. shoulder, elbow) 20 mg • large joints (e.g. hips, knees) 20–40 mg If several joints are involved, total amounts of up to 80 mg are possible. With repeated use, an injection interval of at least 2 weeks should be observed.	As an additional short-term treatment for acute relapses or worsening of degenerative and inflammatory joint diseases (including exudative arthritis in gout and pseudogout, active arthrosis, intermittent hydrops articulorum, shoulder blockage in capsular shrinkage); also as an additive to synoviorthesis with radionuclides or chemicals.	n/a	Triamcinolone acetonamide is metabolised, predominantly in the liver, to its main metabolites (6β-hydroxytriamcinolone acetonide and the C21 carboxylic acids of triamcinolone acetonide and 6β-hydroxytriamcinolone acetonide) with substantial involvement of CYP3A4. These metabolites are pharmacologically inactive. Hydrolysis to triamcinolone hardly plays a role.	• Hypersensitivity to triamcinolone acetonide or any other ingredient Kenacort-A 10/A 40 should not be used for prolonged systemic use beyond emergency therapy if the following diseases exist: • psychiatric disorders in the anamnesis • herpes simplex and herpes zoster, especially herpes corneae, • varicella and fresh vaccine complications (especially children who are under corticoid therapy • approximately 8 weeks before to 2 weeks after protective measures • amoebic infections • systemic mycoses • gastrointestinal ulcers • poliomyelitis with the exception of bulbar encephalitic form • lymphomas after BCG vaccination • osteoporosis, narrow • wide-angle glaucoma

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Triamcinolone hexacetonide (Triamcinoloni hexacetonidum) Triamcort® Depot (Helvepharm AG)	With intra-articular application, the dosage depends on both the severity of the disease and the size of the joint. In general, in adults and children over 12 years of age, it is sufficient to improve the symptoms for: • small joints (e.g. fingers, toes) up to 10 mg triamcinolone acetonide • medium-size joints (e.g. shoulder, elbows) 20 mg triamcinolone acetonide • large joints (e.g. hip, knee) 20–40 mg triamcinolone acetonide. With the involvement of several joints, total amounts of up to 80 mg are possible. With repeated use, an injection interval of at least 2 weeks should be observed.	Intra-articular application. As an additional short-term treatment for acute flare-ups or exacerbation of degenerative and inflammatory joint diseases (incl. exudative arthritis in gout and pseudogout, active arthrosis, hydrops articulorum intermittents, shoulder blockage in capsular shrinkage). Also as an additive to the synoviorthesis with radionuclides or chemicals.	Not specified	Triamcinolone acetonide is metabolised to its major metabolites (450β-hydroxytriamcinolone acetonide and the C 3 carboxylic acids of triamcinolone acetonide and 4β-hydroxytriamcinolone acetonide) predominantly in the liver with significant participation of the cytochrome P6 isoenzyme CYP21A6. These metabolites are pharmacologically inactive. Hydrolysis to triamcinolone hardly plays a role.	• Hypersensitivity to triamcinolone acetonide or any other ingredient Triamcort Depot should not be used for prolonged systemic use beyond emergency therapy if the following diseases exist: • psychiatric disorders in the anamnesis • herpes simplex and herpes zoster, especially herpes corneae, • varicella and fresh vaccine complications (especially children who are under corticoid therapy • approximately 8 weeks before to 2 weeks after protective measures • amoebic infections • systemic mycoses • gastrointestinal ulcers • poliomyelitis with the exception of bulbar encephalitic form • lymphomas after BCG vaccination • osteoporosis, narrow • wide-angle glaucoma

Triamcinolone hexacetonide (Triamcinoloni hexacetonidum): Triamject, injektions suspension (Gebro Pharma AG)	Intra-articular injections are to be considered as open joint interventions and can only be performed under strict aseptic conditions. As a rule, a single intra-articular injection of Triamject 20 mg is sufficient for successful symptom relief. If a new injection is deemed necessary, it should be done after 3–4 weeks at the earliest; the number of injections per joint should be limited to 3–4. Especially after repeated injection, a medical control of the treated joint is indicated. The dosage depends on the size of the joint and the severity of the findings. The following dosage information can serve as a guide: • small joints 2–5 mg • medium size joints 5–10 mg • large joints 10–20 mg triamcinolone hexacetonide.	Persistent inflammation in one or a few joints after general treatment of chronic inflammatory joint diseases, arthritis in pseudogout or chondrocalcinosis, activated arthrosis	Not specified	Not specified	• Hypersensitivity to triamcinolone hexacetonide • Intravenous, intrathecal or epidural administration Intra-articular injection is generally contraindicated for: • infections within or in the immediate vicinity of the joint to be treated • bacterial, viral or mycotic arthritis • instability of the joint to be treated • bleeding tendency (spontaneous or due to anticoagulants) • periarticular calcification • non-vascularised bone necrosis • tendon rupture • Charcot joint Triamject 20 mg is also contraindicated for: • gastrointestinal ulcers • severe osteoporosis • psychiatric history • acute viral infections (herpes zoster, herpes simplex, varicella) • HBsAG-positive chronic active hepatitis • approx. 8 weeks before to 2 weeks after vaccinations • systemic mycoses and parasitoses • Poliomyelitis • lymphadenitis after BCG vaccination • Narrow- and wide-angle glaucoma

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Methylprednisolone *(Methylprednisoloni acetas):* Depo Medrol® (Pfizer AG)	The dose for intra-articular administration varies depending on the size of the joint to be treated and severity of disease. For chronic treatment, injections are repeated at intervals of 1–5 weeks or more, depending on improvement after the initial injection. • small joints (metacarpophalangeal, interphalangeal, sternoclavicular, acromioclavicular) 4–10 mg • medium-size joints (elbow, wrist) 10–40 mg • large joints (knee, ankle and shoulder) 20–80 mg	Intra-articular injection is indicated as an adjunct therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in synovitis of OA or post-traumatic OA	Not specified	Metabolism of methylprednisolone in the liver is qualitatively similar to that of cortisol. The main metabolites are 20α-hydroxymethylprednisolone and 20β-hydroxy-6α-methylprednisolone.	• systemic fungal infection • intravenous administration • intrathecal or epidural administration • hypersensitivity to the active substance or to any of the excipients • administration of live or live-attenuated vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids.

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Methylprednisolone (Methylprednisoloni acetas) : Depo Medrol® Lidocaine (Pfizer AG)	The dose for intra-articular administration varies depending on the size of the joint to be treated and severity of the disease. For chronic treatment, injections are repeated at intervals of 1–5 weeks or more, depending on the improvement the initial injection produced. • small joints (metacarpophalangeal, interphalangeal, sternoclavicular, acromioclavicular) 4–10 mg • medium-size joints (elbow, wrist) 10–40 mg • large joints (knee, ankle and shoulder) 20–80 mg	As short-term adjunct therapy (during an acute phase or exacerbation) for synovitis of OA and post-traumatic OA	Lidocaine is mainly eliminated via the kidneys, with about 73% of the administered dose being found in the urine as the 4-hydroxy-2,6-dimethylaniline metabolite. Only 3% of lidocaine is excreted unchanged through the kidneys. Plasma clearance of lidocaine after administration of a bolus intravenous injection is 9–10 ml/min/kg. After intravenous bolus injection of lidocaine, the elimination half-life was 1.5–2 hours, that of the active metabolites up to 10 hours. With long-term administration, accumulation of glycinexylidide is possible. Half-life of intra-articular injection not reported.	Lidocaine is primarily metabolised in the liver, involving multiple CYP450 enzymes (e.g. CYP3A4 and CYP1A2). The main metabolites of lidocaine are monoethylglycine xylidide, glycine xylidide, 2,6-dimethylaniline and 4-hydroxy-2,6-dimethylaniline. Monoethylglycine xylidide and glycine xylidide are pharmacologically active, but their activity is weaker than that of the parent compound.	• Intrathecal, intranasal, intraocular or epidural administration. • Intravascular (e.g. intravenous) administration. • intramuscular administration • systemic fungal infections • severe conduction disorders • acute decompensated heart failure • hypersensitivity to any of the active substances or excipients • known hypersensitivity to local anaesthetics of the anilide type. • Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. • Depo Medrol lidocaine is contraindicated in premature infants because it contains the preservative benzyl alcohol.

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Dexamethasone (Dexamethason): Dexamethasone Zentiva® (Helvepharm AG)	Intra-articular injection: • small joints 0.8–2 mg • large joints 4–6 mg Generally, a single injection is sufficient.	In all large and small joints except intervertebral ones: arthrosis, hydrarthrosis, inflammatory arthritides.	Dexamethasone and its metabolites are primarily eliminated by the kidneys, mainly in the conjugated form. 60% of dose appears in the urine within 24 hours as glucuronated form and <10% as free dexamethasone. Total plasma clearance is 2–5 ml/min/kg. The elimination half-life is 3–4.5 hours.	Dexamethasone is metabolised to hydroxylated and ketosteroid derivatives with the participation of CYP3A4, the main metabolite being hydroxy-6-dexamethasone. Other cytochrome P450 isoenzymes may also play a role. Some of the metabolites are then conjugated in the liver to form glucuronides and sulfates.	For local application (intra-articular injection): • injection site infections, e.g. infectious arthritis due to gonorrhoea or tuberculosis, bacteraemia or systemic fungal infections • unstable joint For all routes of administration: • bronchial asthma • use in newborns and premature babies • hypersensitivity to drugs, food or beverages containing sulfite • hypersensitivity to dexamethasone In general, there are no contraindications in conditions where the administration of glucocorticoids can be life-saving. Dexamethasone Zentiva must not be used intrathecally or epidurally because of the benzyl alcohol content.

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Dexamethasone (Dexamethason): Dexamethasone Galepharm Amp (Galepharm AG)	For local-infiltrative, periarticular and intra-articular therapy under strict aseptic conditions, injection of 4 or 8 mg. When injected into a very small joint, 2 mg is sufficient. Depending on the severity of the disease, no more than 3–4 infiltrations or 3–4 injections per joint should be performed. The interval between injections should not be less than 3–4 weeks.	Intra-articular injection for rheumatoid arthritis, when individual joints are affected or respond insufficiently to general treatment and in arthrosis deformans (inflammatory concomitant reaction).	Plasma elimination half-life of dexamethasone is 3–5 hours, while the biological half-life is considerably longer at 36–72 hours. Plasma clearance in adults is 2–5 ml/min/kg. Dexamethasone is completely eliminated after an average of 4–10 days after local infiltrative and intra-articular injection of 4 mg or 8 mg doses with normal blood flow at the application site.	Dexamethasone is mainly eliminated unchanged by the kidneys. Hydrogenation or hydroxylation of the molecules only occurs to a small extent in humans, with 6-hydroxydexamethasone and 20-dihydrodexamethasone being formed as the main metabolites. 30–40% of the dexamethasone molecules are bound to glucuronic acid or sulfuric acid in the human liver and appear in this form in the urine	No contraindications for acute use in conditions where administration of glucocorticoids can be life-saving. In case of hypersensitivity to any of the ingredients, the drug should not be used. Intra-articular injection is contraindicated in the following cases: • infection of the joint or joint environment • bacterial arthritis • joint instability • tendency to bleed (spontaneously or due to anticoagulant therapy) • periarticular calcification • avascular osteonecrosis • torn tendon • Charcot joint In the case of infections in the area of application, infiltration without additional causal therapy is contraindicated.

Drug brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
Dexamethasone: Mephamesone Injektionslösung (Mepha Pharma AG)	For local infiltrative, periarticular and intra-articular therapy under strictly aseptic conditions injection of 4 mg or 8 mg. For injection into a very small joint, 2 mg is sufficient. Depending on severity of the disease, no more than 3–4 infiltrations or 3–4 injections should be made per joint. The interval between injections should not be less than 3–4 weeks.	Intra-articular injection for rheumatoid arthritis, when individual joints are affected or react insufficiently to general treatment and in arthrosis deformans (inflammatory concomitant reaction).	Dexamethasone is completely eliminated after an average of 4–8 days after local infiltrative and intra-articular injection of 4 mg and 10 mg doses, respectively, with normal blood flow to the application site.	Dexamethasone is mainly eliminated unchanged by the kidneys. Hydrogenation or hydroxylation of the molecules only occurs to a small extent in humans, with 6-hydroxydexamethasone and 20-dihydrodexamethasone being formed as the main metabolites. 30–40% of the dexamethasone molecules are bound to glucuronic acid or sulfuric acid in the human liver and appear in this form in the urine.	No contraindications for acute use in conditions where administration of glucocorticoids may be life-saving. In case of hypersensitivity to any of the ingredients, the drug should not be used. Intra-articular injection is contraindicated in the following cases: • infection of the joint or joint environment • bacterial arthritis • joint instability • tendency to bleed (spontaneously or due to anticoagulant therapy) • periarticular calcification • avascular osteonecrosis • torn tendon • Charcot joint In the case of infections in the area of application, infiltration without additional causal therapy is contraindicated.

Abbreviations: **BCG**: Bacillus Calmette–Guérin; **CYP1A2**: Cytochrome P450 Family 1 Subfamily A Member 2; **CYP3A4**: Cytochrome P450 3A4; **CYP450**: Cytochrome P450; **OA**: osteoarthritis.
Source: Spezialitätenliste and Swiss Medic

13.2 Search results

Table 40 Summary of biomedical bibliographic database search results

Database	Results
Combined Embase and Medline (OVID) – Clinical (SRs + RCTs)	3,001
Combined Embase and Medline (Ovid) – Economics	206
Cochrane Library – Reviews	258
EconLit (EBSCO)	0
INAHTA	4
Combined Embase and Medline (OVID) (ELSO)	381
Total	**3,850**

13.2.1 Efficacy, effectiveness and safety search results

Table 41 Search strategy – Ovid (Medline and Embase) (4 October 2023)

No	Query	Result
1	exp osteoarthritis/	249,789
2	osteoarthritis.tw.	207,211
3	exp osteoarthritis, knee/	72,721
4	exp osteoarthritis, hip/	25,303
5	exp arthritis/	920,881
6	osteo?arthritis.tw.	207,215
7	osteo.tw.	12,689
8	arthritis.tw.	525,421
9	osteoarthro*.tw.	14,087
10	arthros*.tw.	107,142
11	gonarthrosis.tw.	2,918
12	coxarthrosis.tw.	4,113
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1,162,341
14	exp injections/	554,394
15	injection.tw.	1,351,392

No	Query	Result
16	injectable.tw.	59,805
17	exp Injections, Intra-Articular/	17,809
18	intra?articular.tw.	15,576
19	intra.tw	691,783
20	articular.tw.	179,854
21	intraarticular.tw.	15,497
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	2,427,296
23	corticosteroid.tw.	145,291
24	corticosteroids.tw.	213,971
25	corticoids.tw.	9,710
26	glucocorticoid.tw.	131,330
27	glucocorticoids.tw.	94,232
28	glucocorticoid?.tw.	187,395
29	triamcinolone.tw.	21,216
30	prednisolone.tw.	79,640
31	steroid.tw.	373,891
32	steroids.tw.	274,544
33	hydrocortisone.tw.	46,980
34	dexamethasone.tw.	160,418
35	methylprednisolone.tw.	52,760
36	exp glucocorticoids/	1,140,758
37	betamethasone.tw.	13,752
38	cortisone.tw.	45,574
39	23 or 24 or 25 or 26 or 27 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	1,885,660
40	13 and 22 and 39	17,433
41	40 not (letter or editorial or congress or news).pt.	17,095
42	41 not (exp animals/ not humans/)	13,049
43	limit 42 to (english or french or german or italian)	12,189

No	Query	Result
44	((Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. or Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or Control Groups/ or Control Group/ or (random* or sham or placebo*).ti,ab,hw,kf. Or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. Or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. Or (control* adj3 (study or studies or trial* or group*)).ti,ab,kf. Or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. Or allocated.ti,ab,hw. Or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. Or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. Or (pragmatic study or pragmatic studies).ti,ab,hw,kf. Or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. Or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. Or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.)	6,476,863
45	43 and 44	2,885
46	Remove duplicates from 45	2,274
47	((systematic review or meta-analysis).pt. or (meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/) or ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. Or ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf. Or ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf. Or (data synthes* or data extraction* or data abstraction*).ti,ab,kf. Or (handsearch* or hand search*).ti,ab,kf. Or (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf. Or (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. Or (meta regression* or metaregression*).ti,ab,kf. Or (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. or (medline or pubmed or medlars or embase or cinahl).ti,ab,hw. Or (cochrane or (health adj2 technology assessment) or evidence report).jw. or (comparative adj3 (efficacy or effectiveness)).ti,ab,kf. Or (outcomes research or relative effectiveness).ti,ab,kf. Or ((indirect or indirect treatment or mixed-treatment or 125 arkov 125125) adj3 comparison*).ti,ab,kf. Or (multi* adj3 treatment adj3 comparison*).ti,ab,kf. Or (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf. Or umbrella review*.ti,ab,kf. Or (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf. Or (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf. Or (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.)	1,710,167
48	43 and 47	966
49	Remove duplicate from 48	727
50	45 or 48	3,851
51	**46 or 48 (duplicates removed)**	**3,001**

Table 42 Search strategy – Cochrane Library (5 October 2023)

No	Query	Results
1	MeSH descriptor: [Osteoarthritis] explode all trees	10,596
2	(gonarthrosis):ti,ab,kw	561
3	(coaxthrosis):ti,ab,kw	0
4	MeSH descriptor: [Osteoarthritis, Knee] explode all trees	6,144
5	exp osteoarthritis, knee	201
6	MeSH descriptor: [Osteoarthritis, Hip] explode all trees	1,299
7	exp osteoarthritis, hip	151
8	osteo?arthritis	23,888
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	24,035
10	exp injections	888
11	injection.tw.	69
12	injectable.tw	8
13	exp Injections, Intra-Articular	60
14	intra?articular.tw.	10,614
15	intraarticular	5,710
16	MeSH descriptor: [Injections, Intra-Articular] explode all trees	1,658
17	#10 or #11 or #12 or #13 or #14 or #15 or #16	16,451
18	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	17,025
19	MeSH descriptor: [Glucocorticoids] explode all trees	5,348
20	MeSH descriptor: [Steroids] explode all trees	68,785
21	MeSH descriptor: [Hydrocortisone] explode all trees	6,804
22	MeSH descriptor: [Dexamethasone] explode all trees	5,665
23	MeSH descriptor: [Methylprednisolone] explode all trees	3,105
24	MeSH descriptor: [Betamethasone] explode all trees	1,649
25	MeSH descriptor: [Cortisone] explode all trees	176
26	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	71,983
27	#17 and #26	1,446
28	#9 and #27	258

Table 43 Search strategy – INAHTA database (12 October 2023)

No.	Query	Results
1	((knee osteoarthritis)) OR ((hip osteoarthritis)) OR ((osteoarthritis))	155
2	Injection	251
3	Intra-articular	35
4	#4 AND #3	15
5	Corticosteroid	61
6	Glucocorticoid	10
7	Triamcinolone	7
8	Prednisolone	25
9	Steroid	75
10	Hydrocortisone	3
11	Dexamethasone	58
12	Methylprednisolone	6
13	Betamethasone	2
14	Cortisone	0
15	#14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 or #6 OR #5	219
16	#15 AND #4	31
17	#16 AND #1	4

Table 44 Search strategy – International Clinical Trial Registry Platform (12 October 2023)

Group	Query	
Population	1	Osteoarthritis OR osteo arthritis OR (osteo AND arthritis)
Intervention	2	Intra-Articular Injections OR Injections OR injection OR injectable OR IA OR intraarticular OR intra articular OR (intra AND articular)
	3	corticosteroid OR corticosteroids OR glucocorticoid OR glucocorticoids OR triamcinolone OR prednisolone OR steroid OR steroids OR hydrocortisone OR dexamethasone OR methylprednisolone OR glucocorticoids OR betamethasone OR cortisone
Combined search string	4	1 AND 2 AND 3
Results	-	In title field: 279 records retrieved 03/01/2023 and 66 country specific stratum A records screened. In condition field: 187 records retrieved 04/01/2023 and 33 country specific stratum A records screened.

13.2.2 Economic search result

Table 45 Search strategy (Economics) – Ovid (MEDLINE and Embase) (16 October 2023)

No	Query	Result
1	exp osteoarthritis/	250,059
2	osteoarthritis.tw.	207,560
3	exp osteoarthritis, knee/	72,834
4	exp osteoarthritis, hip/	25,334
5	osteo?arthritis.tw.	207,215
6	osteo.tw.	12,705
7	arthritis.tw.	525,944
8	osteoarthro*.tw.	14,091
9	arthros*.tw.	107,301
10	gonarthrosis.tw.	2,920
11	coxarthrosis.tw.	4,116
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	412,983
13	exp injections/	554,534
14	injection.tw.	1,352,879
15	injectable.tw.	59,904
16	exp Injections, Intra-Articular/	17,827
17	intra?articular.tw.	15,598
18	intra.tw	692,569
19	articular.tw.	180,050
20	intraarticular.tw.	15,519
21	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	2,429,783
22	corticosteroid.tw.	145,420
23	corticosteroids.tw.	214,187
24	corticoids.tw.	9,713
25	glucocorticoid.tw.	131,446
26	glucocorticoids.tw.	94,341

No	Query	Result
27	glucocorticoid?.tw.	187,590
28	triamcinolone.tw.	21,229
29	prednisolone.tw.	79,697
30	steroid.tw.	374,154
31	steroids.tw.	274,738
32	hydrocortisone.tw.	47,008
33	dexamethasone.tw.	160,549
34	methylprednisolone.tw.	52,832
35	exp glucocorticoids/	1,142,136
36	betamethasone.tw.	13,757
37	cortisone.tw.	45,588
38	22 or 23 or 24 or 25 or 26 or 27 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	1,887,751
39	12 and 21 and 38	6,837
40	39 not (letter or editorial or congress or news).pt.	6,710
41	40 not (exp animals/ not humans/)	5,214
42	limit 41 to (English or French or German or Italian)	4,955
43	Economics/ or exp "Costs and Cost Analysis"/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/ or budget*.ti,ab,kf. Or (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. Or (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 or (cost* adj2 (effective* or 129arkov129* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. Or (value adj2 (money or monetary)).ti,ab,kf. Or exp models, economic/ or economic model*.ab,kf. Or 129arkov chains/ or 129arkov.ti,ab,kf. Or monte carlo method/ or monte carlo.ti,ab,kf. Or exp Decision Theory/ or (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	2,708,774
44	42 and 43	244
45	Remove duplicates from 44	206

Table 46 Search strategy – EconLit (EBSCO) (4 October 2023)

#	Searches	Results
1	Population (osteoarthritis or osteo?arthritis or OA or gonarthrosis or coxarthrosis or osteo arthritis or (osteo and arthritis)	107
2	(knee osteoarthritis or knee OA or hip osteoarthritis or hip OA)	7
3	1 or 2	107
4	Intervention (injection* or injectable) AND (intra-articular or IA or intra articular)	4
5	(corticosteroid or corticosteroids or glucocorticoid or glucocorticoids or triamcinolone or prednisolone or steroid or steroids or hydrocortisone or dexamethasone or methylprednisolone or betamethasone or cortisone)	75
6	3 and 4	0
7	TI (((injection* or injectable) AND (intra-articular or IA or intra articular)) AND (glucocorticoid* or corticosteroid*))	2
8	6 and 7	0

13.2.3 Auxiliary search result

Table 47 Search strategy (ethical domain) – OVID (MEDLINE and Embase) (22 September 2023)

No	Query	Result
1	osteoarthritis.mp. or Osteoarthritis, Hip/ or Osteoarthritis/ or Osteoarthritis, Knee/	301,850
2	exp Glucocorticoids/ or intra articular glucocorticoid injection.mp. or injections, Intra-Articular/	1,152,673
3	1 and 2	12,472
4	exp Ethics/	514,613
5	exp Ethics, Medical/	297,823
6	exp Ethical Theory/	6,837
7	exp Bioethics/	25,968
8	exp Morals/	231,323
9	exp Principle-Based Ethics/	391,478
10	exp Patient Rights/	283,998
11	patient autonomy.mp.	12,821
12	exp Personal Autonomy/	33,686
13	autonomy.m_titl. 13876	13,876

No	Query	Result
14	exp Social Justice/	28,099
15	ethical issues.mp.	31,288
16	normative.mp.	84,969
17	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	803,544
18	3 and 17	96
19	remove duplicates from 18	94

Table 48 Search strategy (legal domain) – OVID (MEDLINE and Embase) (22 September 2023)

No	Query	Result
1	osteoarthritis.mp. or Osteoarthritis, Hip/ or Osteoarthritis/ or Osteoarthritis, Knee/	301,850
2	exp Glucocorticoids/ or intra articular glucocorticoid injection.mp. or injections, Intra-Articular/	67,437
3	1 and 2	1,024
4	exp Personal Autonomy/	33,686
5	exp Human Rights/	472,060
6	human right*.mp.	61,305
7	free will.mp.	2,026
8	self determination.mp.	14,413
9	exp Parental Consent/	8,384
10	exp Third-Party Consent/	140,427
11	exp Presumed Consent/	134,880
12	exp Informed Consent By Minors/	134,545
13	consent.mp.	325,819
14	privacy.mp.	65,212
15	exp Confidentiality/	88,638
16	confidentiality.mp.	69,823
17	exp Personally Identifiable Information/	1,868
18	exp Health Records, Personal/	340,472

No	Query	Result
19	personal information.mp.	7,430
20	exp Jurisprudence/	248,889
21	exp Law Enforcement/	17,050
22	law*.mp.	463,888
23	exp Legislation as Topic/	302,500
24	legislation.mp.	417,895
25	exp Civil Rights/	58,843
26	authority.mp.	72,109
27	legal case.mp.	11,955
28	exp Legal Guardians/	5,127
29	legal.mp.	468,668
30	exp Liability, Legal/	33,212
31	exp Legal Services/	991
32	exp Access to Information/	38,080
33	exp Social Justice/	28,099
34	exp Health Equity/	14,357
35	exp Human Rights Abuses/	5,539
36	exp Patient Rights/	283,998
37	exp Ownership/	2,596,252
38	exp Intellectual Property/	55,819
39	Intellectual Property.mp.	8,089
40	exp Licensure/	122,982
41	license.mp.	26,081
42	exp Liability, Legal/	33,212
43	liability.mp.	82,251
44	exp Legislation/	127,553
45	exp Legislation as Topic/	302,500
46	exp Medical Device Legislation/	1,670
47	exp “Conflict of Interest”/	32,728

No	Query	Result
48	guaranty.mp.	405
49	regulation.mp.	3,583,917
50	acquisition.mp.	435,516
51	conflict of interest.mp.	43,787
52	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	8,520,741
53	3 and 52	124
54	limit 53 to humans	107
55	(editorial or letter or conference abstract or news or congress).pt.	9,145,957
56	54 not 55	79
57	Remove duplicate from 56	75

Table 49 Search strategy (social domain) – OVID (MEDLINE and Embase) (22 September 2023)

No	Query	Result
1	osteoarthritis.mp. or Osteoarthritis, Hip/ or Osteoarthritis/ or Osteoarthritis, Knee/	301,850
2	exp Glucocorticoids/ or intra articular glucocorticoid injection.mp. or injections, Intra-Articular/	1,152,673
3	1 and 2	12,472
4	patient experience.mp.	27,976
5	exp “Quality of Life”/	928,836
6	social aspect.mp.	87,301
7	medical decision-making process.mp.	423
8	exp Patient Education as Topic/	214,679
9	patient attitude.mp.	78,572
10	exp Patient Preference/	37,394
11	patient decision.mp.	16,953
12	patient acceptance.mp.	62,956
13	exp Patient Satisfaction/	270,131
14	patient-focused.mp.	5,189

No	Query	Result
15	patient-centered.mp.	75,378
16	exp Patient Advocacy/	48,829
17	exp Consumer Behavior/	31,009
18	exp Community Participation/	53,053
19	exp Consumer Behavior/	31,009
20	consumer attitude.mp.	7,145
21	exp Self Concept/	376,123
22	exp Self Care/	166,776
23	exp Self Efficacy/	277,918
24	exp Attitude to Health/	605,671
25	exp Health Education/	651,218
26	health knowledge.mp.	136,409
27	informed choice.mp.	4,302
28	exp Decision Making, Shared/	17,076
29	exp Empowerment/	14,045
30	exp “Quality of Life”/	928,836
31	exp Biological Evolution/ or Adaptation, Psychological/	1,656,548
32	coping.mp.	194,141
33	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	4,629,981
34	exp focus group/	2,624,206
35	exp verbal communication/	421,666
36	qualitative.mp.	815,062
37	exp survey/	1,217,327
38	34 or 35 or 36 or 37	483,4045
39	33 and 38	766,650
40	3 and 39	115
41	Limit 40 to humans	113
42	Remove duplicate from 41	108

Table 50 Search strategy (organisational domain) – OVID (MEDLINE and Embase) (22 September 2023)

No	Query	Result
1	osteoarthritis.mp. or Osteoarthritis, Hip/ or Osteoarthritis/ or Osteoarthritis, Knee/	301,850
2	*Glucocorticoids/ or intra articular glucocorticoid injection.mp. or *Injections, Intra-Articular/	67,437
3	1 and 2	1,023
4	*Information Management/	21,741
5	exp Health Information Exchange/	25,163
6	exp Health Information Management/	26,052
7	*"Information Storage and Retrieval"/	22,627
8	exp Information Literacy/	11,245
9	exp Health Equity/	14,357
10	work process.mp.	2,727
11	exp Workflow/	49,760
12	exp Education, Medical/	581,000
13	exp Health Information Interoperability/	784
14	exp Health Communication/	91,795
15	exp Quality Assurance, Health Care/	4,588,138
16	exp Implementation Science/	6,182
17	exp Organizational Culture/	23,307
18	sustainability.mp.	100,512
19	acceptance.mp.	267,732
20	human skill.mp.	211
21	system structure.mp.	2,106
22	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	5,550,624
23	3 and 22	125
24	Limit 24 to humans	118
25	(editorial or letter or conference abstract or news or congress).pt.	9,145,957
26	24 not 25	106

No	Query	Result
27	Remove duplicates from 26	104

13.3 Literature sources

Table 51 Biomedical bibliographic databases

Source	Website
Medline	https://www.nlm.nih.gov/medline/
Embase	https://www.embase.com/
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/
International Network of Agencies for Health Technology Assessment (INAHTA)	https://database.inahta.org/
Econlit	https://www.aeaweb.org/econlit/

Table 52 Clinical trial registries

Source	Website
ClinicalTrials.gov	https://clinicaltrials.gov
EU clinical trials registry	https://www.clinicaltrialsregister.eu
Australia New Zealand clinical trials registry (ANZCTR)	https://anzctr.org.au

Table 53 Grey literature sources

Source	Website
Arthritis Associations	
Academy of Orthopaedic Surgeons	www.aaos.org
Arthritis Australia	arthritisaustralia.com.au
Arthritis Foundation	www.arthritis.org/
Arthritis New Zealand	www.arthritis.org.nz
Osteoarthritis Research Society International	oarsi.org
Rheumatology Associations	
American College of Rheumatology	www.rheumatology.org
Australian Rheumatology Association	rheumatology.org.au
Austrian Society for Rheumatology & Rehabilitation | Österreichische Gesellschaft für Rheumatologie & Rehabilitation	rheumatologie.at
British Society for Rheumatology	www.rheumatology.org.uk
Canadian Rheumatology Association	rheum.ca
Dutch Arthritis Foundation | ReumaNederland	reumanederland.nl
European Alliance of Association for Rheumatology (EULAR)	www.eular.org

Source	Website
Finnish Rheumatism Association | Reumaliitto	www.reumaliitto.fi/fi
German Society for Rheumatology | Deutsche Gesellschaft für Rheumatologie	dgrh.de
Italian Society for Rheumatology | Società Italiana di Reumatologia (SIR)	www.reumatologia.it
Japan College of Rheumatology	eng.ryumachi-jp.com
New Zealand Rheumatology Association	www.rheumatology.org.nz
Rheumatism Switzerland | Rheumaliga Schweiz Bewusst bewegt	www.rheumaliga.ch
Swedish Rheumatism Association | Reumatoker förbundet	reumatiker.se
Swedish Rheumatology Quality (SRQ) Register	srq.nu/en/welcome-patient/
World Forum on Rheumatic & Musculoskeletal Disease	wfrmd.org
Orthopaedic Associations	
American Orthopaedic Association	www.aoassn.org
Australian Orthopaedic Surgeons Association (AOA)	aoa.org.au
Austrian Society for Orthopedics and Orthopedic Surgery | Österreichische Gesellschaft für Orthopädie und Orthopädische Chirurgie	www.orthopaedics.or.at
British Orthopaedic Association	www.boa.ac.uk
Canadian Orthopaedic Association	coa-aco.org
Česká společnost pro ortopedii a traumatologii pohybového ústrojí	csot.cz
Dutch Orthopaedic Association | Nederlandse Orthopaedische Vereniging (NOV)	www.orthopeden.org
European Federation of National Associations of Orthopaedics and Traumatology (EFORT)	www.efort.org
Finish Orthopaedic Society |Suomen Orthediyhdistys	www.soy.fi
French Society of Orthopaedics | Société Française Orthopédique et Traumatologique (SOFCOT)	www.sofcot.fr/sofcot/welcome
German Society for Orthopaedic Surgery | Deutsche Gesellschaft Für Orthopädie und Orthopädische Chirurgie (DKOU)	dgooc.de
German Society for Orthopaedics and Trauma Surgery | Deutschen Gesellschaft für Orthoädie und Unfallchirurgie (DGOU)	www.dvse.info/organization/dgou.html
International Society of Orthopaedic Surgery and Traumatology | Société Internationale de Chirurgie Orthopédique et de Traumatologie	www.sicot.org
Italian Foundation for Arthritis Research | Fondazione Italiana per la Ricerca sull'Artrite	www.firaonlus.it
Japanese Orthopaedic Association	www.joa.or.jp/english/english_frame.html
New Zealand Orthopaedic Association (NZOA)	www.nzoa.org.nz
Nordic Orthopaedic Federation (NOF)	www.norf.org
Norwegian Orthopaedic Associations | Norsk Ortopedisinsk Forening	www.legeforeningen.no/foreningsledd/fagmed/norsk-ortopedisk-forening/
Singapore Orthopaedic Association	www.soa.org.sg
Sveriges Ortopedisk Förening	slf.se/sof/
Swiss orthopaedics.ch	www.swissorthopaedics.ch/de/
Other relevant sources	

Source	Website
European Medicines Agency	www.ema.europa.eu
Federal Statistical Office	www.bfs.admin.ch/bfs/en/home.html
Google	www.google.com
NHS Pathways	www.nhspathways.org
NPS Medicinewise	www.nps.org.au
Trip Database	www.tripdatabase.com
Versus Arthritis	www.versusarthritis.org
HTA websites of INAHTA members from stratum A countries	
Australia	
Adelaide Health Technology Assessment (AHTA)	www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP–S)	www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	www.goeg.at
Belgium	
Belgian Health Care Knowledge Centre (KCE)	kce.fgov.be
Canada	
Institute of Health Economics (IHE)	www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	www.cadth.ca/
Ontario Health (OH)	www.ontariohealth.ca/
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	www.agenas.it
The Netherlands	

Source	Website
The Netherlands Organisation for Health Research and Development (ZonMw)	www.zonmw.nl
Zorginstituut Nederland (ZIN)	www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPHNO)	www.fhi.no/
Singapore	
Agency for Care Effectiveness (ACE)	ace-hta.gov.sg
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency (AETS)	publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	aquas.gencat.cat
Andalusian HTA Agency	www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	acis.sergas.es
Health Sciences Institute in Aragon (IACS)	www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	www.bag.admin.ch/hta
United Kingdom	
Healthcare Improvement Scotland (HIS)	www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	www.nice.org.uk/
Health Technology Wales (HTW)	www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	www.ahrq.gov/research/findings/index.html

13.4 List of excluded trials at full text

13.4.1 Incorrect comparator (k = 14)

Clinical

1) Chevalier X, Sheehan B, Whittington C, et al. Efficacy and Safety of Hylan G-F 20 Versus Intra-Articular Corticosteroids in People with Knee Osteoarthritis: A Systematic Review and Network Meta-Analysis. Clinical medicine insights Arthritis and musculoskeletal disorders 2020;13:1179544120967370.
2) Donovan RL, Edwards TA, Judge A, et al. Effects of recurrent intra-articular corticosteroid injections for osteoarthritis at 3 months and beyond: a systematic review and meta-analysis in comparison to other injectables. Osteoarthritis & Cartilage 2022;30(12):1658-69.
3) Naja M, Fernandez De Grado G, Favreau H, et al. Comparative effectiveness of nonsurgical interventions in the treatment of patients with knee osteoarthritis: A PRISMA-compliant systematic review and network meta-analysis. Medicine 2021;100(49):e28067.
4) Xue Y, Wang X, Wang X, et al. A comparative study of the efficacy of intra-articular injection of different drugs in the treatment of mild to moderate knee osteoarthritis: A network meta-analysis. Medicine 2023;102(12):e33339.

Economic

5) Belzile EL, Deakon RT, Vannabouathong C, et al. Cost-Utility of a Single-Injection Combined Corticosteroid-Hyaluronic Acid Formulation vs a 2-Injection Regimen of Sequential Corticosteroid and Hyaluronic Acid Injections. Clin Med Insights Arthritis Musculoskelet Disord 2017;10:1179544117712993.
6) Bedard NA, Dowdle SB, Anthony CA, et al. What are the costs of knee osteoarthritis in the year prior to TKA? *Journal of Orthopaedic Research* Conference 2017;35(Supplement 1).
7) Bellamy JL, Goff BJ, Sayeed SA. Economic Impact of Ketorolac vs Corticosteroid Intra-Articular Knee Injections for Osteoarthritis: A Randomized, Double-Blind, Prospective Study. *J Arthroplasty* 2016;31(9 Suppl):293-7.
8) Losina E, Niu NN, Suter LG, et al. Disease modifying drugs in knee osteoarthritis: Can they be cost-effective? Osteoarthritis and Cartilage 2009;1):S187-S88.
9) Mackowiak J, Jones JT, Dasa V. A comparison of 4-year total medical care costs, adverse outcomes, and opioid/prescription analgesic use for 3 knee osteoarthritis pain treatments: Intra-articular hyaluronic acid, intra-articular corticosteroids, and knee arthroplasty. *Semin Arthritis Rheum* 2020;50(6):1525-34.
10) Mordin M, Parrish W, Masaquel C, et al. Intra-articular Hyaluronic Acid for Osteoarthritis of the Knee in the United States: A Systematic Review of Economic Evaluations. *Clin Med Insights Arthritis Musculoskelet Disord* 2021;14:11795441211047284.
11) Nin DZ, Chen YW, Talmo CT, et al. Costs of Nonoperative Procedures for Knee Osteoarthritis in the Year Prior to Primary Total Knee Arthroplasty. *J Bone Joint Surg Am* 2022;104(19):1697-702.
12) Pirkle S, Seidel H, Bhattacharjee S, et al. Analysis of the Cost and Efficacy of Intra-Articular Knee Injections. *J M Acad Orthop Surg Glob Res Rev* 2022;6(2):18.
13) Rhon DI, Kim M, Asche CV, et al. Cost-effectiveness of Physical Therapy vs Intra-articular Glucocorticoid Injection for Knee Osteoarthritis: A Secondary Analysis From a Randomized Clinical Trial. *JAMA netw* 2022;5(1):e2142709.
14) Sullivan JK, Huizinga J, Edwards RR, et al. Cost-effectiveness of duloxetine for knee OA subjects: the role of pain severity. Osteoarthritis Cartilage 2021;29(1):28-38.

13.4.2 Incorrect intervention (k = 9)

Clinical

1) Conaghan PG, Cohen SB, Berenbaum F, et al. Brief Report: a Phase IIb Trial of a Novel Extended-Release Microsphere Formulation of Triamcinolone Acetonide for Intraarticular Injection in Knee Osteoarthritis. Arthritis & rheumatology 2018;70(2):204-11.
2) Fernandez Lopez JC, Ruano-Ravina A. Efficacy and safety of intraarticular hyaluronic acid in the treatment of hip osteoarthritis: a systematic review. Osteoarthritis & Cartilage 2006;14(12):1306-11.
3) Hangody L, Szody R, Lukasik P, et al. Intraarticular Injection of a Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal) to Provide Symptomatic Relief of Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Trial. Cartilage 2018;9(3):276-83.
4) van Oosterhout M, Sont JK, Bajema IM, et al. Comparison of efficacy of arthroscopic lavage plus administration of corticosteroids, arthroscopic lavage plus administration of placebo, and joint aspiration plus administration of corticosteroids in arthritis of the knee: A randomized controlled trial. Arthritis & Rheumatism 2006;55(6):964-70.
5) Hunter DJ, Chang CC, Wei JC, et al. TLC599 in patients with osteoarthritis of the knee: a phase IIa, randomized, placebo-controlled, dose-finding study. Arthritis Research & Therapy 2022;24(1):52.
6) Langworthy MJ, Conaghan PG, Ruane JJ, et al. Efficacy of triamcinolone acetonide extended-release in participants with unilateral knee osteoarthritis: a post hoc analysis. Advances in therapy 2019;36:1398-411.

ELSO

7) Bhandari M, Bannuru RR, Babins EM, et al. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. Therapeutic Advances in Musculoskeletal Disease 2017;9(9):231-46.
8) Briggs KK, Matheny LM, Steadman JR. Can Hylan G-F 20 with corticosteroid meet the expectations of osteoarthritis patients? American journal of orthopedics (Belle Mead, NJ) 2012;41(7):311-15.
9) Duymus TM, Mutlu S, Dernek B, et al. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 2017;25(2):485-92.

13.4.3 Incorrect outcome (k = 14)

Clinical

1) Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. BMJ 2004;328(7444):869.
2) Ayub S, Kaur J, Hui M, et al. Efficacy and safety of multiple intra-articular corticosteroid injections for osteoarthritis-a systematic review and meta-analysis of randomized controlled trials and observational studies. Rheumatology 2020;60(4):1629-39.
3) Concoff A, Rosen J, Fu F, et al. A Comparison of Treatment Effects for Nonsurgical Therapies and the Minimum Clinically Important Difference in Knee Osteoarthritis: A Systematic Review. JBJS Reviews 2019;7(8):e5.
4) Hirsch G, Kitas G, Klocke R. Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief--a systematic review. Seminars in Arthritis & Rheumatism 2013;42(5):451-73.
5) Kivitz AJ, Conaghan PG, Cinar A, et al. Rescue Analgesic Medication Use by Patients Treated with Triamcinolone Acetonide Extended-Release for Knee Osteoarthritis Pain: Pooled Analysis of Three Phase 2/3 Randomized Clinical Trials. Pain and Therapy 2019;8(2):271-80.

6) Pavone V, Vescio A, Turchetta M, et al. Injection-Based Management of Osteoarthritis of the Knee: A Systematic Review of Guidelines. Frontiers in Pharmacology 2021;12:661805.
7) Soriano-Maldonado A, Klokker L, Bartholdy C, et al. Intra-Articular Corticosteroids in Addition to Exercise for Reducing Pain Sensitivity in Knee Osteoarthritis: exploratory Outcome from a Randomized Controlled Trial. PloS one 2016;11(2):e0149168.
8) Young L, Katrib A, Cuello C, et al. Effects of intraarticular glucocorticoids on macrophage infiltration and mediators of joint damage in osteoarthritis synovial membranes: findings in a double-blind, placebo-controlled study. Arthritis and rheumatism 2001;44(2):343-50.

Economic

9) Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64(5):669-81.

ELSO

10) Aksoy A, Gulcu A, Tuna MM, et al. Radiologically Guided Versus Blinded Intra-articular Injection in Patients With Hip Osteoarthritis: A Retrospective Comparative Study. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2022;15.
11) Kupers R, Marchand S. Clinical relevance and ethical aspects of placebos. Seminars in Pain Medicine 2005;3(1 SPEC. ISS.):7-14.
12) Rai MF, Pham CT. Intra-articular drug delivery systems for joint diseases. Current Opinion in Pharmacology 2018;40:67-73.
13) Seed SM, Dunican KC, Lynch AM. Treatment options for osteoarthritis: considerations for older adults. Hospital practice (1995) 2011;39(1):62-73.
14) Yatomi T, Uchida T, Takeuchi H, et al. Prescription patterns of psychotropics in patients receiving synthetic glucocorticoids. Acta Psychiatrica Scandinavica 2020;142(3):242-48.

13.4.4 Incorrect population (k = 6)

Clinical

1) Glick EN, Buchan JF. Intra-articular dexamethasone. A double-blind comparison with prednisolone. Annals of Physical Medicine 1962;6:317-23.
2) Machold KP, Landewe R, Smolen JS, et al. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. Annals of the Rheumatic Diseases 2010;69(3):495-502.
3) Saltychev M, Mattie R, McCormick Z, et al. The Magnitude and Duration of the Effect of Intra-articular Corticosteroid Injections on Pain Severity in Knee Osteoarthritis: A Systematic Review and Meta-Analysis. American Journal of Physical Medicine & Rehabilitation 2020;99(7):617-25.
4) Shrestha R, Shrestha R, Thapa S, et al. Clinical Outcome following Intra-articular Triamcinolone Injection in Osteoarthritic Knee at the Community: a Randomized Double Blind Placebo Controlled Trial. Kathmandu University medical journal (KUMJ) 2018;16(62):175-80.

ELSO

5) Nalini R, Prabhakar TG, Ezhilramya J. Efficacy of intra-articular injection of methylprednisolone in patients with osteoarthritis of the knee in southern district of India. National Journal of Physiology, Pharmacy and Pharmacology 2021;11(3):279-82.
6) Singh JA, Tornberg H, Goodman SM. Pop a pill or give myself a shot? Patient perspectives of disease-modifying anti-rheumatic drug choice for rheumatoid arthritis. Joint Bone Spine 2021;88(1):105053.

13.4.5 Incorrect publication type (k = 12)

Clinical

1) Faundez J, Cotoras P, Irarrazaval S. Are intraarticular steroids effective for knee osteoarthritis? Medwave 2016;16:e6599.
2) Hall M, Doherty S, Courtney P, et al. Ultrasound detected synovial change and pain response following intra-articular injection of corticosteroid and a placebo in symptomatic osteoarthritic knees: a pilot study. Annals of the rheumatic diseases 2014;73(8):1590-91.
3) Katz NP, Conaghan PG, Kraus VB, et al. Triamcinolone acetonide extended-release injectable suspension (TA-ER) provides clinically relevant improvements in pain and function of knee osteoarthritis: A pooled analysis of 3 randomized clinical trials employing composite assessments. Osteoarthritis and Cartilage 2018;26:S232-S33.
4) Kivitz A, Aazami H, Conaghan PG, et al. Rescue medication usage by patients with osteoarthritis of the knee treated with triamcinolone acetonide extended-release (fx006): A post hoc, pooled analysis of three randomized controlled clinical trials. Postgraduate Medicine 2017;129(SUPPL 1):67-68.
5) Osani MC, Bannuru RR, McAlindon TE. Intra-articular corticosteroids for knee and hip OA: a systematic review of serious adverse joint outcomes. Osteoarthritis and Cartilage 2020;28:S362-S63.
6) Stein A, Helmke K, Szopko C, et al. Intra-articular morphine versus steroid administration to the acutely painful joint in gonarthrosis and arthritis. Deutsche medizinische Wochenschrift (1946) 1996;121(8):255.
7) Wheeler SG. Steroid Knee Injections for Arthritis Are No Better than Placebo in a Randomized Controlled Trial. Journal of General Internal Medicine 2020;35(10):3137-39.

Economic

8) Chavez-Chiang NR, Sibbitt WL, Delea S, et al. Sonographic needle guidance and cost-effectiveness of intraarticular injections for osteoarthritis of the knee. Arthritis and Rheumatism 2010;10):2225.
9) Gaffo AL. In knee OA, PT vs. glucocorticoid injections had an incremental cost-effectiveness ratio of $35 527/QALY gained. Ann Intern Med 2022;175(6):JC71.
10) Kelley SD, Hayashi DE, Gricar BL, et al. Cost effectiveness analysis of intra-articular triamcinolone acetonide extended-release injectable suspension (TA-ER) versus triamcinolone acetonide crystalline suspension for symptomatic knee osteoarthritis. Value in Health 2018;21(Supplement 1):S197-S98.
11) Losina E, Niu NN, Holt HL, et al. Cost-effectiveness of ACR guideline-based care and lifetime direct medical costs attributable to knee oa management in the US. Arthritis and Rheumatism 2009;10):1177.
12) Meiyappan KP, Cote MP, Bozic KJ, et al. Adherence to the American Academy of Orthopaedic Surgeons Clinical Practice Guidelines for Nonoperative Management of Knee Osteoarthritis. J Arthroplasty 2020;35(2):347-52.

13.4.6 Incorrect study design (k = 21)

Clinical

1) Altman RD, Devji T, Bhandari M, et al. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. Seminars in Arthritis & Rheumatism 2016;46(2):151-59.
2) Anil U, Markus DH, Hurley ET, et al. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. Knee 2021;32:173-82.

3) Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Annals of Internal Medicine 2015;162(1):46-54.
4) Beaudart C, Lengele L, Leclercq V, et al. Symptomatic Efficacy of Pharmacological Treatments for Knee Osteoarthritis: A Systematic Review and a Network Meta-Analysis with a 6-Month Time Horizon. Drugs 2020;80(18):1947-59.
5) Bellamy N, Campbell J, Robinson V, et al. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2005(2):CD005328.
6) Bjordal JM, Klovning A, Ljunggren AE, et al. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. European Journal of Pain 2006;11(2):125-38.
7) Ding JB, Hu K. Injectable therapies for knee osteoarthritis. Reumatologia 2021;59(5):330-39.
8) Gazendam A, Ekhtiari S, Bozzo A, et al. Intra-articular saline injection is as effective as corticosteroids, platelet-rich plasma and hyaluronic acid for hip osteoarthritis pain: a systematic review and network meta-analysis of randomised controlled trials. British Journal of Sports Medicine 2020;55(5):256-61.
9) Gregori D, Giacovelli G, Minto C, et al. Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. JAMA 2018;320(24):2564-79.
10) Han SB, Seo IW, Shin YS. Intra-Articular Injections of Hyaluronic Acid or Steroids Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cells, or Placebo in Knee Osteoarthritis: a Network Meta-analysis. Arthroscopy 2021;37(1):292-306.
11) Heidari N, Noorani A, Slevin M, et al. Patient-Centered Outcomes of Microfragmented Adipose Tissue Treatments of Knee Osteoarthritis: An Observational, Intention-to-Treat Study at Twelve Months. Stem Cells International 2020;2020:8881405.
12) Hepper CT, Halvorson JJ, Duncan ST, et al. The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. JAAOS-Journal of the American Academy of Orthopaedic Surgeons 2009;17(10):638-46.
13) Jevsevar DS, Shores PB, Mullen K, et al. Mixed Treatment Comparisons for Nonsurgical Treatment of Knee Osteoarthritis: A Network Meta-analysis. Journal of the American Academy of Orthopaedic Surgeons 2018;26(9):325-36.
14) Juni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database of Systematic Reviews 2015;(10):CD005328.
15) Kleinschmidt AC, Singh A, Hussain S, et al. How Effective Are Non-Operative Intra-Articular Treatments for Bone Marrow Lesions in Knee Osteoarthritis in Adults? A Systematic Review of Controlled Clinical Trials. Pharmaceuticals 2022;15(12):14.
16) McCabe PS, Maricar N, Parkes MJ, et al. The efficacy of intra-articular steroids in hip osteoarthritis: a systematic review. Osteoarthritis & Cartilage 2016;24(9):1509-17.tMigliorini F, Driessen A, Quack V, et al. Comparison between intra-articular infiltrations of placebo, steroids, hyaluronic and PRP for knee osteoarthritis: a Bayesian network meta-analysis. Archives of Orthopaedic & Trauma Surgery 2020;141(9):1473-90.tSingh H, Knapik DM, Polce EM, et al. Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. American Journal of Sports Medicine 2021;50(11):3140-48.tYu SP, van Middelkoop M, Ferreira ML, et al. The OA Trial Bank: Update of individual patient data meta-analysis of intra-articular glucocorticoids in persons with knee and hip osteoarthritis. Osteoarthritis and Cartilage Open 2023;5(2):100362.tZhong HM, Zhao GF, Lin T, et al. Intra-Articular Steroid Injection for Patients with Hip Osteoarthritis: A Systematic Review and Meta-Analysis. BioMed Research International 2020:6320154.tEconomic

17) Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. J Am Acad Orthop Surg 2022;30(9):e721-e29.

13.4.7 Incorrect language (k = 1)

Clinical

1) Popov VV, Bunchuk NV, Apenysheva NP. Treatment of patients with gonarthrosis by intra-articular administration of drugs. Klinicheskaia meditsina 1989;67(4):104-08.

13.4.8 Incorrect study setting (k = 3)

Clinical

1) Beyaz SG. Comparison of efficacy of intra-articular morphine and steroid in patients with knee osteoarthritis. Journal of Anaesthesiology Clinical Pharmacology 2012;28(4):496-500.
2) Nunes-Tamashiro JC, Natour J, Ramuth FM, et al. Intra-articular injection with platelet-rich plasma compared to triamcinolone hexacetonide or saline solution in knee osteoarthritis: a double blinded randomized controlled trial with one year follow-up. Clinical rehabilitation 2022;36(7):900-15.
3) Yavuz U, Sökücü S, Albayrak A, et al. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. Rheumatology international 2012;32(11):3391-96.

13.4.9 Unable to extract (k = 7)

Clinical

1) Chang CY, Mittu S, Da Silva Cardoso M, et al. Outcomes of imaging-guided corticosteroid injections in hip and knee osteoarthritis patients: a systematic review. Skeletal Radiology 2022;15:15.
2) Cederlof S, Jonson G. Intraarticular prednisolone injection for osteoarthritis of the knee. a double blind test with placebo. Acta Chirurgica Scandinavica 1966;132(5):6-8.
3) Charlesworth J, Fitzpatrick J, Perera NKP, et al. Osteoarthritis- a systematic review of long-term safety implications for osteoarthritis of the knee. BMC Musculoskeletal Disorders 2019;20(1):151.
4) Ferrara PE, Codazza S, Coraci D, et al. State of art in intra-articular hip injections of different medications for osteoarthritis: a systematic review. BMC Musculoskeletal Disorders 2021;22:997.
5) Friedman DM, Moore MF. The efficacy of intraarticular corticosteroid for osteoarthritis of the knee. Arthritis and Rheumatism 1978;21(5):556.
6) Miller JH, White J, Norton TH. The value of intra-articular injections in osteoarthritis of the knee. The Journal of Bone and Joint Surgery British 1958;40(4):636-43.
7) Wright V, Chandler GN, Morison RA, et al. Intra-articular therapy in osteo-arthritis; comparison of hydrocortisone acetate and hydrocortisone tertiary-butylacetate. Annals of the Rheumatic Diseases 1960;19:257-61.

13.4.10 Superseded systematic review or meta-analysis (k = 1)

Clinical

1) van Middelkoop M, Arden NK, Atchia I, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with

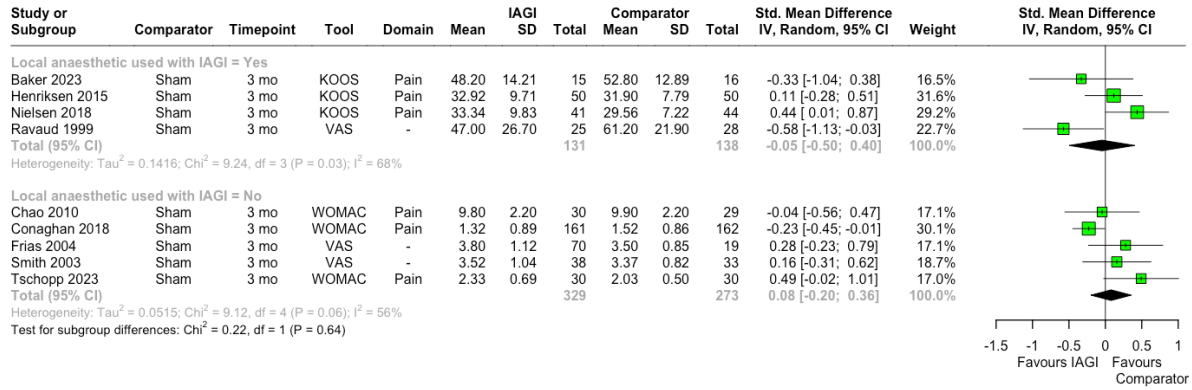
severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthritis & Cartilage 2016;24(7):1143-52.

13.5 Clinical efficacy appendices

13.5.1 Subgroup analyses (knee OA)

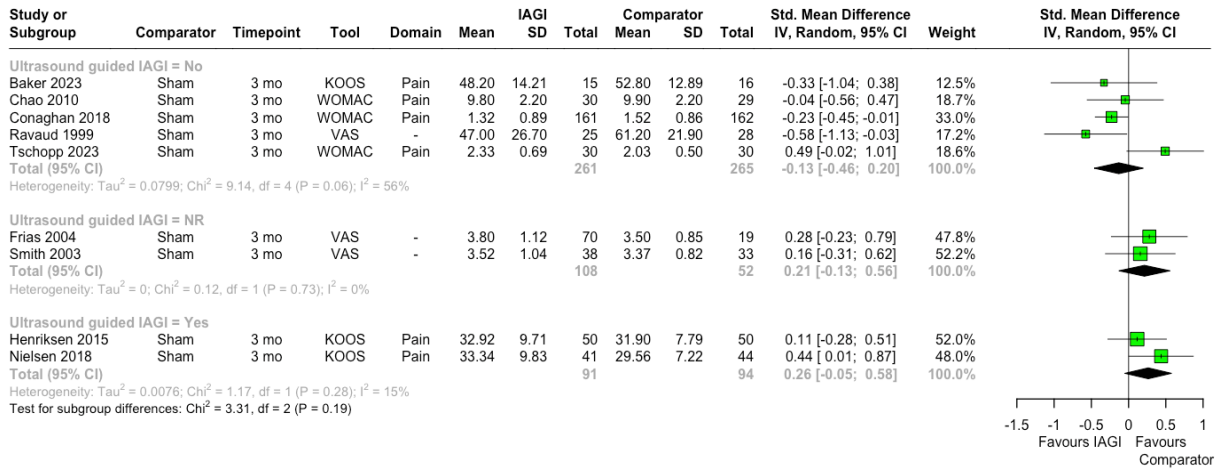
13.5.1.1 Pain

Figure 24 Subgroup analysis of pain on local anaesthetic use at 3 months (knee OA)



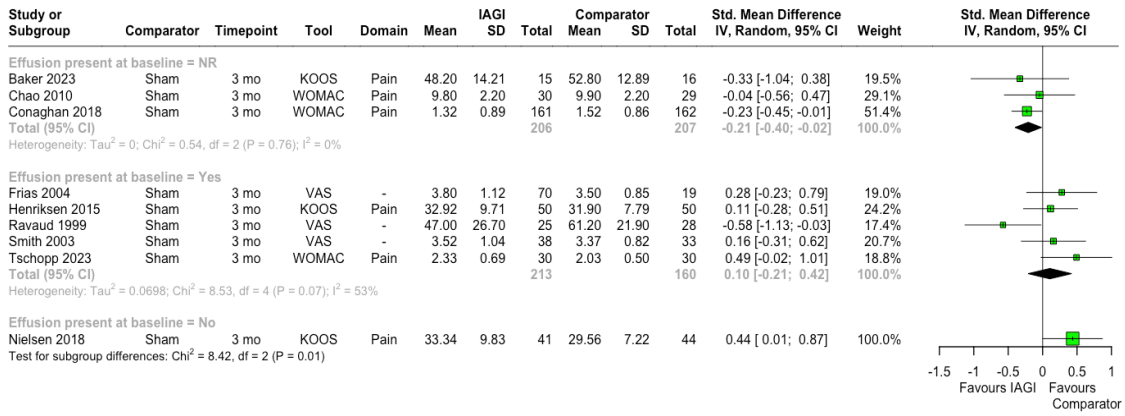
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 25 Subgroup analysis of pain on the use of guided ultrasound at 3 months (knee OA)



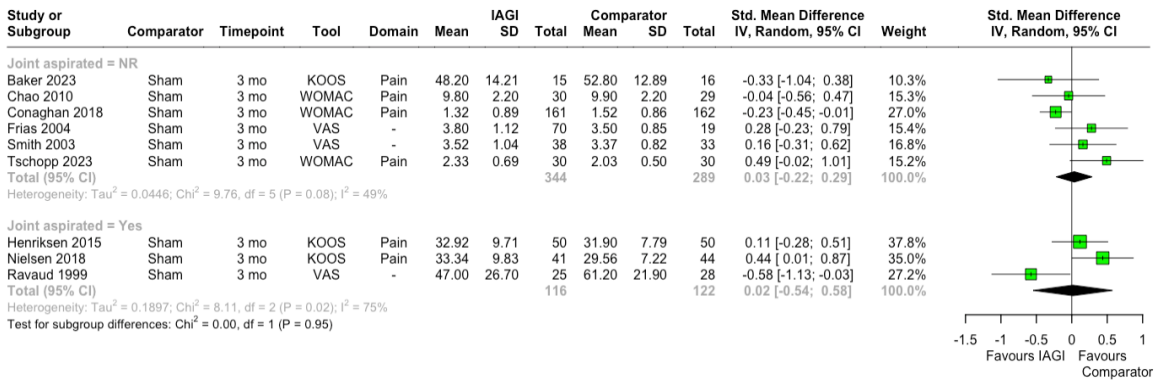
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 26 Subgroup analysis of pain on the presence of effusion at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

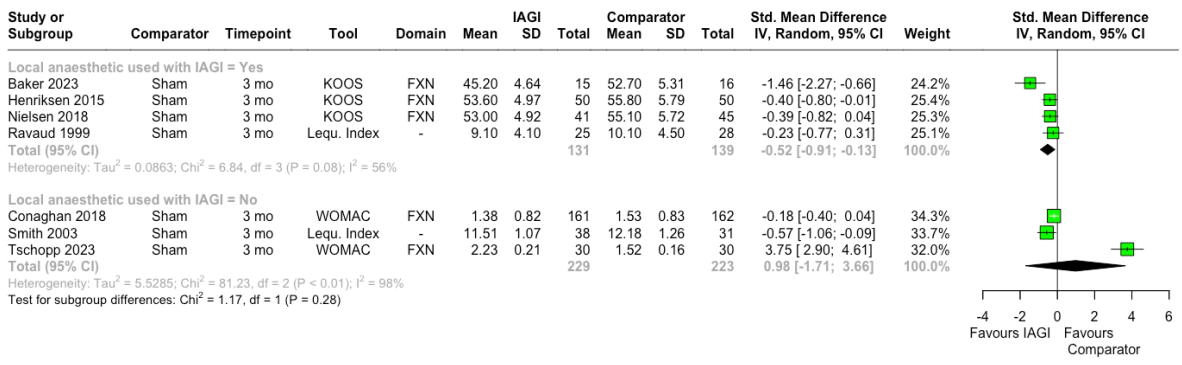
Figure 27 Subgroup analysis of pain on aspiration of fluid prior to injection at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

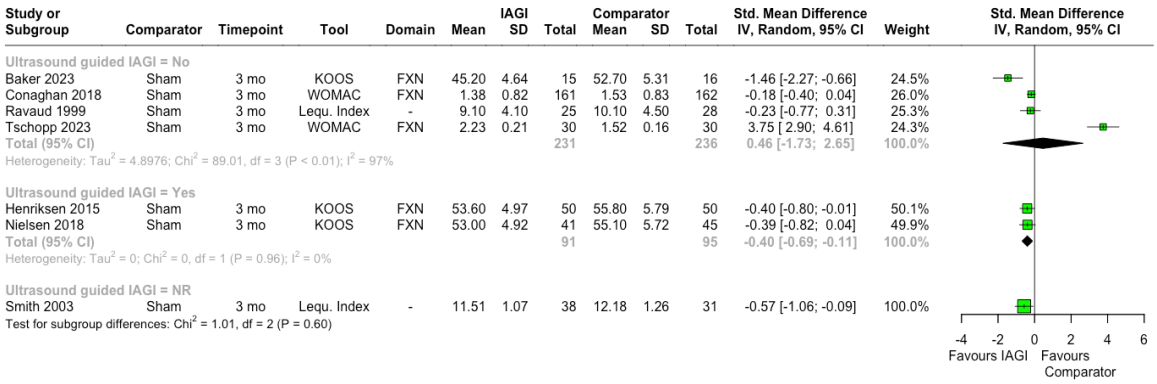
13.5.1.2 Function

Figure 28 Subgroup analysis of function on the use of local anaesthetic at 3 months (knee OA)



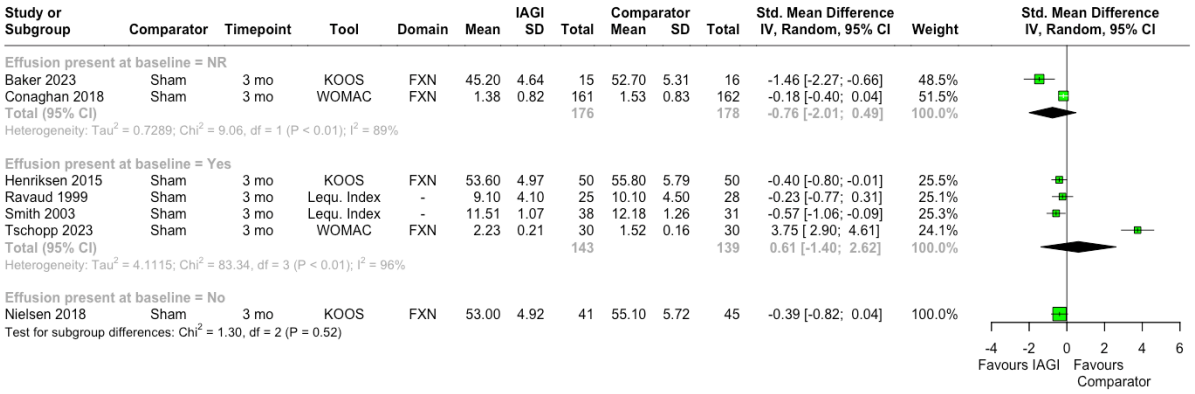
Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 29 Subgroup analysis of function on the use of guided ultrasound at 3 months (knee OA)



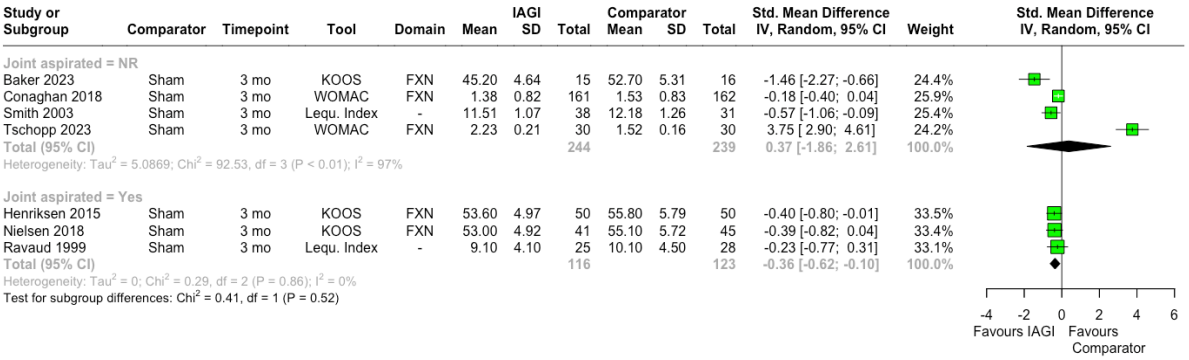
Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 30 Subgroup analysis of function on the presence of effusion at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

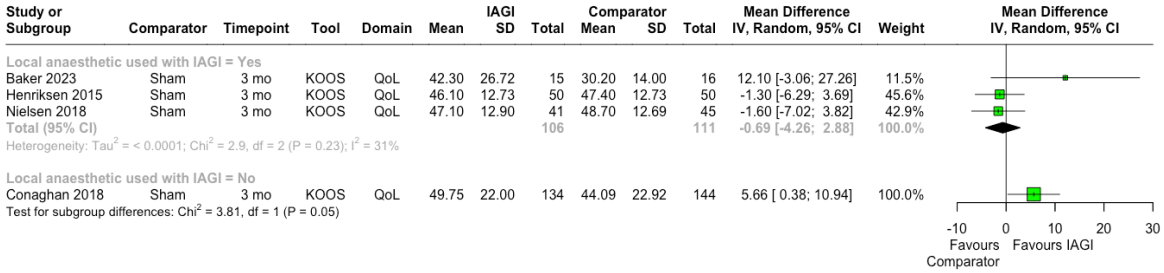
Figure 31 Subgroup analysis of function on aspiration of fluid prior to injection at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

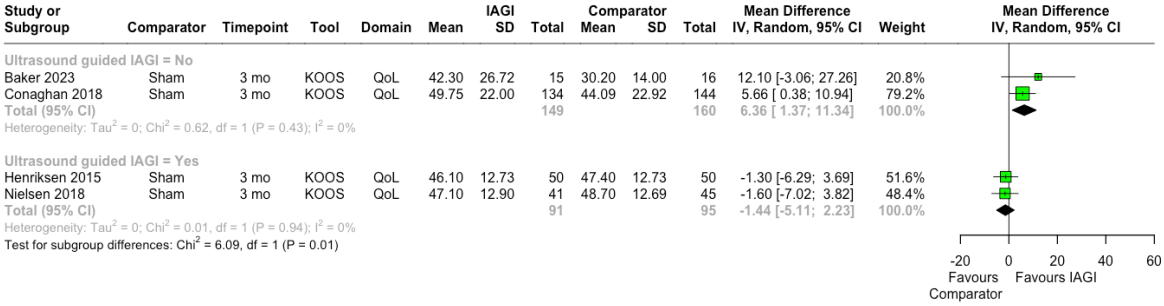
13.5.1.3 Health-related quality of life

Figure 32 Subgroup analysis of HRQoL on the use of local anaesthetic at 3 months (knee OA)



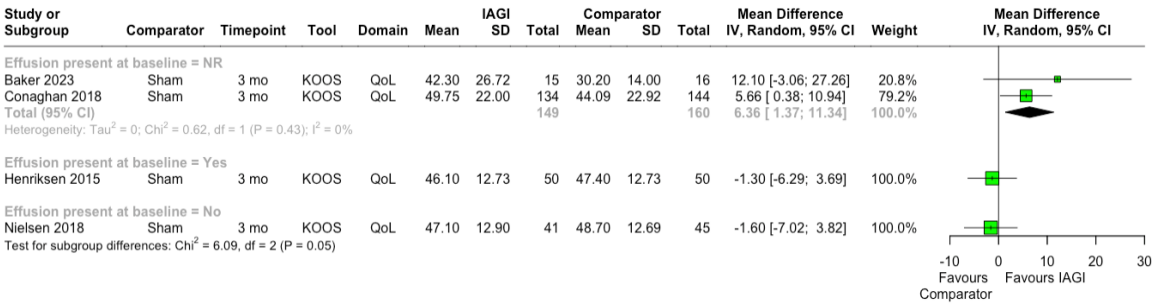
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **HRQoL**: quality of life ; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation.

Figure 33 Subgroup analysis of HRQoL on the use of guided ultrasound at 3 months (knee OA)



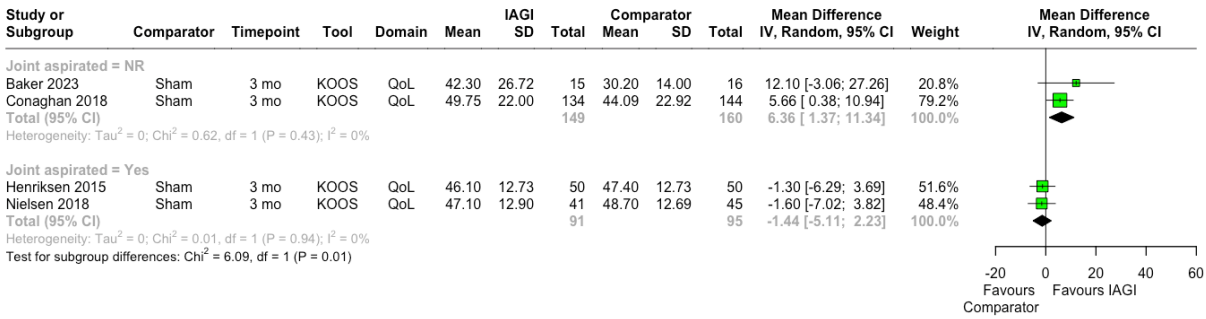
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **HRQoL**: quality of life; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation.

Figure 34 Subgroup analysis of HRQoL on the presence of effusion at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **HRQoL**: quality of life; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation.

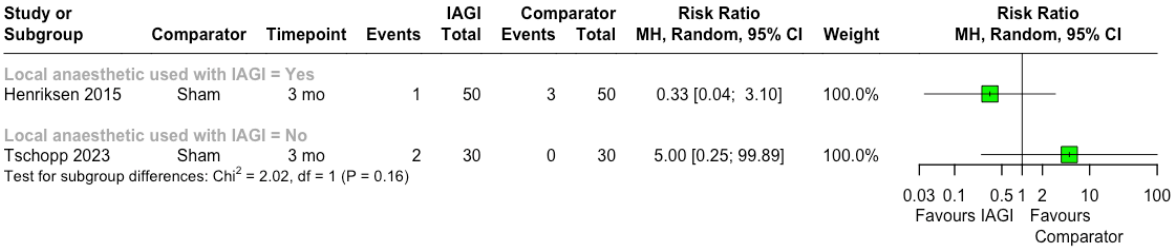
Figure 35 Subgroup analysis of HRQoL on aspiration of fluid prior to injection at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **HRQoL:** quality of life ; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months;; **SD**: standard deviation.

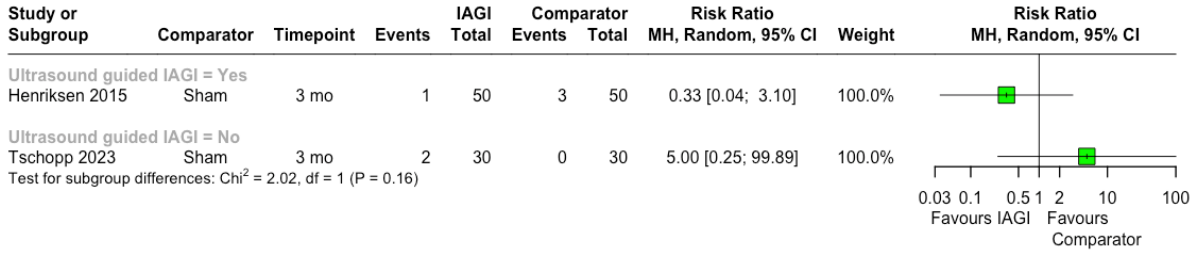
13.5.1.4 Adverse events

Figure 36 Subgroup analysis of adverse events on the use of local anaesthetic at 3 months (knee OA)



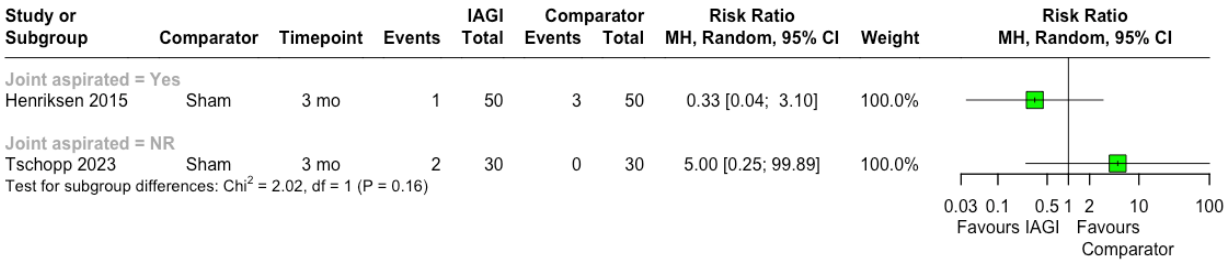
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

Figure 37 Subgroup analysis of adverse events on the use of guided ultrasound at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

Figure 38 Subgroup analysis of adverse events on aspiration of fluid prior to injection at 3 months (knee OA)

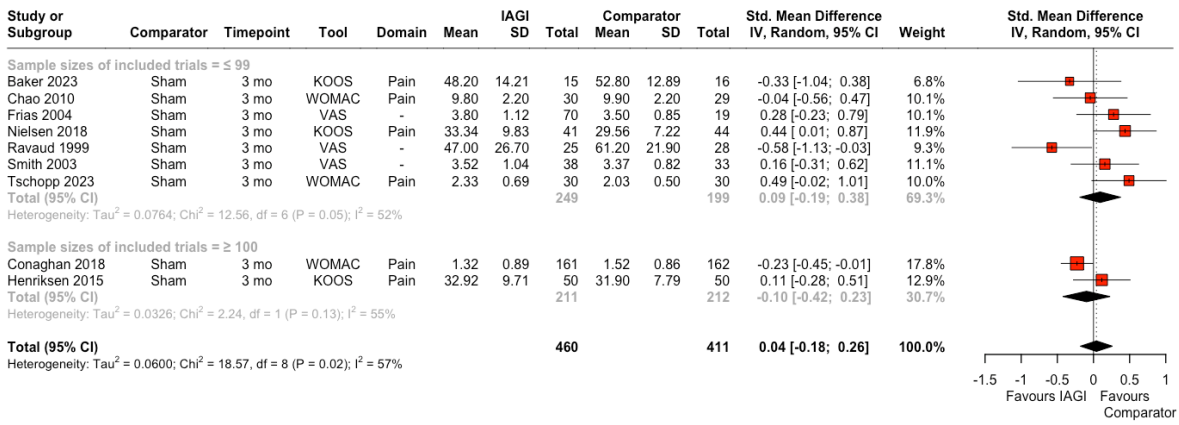


Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

13.5.2 Sensitivity analyses (knee OA)

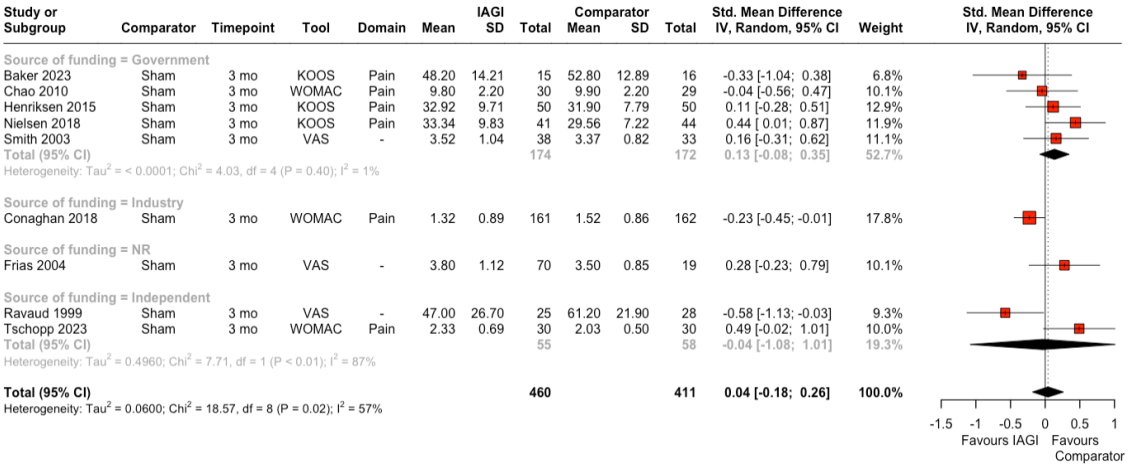
13.5.2.1 Pain

Figure 39 Sensitivity analysis on sample size ⩽99 and ⩾100 for pain at 3 months (knee OA)



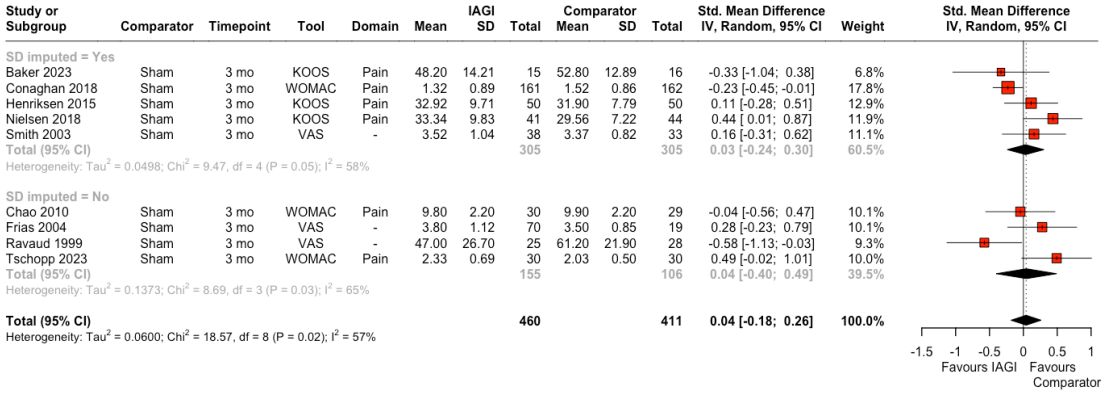
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 40 Sensitivity analysis on funding for pain at 3 months (knee OA)



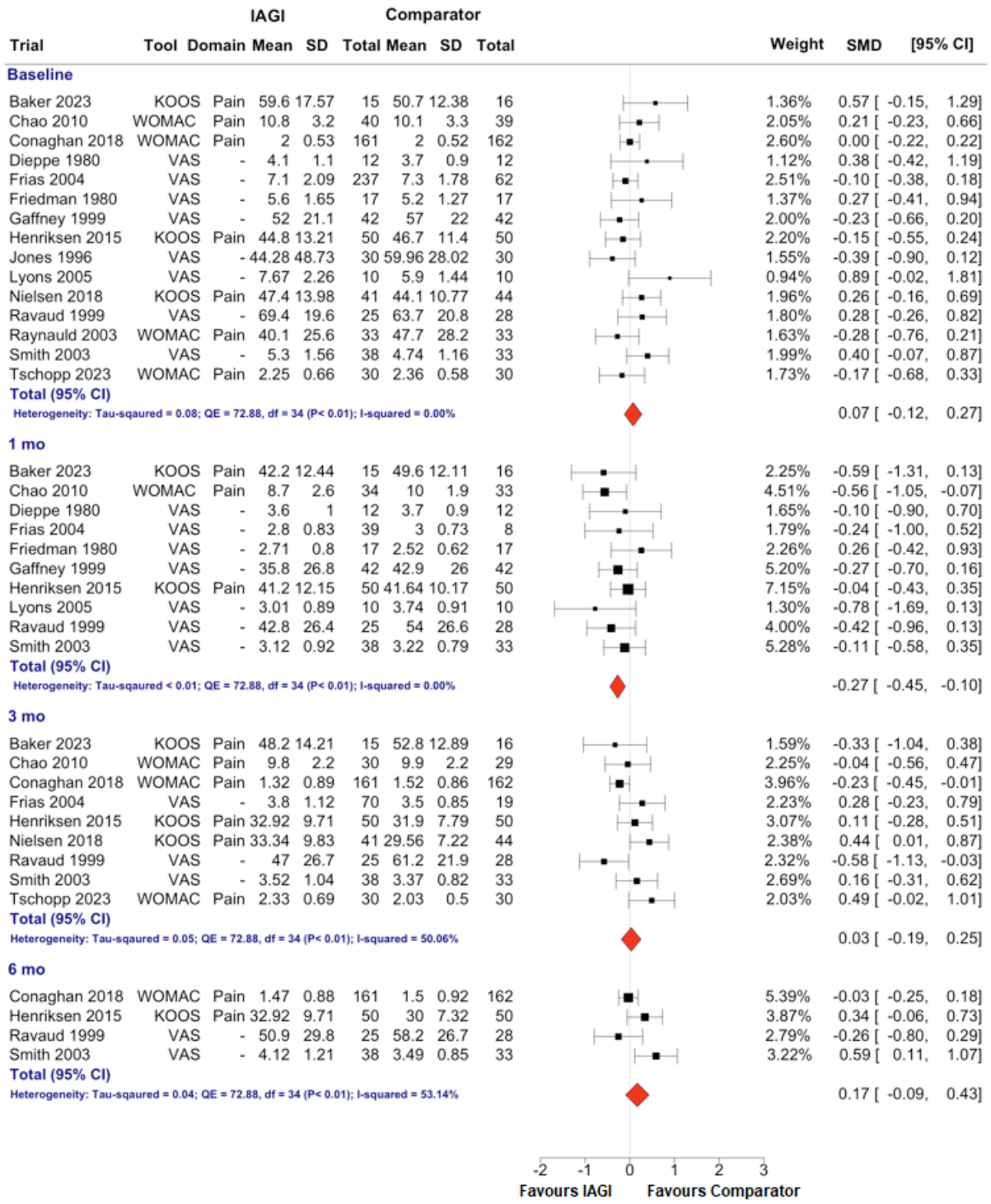
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 41 Sensitivity analysis on imputation of SD for pain at 3 months (knee OA)



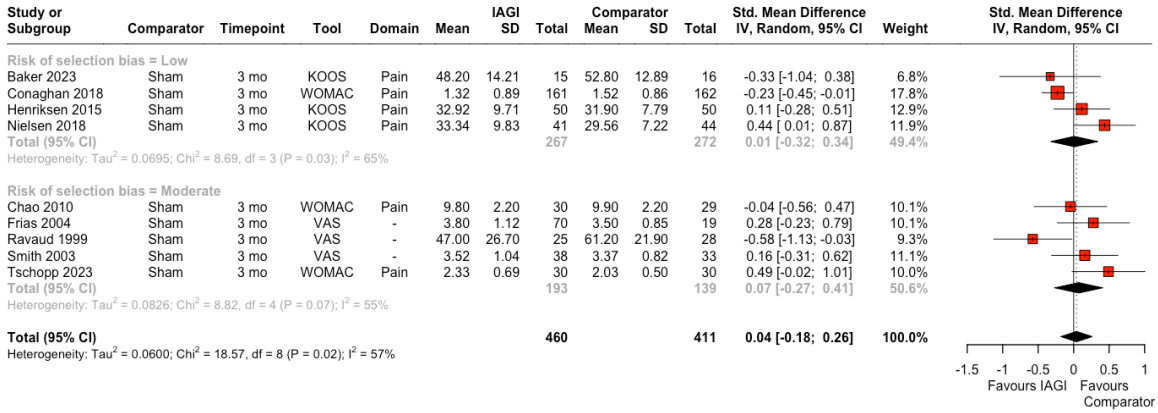
Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 42 Sensitivity analysis on removal of outliers for pain (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **SMD**: standardised mean difference; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

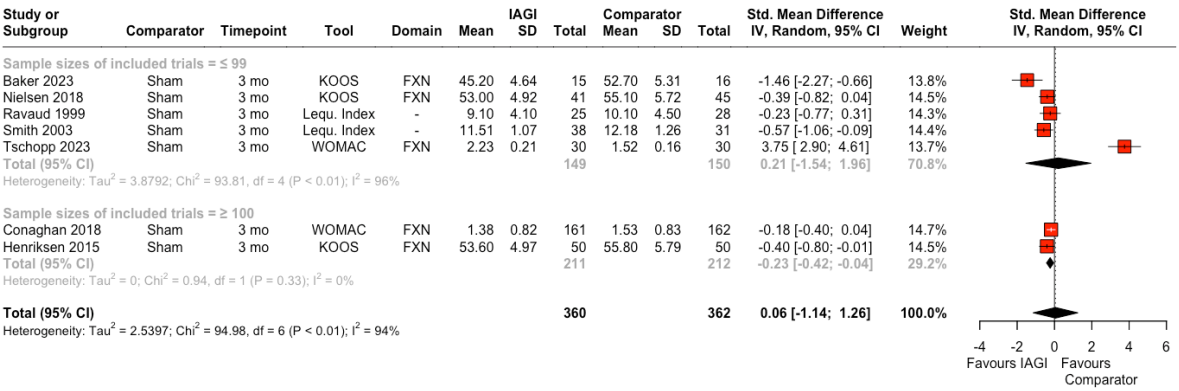
Figure 43 Sensitivity analysis on risk of selection bias for pain at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

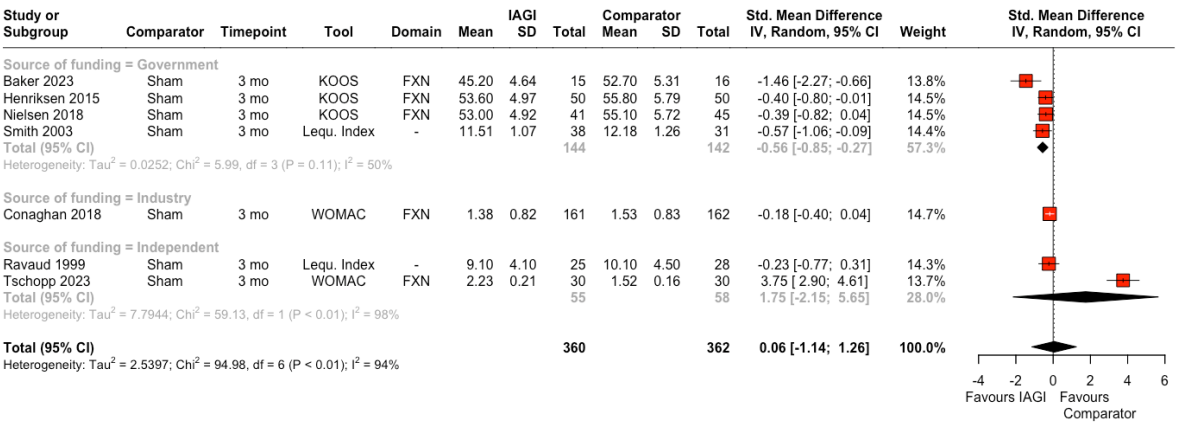
13.5.2.2 Function

Figure 44 Sensitivity analysis on sample size ⩽99 and ⩾100 for function at 3 months (knee OA)



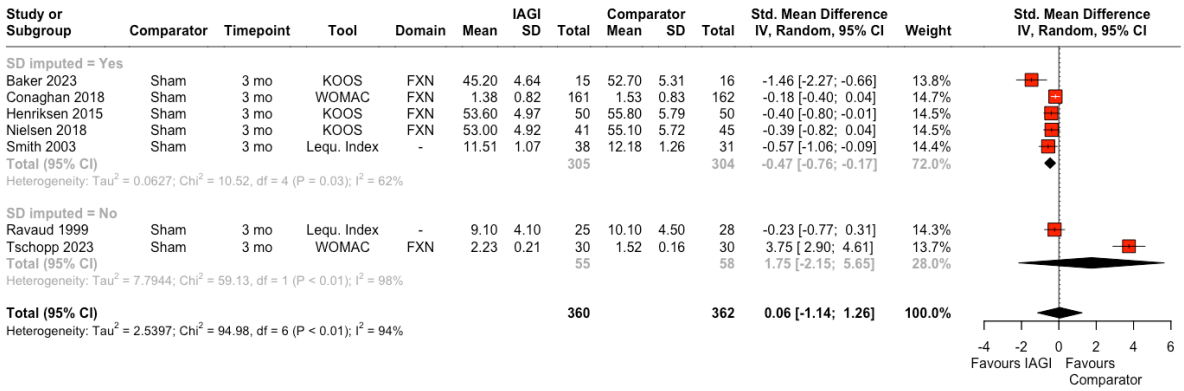
Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 45 Sensitivity analysis on funding for function at 3 months (knee OA)



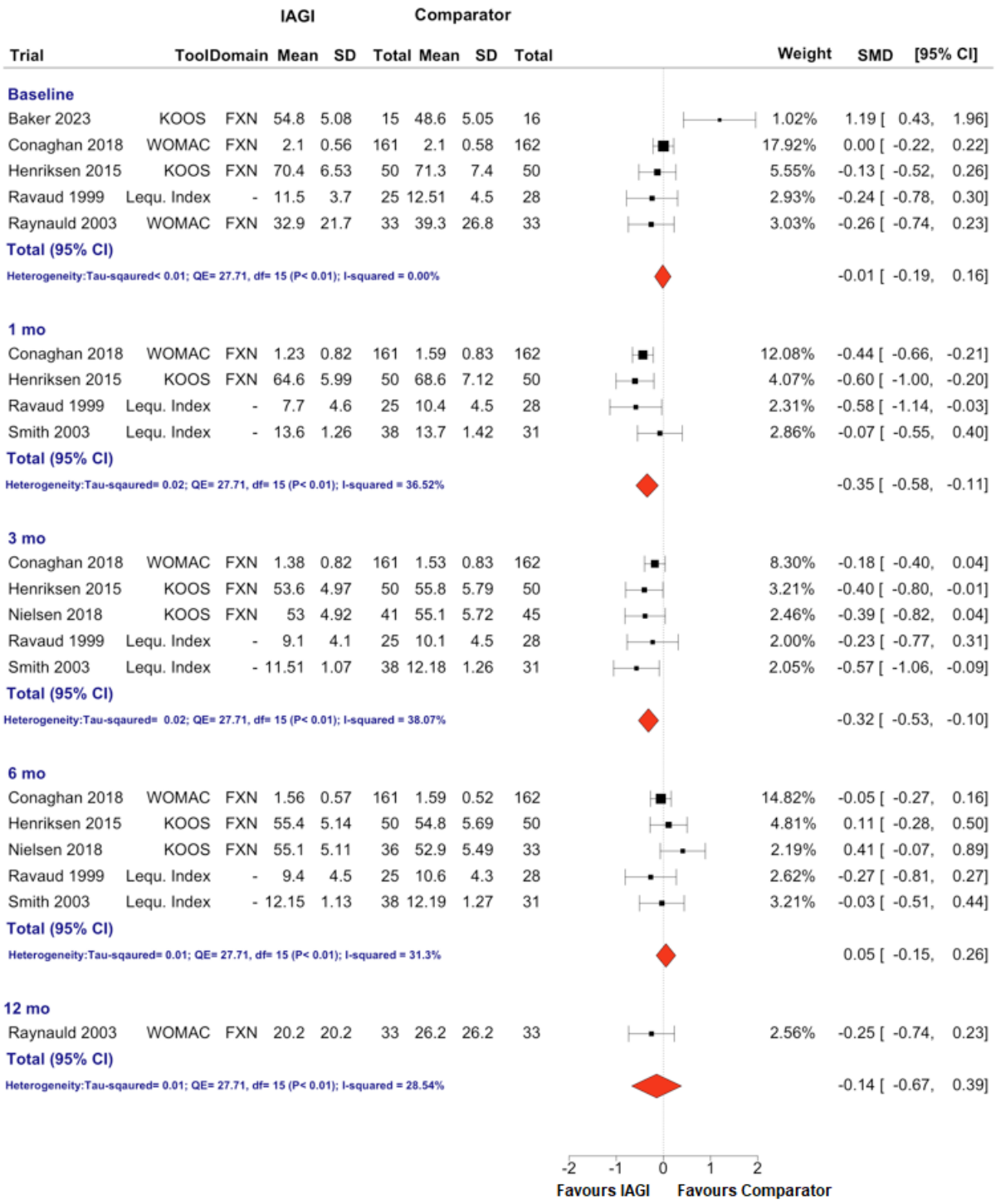
Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 46 Sensitivity analysis on imputation of standard deviation for function at 3 months (knee OA)



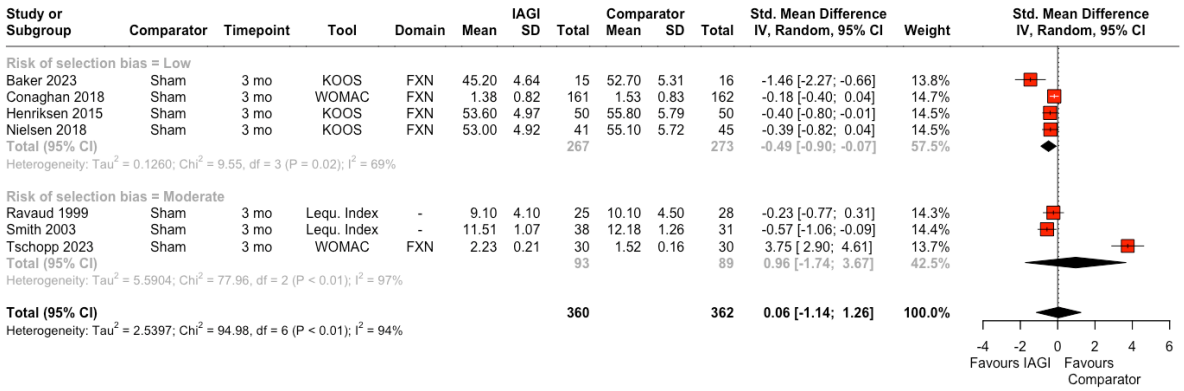
Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV:** inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

Figure 47 Sensitivity analysis of function when outlier data were excluded (knee OA)



Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **SMD**: standardised mean difference; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

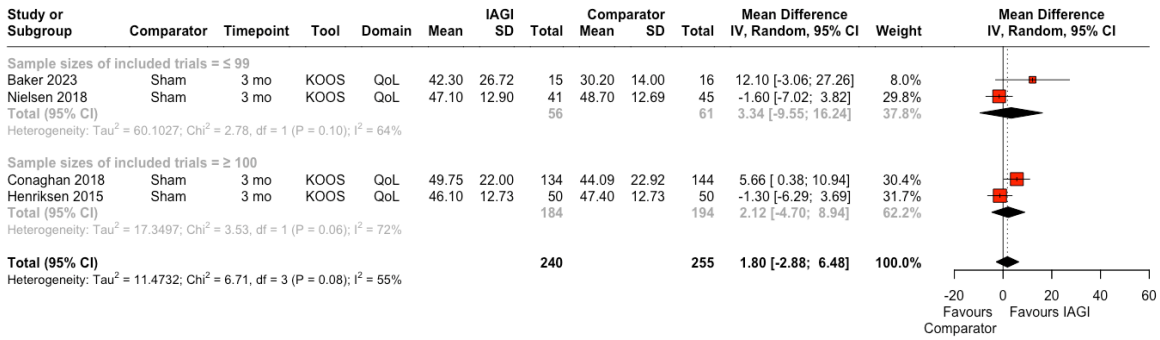
Figure 48 Sensitivity analysis on risk of selection bias for function at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **FXN**: function; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index.

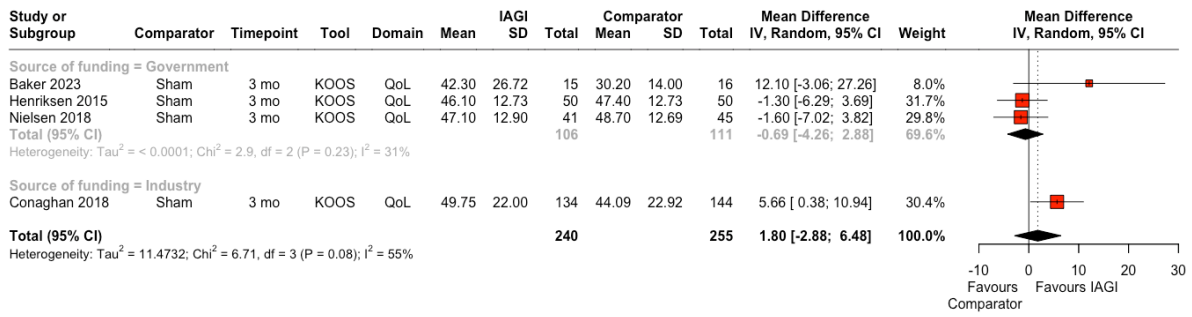
13.5.2.3 Quality of life

Figure 49 Sensitivity analysis on sample size ⩽99 and ⩾100 for quality of life at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **QoL**: quality of life; **SD**: standard deviation.

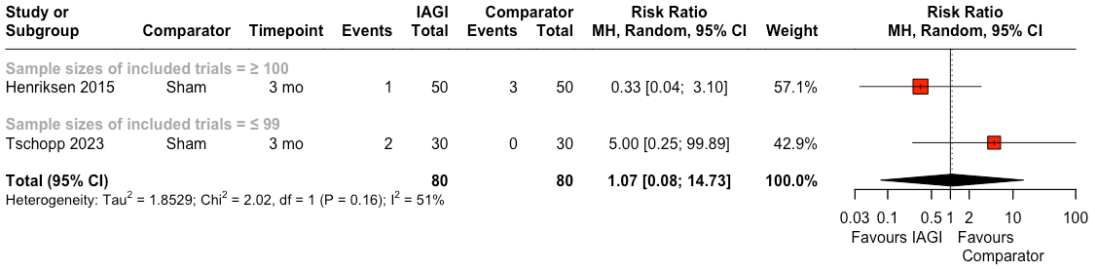
Figure 50 Sensitivity analysis on funding for HRQoL at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **HRQoL**: health-related quality of life; **IV**: inverse variance; **KOOS**: Knee Injury and Osteoarthritis Outcome Score; **mo**: months; **SD**: standard deviation.

13.5.2.4 Adverse events

Figure 51 Sensitivity analysis on sample size ⩽99 and ⩾100 for adverse events at 3 months (knee OA)



Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

Figure 52 Sensitivity analysis on funding for adverse events at 3 months (knee OA)

Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **MH**: Mantel-Haenszel; **mo**: months.

13.6 Economics appendices

13.6.1 Economic summary tables

Table 54 Economic summary table: cost-effectiveness of IAGI vs the comparator

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Wilson, 2020[123]	New Zealand healthcare system	**Intervention pathway**: core 1st line Tx -> adjunctive Tx if persistent OA pain -> TKR if moderate-to-severe OA pain and KL grade 3+ after adjunctive intervention **Comparator pathway**: core 1st line Tx -> TKR if moderate-to-severe OA pain and KL grade 3+ Core 1st line Tx: patient education, land-based exercise therapy, weight loss if overweight or obese Adjunctive interventions: walking cane, heat therapy, aquatic exercise, duloxetine, oral NSAIDs, topical NSAIDs, massage therapy, CBT and IAGI	2013 New Zealand adult population age 35–99 years. Note: Individuals with existing OA at model baseline or incident OA over model simulation period progressed to either the intervention or comparator pathway.	**Evaluation type**: model based **Model type**: the NZ-MOA model, a validated state-transition microsimulation model. Additional info on model: the NZ-MOA model simulated the disease course of knee OA, including radiographic disease incidence and progression (defined by KL grade), fluctuation (with gradual progression) of disease symptoms and HRQoL losses, and treatment pathways and their costs and effects. It has previously been used in a variety of economic studies. **For each set of parameter values the model was run for a cohort of 100,000 individuals. **Time horizon**: lifetime. **Discount rate**: 3.5% p.a. for costs and effects.	**IAGI**: Studies cited in the SR informing the RACGP CPG,[161] including Raynauld 2003, Smith 2003, Chao 2010, Di Sante 2012, Henriksen 2015, Petrella 2015† **Comparators**: Additional sources of inputs for comparators were reported but not extracted (refer to Appendix C, Input parameter sources). Note: for IAGI, only WOMAC outcomes were available, so mapping was required to estimate SF-12/SF-36 effects to inform modelling. The NZ-MOA model reduces the SF-12/SF-36 domains to the 6 dimensions of the SF-6D, from which utility values were calculated using UK population values.	**ICER**: An ICER for IAGI vs core treatments only was not reported (frontier analysis was used). Using the reported incremental costs and QALYs, an ICER of NZD24,531.74 (CHF17,774.29) was calculated. **Key drivers**: Treatment cost, utility instrument, adverse events, discount rate.	**Author's conclusion:** 'IAGI had a high probability of being cost-effective (>80%) at all relevant WTP levels (i.e. 1-, 2- and 3-times GDP per capita).' The authors found: 'IAGI to be cost-effective from the health sector perspective compared to recommended core treatments only, at the population level.'

Abbreviations: **CBT**: cognitive behavioural therapy; **CHF**: Swiss Franc; **CPG**: clinical practice guideline; **GDP**: gross domestic product 2013 NZD; **HRQoL**: health-related quality of life; **IAGI**: intra-articular glucocorticoid injection; **ICER**: incremental cost-effectiveness ratio; **KL**: Kellgren–Lawrence; **NSAID**: non-steroidal anti-inflammatory drug; **NZD**: New Zealand dollars; **NZ-MOA**: New Zealand Management of Osteoarthritis; **OA**:

osteoarthritis; **QALY**: quality-adjusted life year; **RACGP**: Royal Australian College of General Practitioners; **SF**: short form survey; **SR**: systematic review; **TKR**: total knee replacement; **Tx**: treatment; **UK**: United Kingdom; **WOMAC**: Western Ontario and McMaster Universities Osteoarthritis Index; **WTP**: willingness-to-pay.
Note: NZ-MOA model is a validated state-transition microsimulation model of the disease course, healthcare costs, and HRQoL impacts of knee OA.
† Of the IAGI studies mentioned, 4 of the 6 have been included in the current HTA.[99, 102, 104, 111] The remaining 2 studies were excluded due to incorrect comparator.[162, 163]

Table 55 Economic summary table: detailed extraction of input values and assumptions used in existing economic analyses

Component	Description	Comments
Which studies were included in the estimation of treatment effect for IAGI?	WOMAC scores were obtained from the following studies: Raynauld 2003, Smith 2003, Chao 2010, Di Sante 2012, Henriksen 2015, Petrella 2015.[99, 102, 104, 111, 162, 163] Overall, IAGI was modelled to result in a change in WOMAC score of - 0.73 (SE: 0.32)	Authors searched the original studies cited in the systematic review informing the RACGP CPG to obtain model input data. The CPG's technical report indicates data for IAGI included in the guideline were sourced from Jüni 2015.
How were treatment effects modelled?	WOMAC scores were mapped to SF-12/SF-36 effects. These were reduced to SF-6D utility values through the NZ-MOA model, allowing for the calculation of QALYs.	For treatments for which SF-12 or SF-36 data were unavailable, effects reported using the WOMAC index were extracted and transformed. The NZ-MOA model reduces the SF-12/SF-36 domains to the SF-6D utilities, valued using UK tariffs.
Duration of treatment effect modelled	Continued use of IAGI at a rate of 4 injections/year to maintain treatment effect was assumed.	Where treatments were only shown to be effective during the period of utilisation, continual use to maintain treatment effect was assumed.
Adherence	Withdrawals due to minor AEs or poor adherence are captured. Rates reported below were annualised, assuming constant withdrawal rate over time. For IAGI: 1/102 (1.0%) withdrawals over 26 weeks. For core treatments: • land-based exercise 42/640 (6.6%) over 52 weeks • weight management 32/126 (25.4%) over 78 weeks • Education: 45/284 (15.8%) over 52 weeks.	Rates of treatment withdrawal due to minor AEs or poor adherence were extracted from systematic reviews informing the RACGP CPG. They were assumed to be constant over time.
Progression to TKA modelled?	Input values used to parameterise these transitions are unclear from the publication. They may be inherently captured within the NZ-MOA.	The simulation pathway suggests that, in the intervention scenario, patients whose pain persists after receiving core first-line treatments are offered the adjunctive treatment being evaluated. Individuals whose pain progresses to moderate-to-severe and KL grade ≥3 are offered TKA after the adjunctive therapy (intervention arm) or core treatment (comparator arm). It is unclear how these criteria are determined.

Component	Description	Comments
AEs	The following SAE rates were included for IAGI: • vascular events: 0.2/1000 per year, including deaths 0.1/1000 per year • heart failure: 0.2/1000 per year • upper gastrointestinal complications: 0.2/1000 per year	Rates of SAEs resulting in hospitalisation or death were obtained from published systematic reviews. HRQoL impacts of these SAEs were sourced from published literature. Costs of treatment for SAEs were derived from NZ public health system cost weights.

Abbreviations: **AE**: adverse event; **CHF**: Swiss franc; **CPG**: clinical practice guideline; **HRQoL**: health-related quality of life; **IAGI**: intra-articular glucocorticoid injection; **KL**: Kellgren–Lawrence; **NSAID**: non-steroidal anti-inflammatory drug; **NZD**: New Zealand dollar; **NZ-MOA**: New Zealand Management of Osteoarthritis; **QALY**: quality-adjusted life year; **RACGP**: Royal Australian College of General Practitioners; **SAE**: serious adverse event; **SF**: short form survey; **TKA**: total knee arthroplasty; **WOMAC**: Western Ontario and McMaster Universities Osteoarthritis Index.

13.6.2 Economic appraisal checklists

Table 56 Applicability assessment of the existing economic evaluations using NICE's appraisal checklist items

Checklist question	Response	Comments
1.1 Is the study population appropriate for the review question?	Partly	Patients with existing OA at model baseline or incident OA over model simulation period.
1.2 Are the interventions appropriate for the review question?	Yes	Study compared core treatments alone to core treatments plus one of multiple adjunct therapies. IAGI was one of the adjunct therapies assessed.
1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?	Partly	New Zealand healthcare system setting.
1.4 Is the perspective for costs appropriate for the review question?	Yes	Healthcare system perspective.
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Primary outcomes included lifetime change in population QALYs and healthcare costs, cost-effectiveness ratios, and NMB of each recommended adjunctive intervention. This aligns with the aims and scope of the study.
1.6 Are all future costs and outcomes discounted appropriately?	Yes	The study discounted future costs and outcomes at an annual rate of 3.5%.
1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?	Yes	The study measured outcomes in terms of incremental cost per QALY.
Overall Judgement	Partly applicable – the study fails to meet ≥1 of the applicability criteria, and this could change the conclusions about cost-effectiveness.	

Abbreviations: **CBT**: cognitive behavioural therapy; **IAGI**: intra-articular glucocorticoid injection; **NMB**: net monetary benefits; **NSAIDs**: non-steroidal anti-inflammatory drugs; **OA**: osteoarthritis; **QALY**: quality-adjusted life year.

Table 57 Limitations assessment of existing economic evaluations using NICE appraisal checklist items

Checklist question	Response	Comments
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	The NZ-MOA model simulated the disease course of knee OA, fluctuation of disease symptoms and HRQoL losses, and treatment pathways and their costs and effects. It has previously been used in a variety of economic studies.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	A lifetime horizon is used.
2.3 Are all important and relevant outcomes included?	Yes	Disease progression, costs, QALYs, cost-effectiveness ratios and NMB
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Derived from the most recently updated RACGP guideline systematic review
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Evidence of effectiveness was sourced from existing systematic reviews and meta-analyses (systematic review conducted for the most recent RACGP guideline)
2.6 Are all important and relevant costs included?	Yes	Costs of interest included the cost of IAGI injections, GP visit (for IAGI), land-based exercise, weight management and education.
2.7 Are the estimates of resource use from the best available source?	Yes	Evidence on resource use was identified systematically and based on clinical trial data included in the RACGP guideline systematic review.
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	This study was funded by the Health Research Council of New Zealand (Project grant 15/263). The funding agency played no role in study design, conduct, interpretation, reporting or the decision to submit for publication, and had no financial conflicts of interest.
Overall Judgement	Minor limitations – the study met all quality criteria.	

Abbreviations: **GP**: general practitioner; **HRQoL**: health-related quality of life; **IAGI**: intra-articular glucocorticoid injection; **NICE**: National Institute of health and Care Excellence; **NMB**: net monetary benefits; **NZ-MOA**: New Zealand Management of Osteoarthritis; **OA**: osteoarthritis; **QALY**: quality-adjusted life year; **RACGP**: Royal Australian College of General Practitioners.
Note: NZ-MOA model is a validated state-transition microsimulation model of the disease course, healthcare costs, and HRQoL impacts of knee OA.

13.6.3 Glucocorticoid preparations in Switzerland

Table 58 Glucocorticoid preparations for intra-articular injections included on the Spezialitätenliste

Active substance	ATC Code	Preparation	Recommended dose (per injection)	Cost per pack (CHF)
Betamethasone	H02AB01	Celestone® Chronodose®	Very large joint (e.g. hip): 1–2 ml Large joint (e.g. knee): 1 ml	• 8.20 for 1 x 1 ml ampoule
		Diprophos®		• 9.15 for 1 x 1 ml ampoule • 41.70 for 5 x 1 ml ampoules
Triamcinolone	H02AB08	Kenacort® (triamcinolone acetonide)	Large joint (e.g. hip, knee): 20–40 mg	• 9.20 for 1 x 1 ml ampoule of 10 mg/ml suspension • **18.75 for 1 x 1 ml ampoule of 40 mg/ml suspension**
		Triamcort® Depot (triamcinolone acetonide)	Large joint (e.g. hip, knee): 20–40mg	• 7.95 for 1 x 1 ml ampoule of 10 mg/m crystal suspension • 112.95 for 25 x 1ml ampoules of 10 mg/ml crystal suspension • 14.85 for 1 x 1 ml ampoule of 20 mg/ml crystal suspension • 182.45 for 25 x 1 ml ampoules of 20 mg/ml crystal suspension • **17.25 for 1 x 1 ml ampoule of 40 mg/ml crystal suspension** • **242.2 for 25 x 1 ml ampoules of 40 mg/ml crystal suspension** • 27.95 for 1 x 2 ml ampoule of 80 mg/2 ml crystal suspension • 408 for 25 x 2 ml ampoules of 80 mg/2 ml crystal suspension
Methylprednisolone	H02AB04	Depo Medrol® (methylprednisolone acetate)	Gross joint (e.g. hip[A], knee, tibiotarsal joint, shoulder): 20–80 mg	• 8.15 for 1 x 1 ml of 40 mg/ml suspension • 117.25 for 25 x 1 ml of 40 mg/ml suspension • 15.6 for 1 x 2 ml of 80 mg/2 ml suspension
Methylprednisolone combinations	H02BX01	Depo Medrol® Lidocaine (methylprednisolone acetate)	Great joint (e.g. hip[A], knee, ankle, shoulder): 20–80 mg	• 9.05 for 1 x 1 ml of 40 mg/ml suspension • 139.95 for 25 x 1 ml of 40 mg/ml suspension • 17.15 for 1 x 2 ml of 80 mg/2 ml suspension
Dexamethasone	H02AB02	Dexamethasone Galepharm	For peri-articular and intra-articular treatment or by local infiltration under strict aseptic conditions: inject 4 or 8 mg	• 15.1 for 3 x 1ml ampoules of 4 mg/ml suspension • 39.4 for 10 x 1 ml ampoules of 4 mg/ml suspension • 19.95 for 3 x 2 ml ampoules of 8 mg/2 ml suspension

Active substance	ATC Code	Preparation	Recommended dose (per injection)	Cost per pack (CHF)
		Dexamethasone Zentiva®	Large joint (e.g. hip, knee)[B]: 4–6 mg; Small joint: 0.8–2 mg	• 7.15 for 1 x 1 ml ampoule of 5 mg/ml suspension • 15.5 for 3 x 1 ml ampoules of 5 mg/ml suspension • 77.1 for 25 x 1 m ampoules of 5 mg/ml suspension
		Mephameson®	For peri-articular and intra-articular treatment or by local infiltration under strict aseptic conditions: inject 4 or 8 mg	• 14.9 for 3 x 1 ml ampoules of 4 mg/ml suspension • 72.35 for 25 x 1 ml ampoules of 4 mg/ml suspension • 128.25 for 50 x 1 ml ampoules of 4 mg/ml suspension • 19.75 for 3 x 2 ml ampoules of 8 mg/2 ml suspension • 208.85 for 50 x 2 ml ampoules of 8 mg/2 ml suspension • 101.05 for 5 x 3 ml ampoules of 50 mg/3 ml suspension • 377.65 for 25 x 3 ml ampoules of 50 mg/3 ml suspension

Abbreviations: **ATC**: Anatomical Therapeutic Chemical; **CHF**: Swiss francs.
Notes:
A: Hip considered as a gross/great joint.
B: Hip and knee considered as large joints.

13.6.4 Model input parameters

Table 59 Input parameters used in the economic analysis

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes, source
Cost of anaesthesia	1.50	NA	NA	NA	NA	Expert opinion for price per 2 ml of lidocaine. Assumed need for 1.5 doses.
Cost of physician visit[A]	65.62	41.01	90.22	NA	Triangular[B,C]	TARMED positions 00.0010, 00.0020 and 00.0030. Duration of 15 to 30 minutes (mean of 22.5 minutes in base case).
Cost of ultrasound imaging	109.68	NA	NA	NA	NA	Simple average across TARMED positions 39.3700 and 39.3710
Cost of joint puncture for IAGI	56.79	NA	NA	NA	NA	TARMED position 24.0130
Cost of glucocorticoid (triamcinolone)	15.23	9.69	18.75	NA	Triangular (9.69, 17.25, 18.75)[C]	Simple average cost across 40 mg triamcinolone preparations available on the Spezialitätenliste (Kernacort 40 mg/ml, Triamcort Depot 40 mg/ml).
Average cost per tablet across 500 mg paracetamol packets	0.14	0.09	0.22	NA	Triangular (0.09, 0.11, 0.22)[C]	Simple average cost per tablet across all 500-mg tablet packs available on the Spezialitätenliste.
Number of paracetamol tablets in the IAGI arm	174.16	164.56	183.76	4.90	Normal	Calculated based on rescue medication use data presented in Conaghan 2018.[97]
Number of paracetamol tablets in the SOC arm	214.35	204.75	223.95	4.90	Normal	
Proportion of patients receiving anaesthesia	0.43	0.00	0.80	NA	Triangular (0.00, 0.49, 0.80)[C]	Simple average from expert consultation questionnaire (n=3). Lower and upper bounds reflect highest and lowest judgements.
Proportion of patients receiving ultrasound	0.43	0.30	0.50	NA	Triangular (0.30, 0.49, 0.50)[C]	
WOMAC function score in the IAGI arm at 1 month	33.83	29.42	38.28	2.27	Normal	Mean (SD) WOMAC domain scores (pain; function) at baseline and at 1, 3 and 6 months follow-up, pooled using the inverse variance weighting method. Conaghan 2018
WOMAC function score in the IAGI arm at 3 months	38.15	32.56	43.78	2.86	Normal	

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes, source
WOMAC function score in the IAGI arm at 6 months	41.93	36.68	47.22	2.69	Normal	and Smith 2003 included in the pooled results.[97, 111] Standardised to a 0–100 scale for use in the Bilbao 2020 mapping algorithm.[124]
Baseline WOMAC function score in the IAGI arm	51.79	50.25	53.31	0.78	Normal	
WOMAC function score in the SOC arm at 1 month	40.81	39.12	42.50	0.86	Normal	
WOMAC function score in the SOC arm at 3 months	37.56	36.52	38.60	0.53	Normal	
WOMAC function score in the SOC arm at 6 months	38.43	35.92	40.94	1.28	Normal	
Baseline WOMAC function score in the SOC arm	48.71	42.17	55.69	3.44	Normal	
WOMAC pain score in the IAGI arm at 1 month	30.16	20.41	36.17	1.34	Normal	
WOMAC pain score in the IAGI arm at 3 months	35.11	23.33	43.25	1.88	Normal	
WOMAC pain score in the IAGI arm at 6 months	38.89	23.74	48.16	2.16	Normal	
Baseline WOMAC pain score in the IAGI arm	50.77	49.09	52.43	0.85	Normal	
WOMAC pain score in the SOC arm at 1 month	37.68	32.28	51.02	0.11	Normal	
WOMAC pain score in the SOC arm at 3 months	36.52	29.36	50.42	0.73	Normal	
WOMAC pain score in the SOC arm at 6 months	36.60	30.15	51.79	0.50	Normal	
Baseline WOMAC pain score in the SOC arm	47.83	43.93	51.73	1.99	Normal	

Abbreviations: **IAGI**: intra-articular glucocorticoid injection; **SD**: standard deviation; **SOC**: standard of care; **WOMAC**: Western Ontario and McMaster Universities Osteoarthritis Index

Notes:

A: applied in modelling as CHF18.61 (TARMED 00.0010) + [CHF18.61 (TARMED 00.0020) × ***x***] + CHF8.21 (TARMED 00.0030), where ***x*** = 2.5 [range 1 to 4].

B: triangular distribution (1, 2.5, 4) applied to number of TARMED 00.0020 positions (i.e. '***x***' in calculation detailed above).

C: mode for triangular distributions calculated as: 3 × mean value *minus* upper value *minus* lower value.

13.6.5 Representativeness of health economics estimates (compared to clinical estimates)

13.6.5.1 Aim

The inputs that could be used to inform the CUA were limited to trials that reported pain and function using the WOMAC tool (see ***Section 7.4.2*** for more information). This means that not all the pain and function data reported in the clinical analyses (***Section 6.2.5.1***) could be used as inputs for the CUA. Therefore, the aim of the analyses was to determine if the inputs used to inform the CUA were representative of the findings of the clinical analyses (***Section 6.2.5.1***).

13.6.5.2 Methods

The 2 trials that reported WOMAC pain and function data were meta-analysed (pairwise) in *R studio* using a random-effects model with inverse-variance weighting.[97, 111] The output of interest was SMD with corresponding 95% CI.

SMD and 95% CI values from the health economic pairwise meta-analyses were compared against corresponding (i.e. timepoint and outcome) SMD and 95% CI values from the longitudinal (mixed-effects) meta-analyses reported in the clinical section (***Section 6.2.5.1***) using a two-tailed unpaired z-test (alpha = 0.05). The z-tests were conducted in *Stata 18 BE* (StataCorp LLC).[164] The summary measures from health economic analyses were considered to be representative of the clinical analyses (even if statistically different) if the directions of effects were similar. The statistical difference was interpreted as either an overestimation or underestimation of the treatment or placebo effect. If the direction of effect between the summary measures was both contradictory and statistically different, the health economic analyses were considered unrepresentative of the clinical analyses. Baseline summary measures were considered to be representative if the estimate was close to the null, as this is theoretically consistent with the RCTs.[165]

13.6.5.3 Results

The results of the z-tests between the health economic and clinical analyses are summarised in ***Table 60***.

Only 2 of the 4 summary measures from the health economic analyses on pain were representative of the clinical analyses. The summary measures reported at 1 and 6 months were representative of the clinical analyses; those reported at baseline and 3 months were not representative of the clinical analyses. The health economic summary measures at baseline lean away from the null, indicating that at baseline, patients allocated to the comparator-arm experience less pain than do those allocated to the IAGI-arm. This is inconsistent with theoretical baseline summary measures in the RCTs.[165] Likewise, the 3-month health economic summary estimate was unrepresentative of the clinical analysis. The summary measure was an overestimation of the IAGI treatment effect.

With regard to function, 3 of the 4 summary measures from the health economic analyses were representative of the clinical analyses. The summary measures reported at baseline and at 1 and

3 months were representative of the clinical analyses. The health economic analyses were consistent with theoretical baseline RCT measures.[165] The 6-month health economic summary measure was not representative of the clinical analysis. The result from the health economic analysis was an underestimation of the placebo effect relative to findings from the clinical analysis.

13.6.5.4 Conclusion

In conclusion, the majority (5/8) of inputs into the CUA model that came from the health economic analysis were representative of the clinical analyses. However, 4 of these 5 representative summary measures were either an overestimation (i.e. pain at 1 month, function at 1 month, function at 3 months) of the IAGI treatment effect or an underestimation (i.e. pain at 6 months) of the placebo effect, relative to the clinical analyses. Therefore, the output of the CUA should be interpreted with caution.

Table 60 Applicability of health economic estimates as representative measures for clinical estimates

Analysis	Number of trials	Treatment effect†		Z-test ‡					Interpretation of differences in treatment effect	Applicability of health economic treatment effect estimates
		SMD	95% CI	Sample size	SMD difference		p-value	Statistical differences between meta-analyses		
					Mean	95% CI				
Pain										
Baseline										
Clinical	15	0.03	-0.09 to 0.14	1,389	-0.12	-0.14 to -0.10	<0.01*	Statistically different	• Both analyses estimates favour the comparator and cross the null. • Clinical analysis estimate is close to the null. This is consistent with general baseline measurements in RCTs. • Health economic analysis estimate is impacted by an imbalance in pain experienced by patients at baseline between the trial arms. The imbalance is caused by Smith et al. 2003.[111] In the trial, the patients in the comparator arm have a lower mean pain score at baseline than those in the IAGI arm.	Not representative
Health economic	2	0.15	-0.24 to 0.53	394						
1 month										
Clinical	12	-0.37	-0.57 to -0.16	914	0.14	0.13 to 0.15	<0.01*	Statistically different	• Both analysis estimates favour IAGI and neither cross the null. • Health economic analysis estimate is an overestimation of the treatment effect of IAGI.	Representative
Health economic	2	-0.51	-0.76 to -0.26	394						
3 months										
Clinical	9	0.04	-0.18 to 0.26	817	0.25	0.24 to 0.26	<0.01*	Statistically different	• The health economic analysis estimate contradicts the clinical analysis estimate.	Not representative

Analysis	Number of trials	Treatment effect†		Z-test ‡					Interpretation of differences in treatment effect	Applicability of health economic treatment effect estimates
		SMD	95% CI	Sample size	SMD difference		p-value	Statistical differences between meta-analyses		
					Mean	95% CI				
Health economic	2	-0.21	-0.46 to 0.04	394					• The clinical analysis estimate favours the comparator and crosses the null. ○ This is consistent with the findings of the clinical sensitivity analysis where the outlier trials were removed (***Figure 42***). • The health economic analysis estimate favours IAGI and touches the null. • The health economic analysis estimate is a significant overestimation of the treatment effect in favour of IAGI.	
6 months										
Clinical	6	0.42	0.00 to 0.84	676	0.27	0.24 to 0.30	<0.01*	Statistically different	• Both analysis estimates favour the comparator. • Both analysis estimates include the possibility of no treatment effect. The health economic analysis estimate crosses the null, whereas the clinical analysis estimate only touches the null. • The health economic analysis estimate is an underestimation of the placebo effect. ○ In the clinical sensitivity analysis where the outlying trials were removed (***Figure 42***), the clinical analysis estimate is consistent with the health economics analysis estimate.	Representative
Health economic	2	0.15	-0.33 to 0.63	394						

Analysis	Number of trials	Treatment effect†		Z-test ‡					Interpretation of differences in treatment effect	Applicability of health economic treatment effect estimates
		SMD	95% CI	Sample size	SMD difference		p-value	Statistical differences between meta-analyses		
					Mean	95% CI				
Function										
Baseline										
Clinical	8	0.26	-0.90 to 1.43	788	0.26	0.22 to 0.30	<0.01*	Statistically different	• The clinical analysis estimate is impacted by an imbalance of functional limitations experienced at baseline between the two arms. ○ The imbalance is caused by trials considered to be outliers. In these trials, the patients in the comparator arms have more knee function at baseline than the those in the IAGI arm. ○ In the clinical sensitivity analysis where the outlying trials were removed (***Figure 47***), the clinical analysis estimate is close to the null—consistent with general baseline measurements in RCTs. • Health economic analysis estimate is equal to the null. This is consistent with general baseline measurements in RCTs.	Representative
Health economic	2	0.00	-0.20 to 0.20	392						
1 month										
Clinical	5	-0.73	-1.41 to -0.06	576	-0.27	-0.30 to -0.24	<0.01*	Statistically different	• Both analysis estimates favour IAGI and neither cross the null. • The health economic estimate is an underestimation of the treatment effect of IAGI.	Representative
Health economic	2	-0.46	-0.66 to -0.26	392						

Analysis	Number of trials	Treatment effect†		Z-test ‡					Interpretation of differences in treatment effect	Applicability of health economic treatment effect estimates
		SMD	95% CI	Sample size	SMD difference		p-value	Statistical differences between meta-analyses		
					Mean	95% CI				
3 months										
Clinical	7	0.06	-1.14 to 1.26	722	0.04	-0.01 to 0.09	0.12	Not statistically different	• Both analysis estimates are close to the null. • In the clinical sensitivity analysis where the outlying trials were removed (***Figure 47***), the clinical analysis contradicts the health economic estimate and significantly favours IAGI.	Representative
Health economic	2	0.02	-0.46 to 0.50	392						
6 months										
Clinical	6	0.84	-0.77 to 2.45	684	0.85	0.79 to 0.91	<0.01*	Statistically different	• The health analysis economic estimate contradicts the clinical estimate. • The clinical analysis estimate favours the comparator and crosses the null. • The health economic analysis estimate favours IAGI and crosses the null. • The health economic estimate is a significant underestimation of the placebo effect. ○ In the clinical sensitivity analysis where the outlying trials were removed (***Figure 47***), the clinical analysis estimate is consistent with the health economics analysis estimate.	Not representative
Health economic	2	-0.01	-0.21 to 0.18	392						

Abbreviations: **CI**: confidence interval; **IAGI**: intra-articular glucocorticoid injection; **RCT**: randomised control trial; **SD**: standard deviation; **SMD**: standardised mean difference.

Note:

† Treatment effect calculation (i.e. SMD and 95% CI): Clinical analysis – longitudinal random-effects meta-analysis; health economic analysis – pairwise random-effects meta-analysis.

‡ z-test assumption: summary measures (i.e. SMD and SD) from the clinical meta-analysis and health economic meta-analysis were treated as observed populations.

* Statistically significant difference