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Health Technology Assessment (HTA)

HTA Protocol

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

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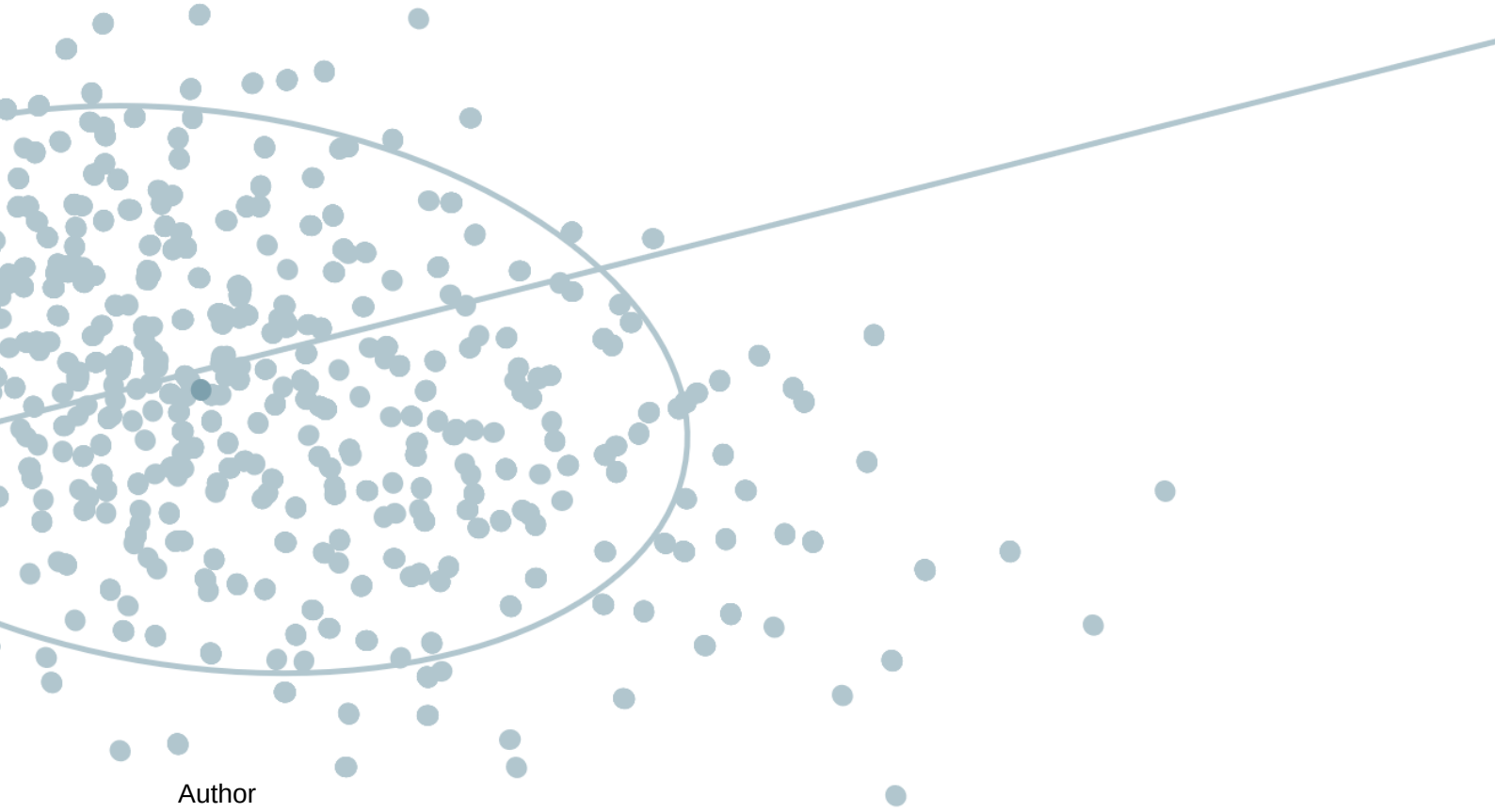

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The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

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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

Patients with knee and hip osteoarthritis (OA) may be treated with intra-articular glucocorticoid injections (IAGI), which are publicly reimbursed in Switzerland. However, the efficacy of IAGI in patients with knee or hip OA remains unclear, with conflicting recommendations from different clinical guidelines. The Federal Office of Public Health has contracted an independent evaluation of IAGI. This protocol outlines the proposed method for a health technology assessment (HTA) report evaluating the safety, efficacy, costs, cost-effectiveness and budget impact of IAGI compared to no treatment or placebo (including oral placebo or sham injection) in patients with hip or knee OA.

For the clinical evaluation, a systematic literature search of 5 databases (MEDLINE [Ovid], Embase [Ovid], the Cochrane Library, the INAHTA database and Econlit), grey literature and specialist orthopaedic and rehabilitation websites will be conducted to capture contemporary literature. Recent systematic reviews and meta-analyses that answer the research questions will be considered. Randomised controlled trials (RCTs) will be included in the absence of, or to update, existing systematic reviews and meta-analyses. Adverse event data may be supplemented with non-RCT data. A pairwise meta-analysis will be performed to evaluate the safety, efficacy and effectiveness outcomes in patients with hip or knee OA. Subgrouping and sensitivity analyses will also be performed to investigate heterogeneity in the meta-analyses.

Studies relevant to the cost or cost-effectiveness of the intervention will be identified as part of the systematic literature review. The approaches taken by existing studies and their results will be tabulated and synthesised narratively. In the absence of existing studies relevant to Swiss practice, the preferred approach is a de novo cost-utility analysis; however, this depends on the findings of the clinical review and the availability of reliable health-related quality of life data. Model type, structure and modelling technique will be presented in the Economic Analysis Plan. A budget impact analysis will be performed. Scenarios to be considered will be defined during the HTA process.

Social, legal, ethical and organisational issues will be addressed through non-systematic, targeted searches. Issues highlighted in studies within the clinical section will also be included. The findings will be summarised narratively.

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Abbreviations and acronyms

AAOS	American Academy of Orthopedic Surgeons
ACR	American College of Rheumatology
AE	adverse event
ARTS	osteoARthritis Treatment Satisfaction
BAG	Bundesamt für Gesundheit
CUA	cost-utility analysis
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis
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
HRQoL	health-related quality of life
HTA	health technology assessment
HOOS	Hip dysfunction and Osteoarthritis Outcome Score
IAGI	intra-articular glucocorticoid injection
INAHTA	International Network of Agencies for Health Technology Assessment
KOOS	Knee injury and Osteoarthritis Outcome Score
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSAIDs	non-steroidal anti-inflammatory drugs
NRS	numeric rating scale
OA	osteoarthritis
OAKHQOL	Osteoarthritis Knee and Hip Quality of Life questionnaire
OARSI	Osteoarthritis Research Society International
OKP	Obligatorische Krankenpflegeversicherung (mandatory health insurance)
PSA	probabilistic sensitivity analysis
PICO	population, intervention, comparator, outcome
QALY	quality-adjusted life year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SMD	standardised mean difference
TSQM 1.4	treatment satisfaction questionnaire version 1.4
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

Objective of the HTA Protocol

Based on a preliminary screening of the literature, the objectives of the health technology assessment (HTA) protocol are to formulate the research question; define the population, intervention, comparator and outcomes (PICO); and describe the methodology to conduct a systematic literature search and extract, analyse and synthesise the data in an HTA report on the topic. For this HTA report, key questions will be formulated addressing the HTA domains of efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, and ethical/legal/social and organisational issues.

1. Policy question and context

Each HTA topic entails addressing policy and research questions. In healthcare, a ***policy question*** is a request to regulate a reimbursement policy. It is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology. This HTA report addresses the policy question brought forward by the applicant, that of determining whether the criteria of effectiveness, appropriateness and economic efficiency (EAE) of intra-articular glucocorticoid injection (IAGI) justify the coverage of these services by mandatory health insurance for patients with osteoarthritis (OA) of the hip and knee in Switzerland.

Patients diagnosed with knee or hip OA may be managed with non-surgical active interventions, including IAGI, oral analgesics and physiotherapy.[1-4] These interventions aim to reduce pain, increase function and improve health-related quality of life (HRQoL). In Switzerland, intra-articular glucocorticoids such as betamethasone acetate, dexamethasone, methylprednisolone and triamcinolone, are currently covered by the mandatory health insurance (OKP) for the treatment of patients diagnosed with knee or hip OA.[5]

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. While it was previously viewed as a disease that solely caused mechanical cartilage degradation, it is now known to be a complex, fluctuating condition affecting the entire joint, with activated disease presenting as acute pain and swelling in the affected joint.[6] The knees, hips and hands are most affected.[3]

2.1 Pathogenesis, risk factors and diagnosis

The cause of OA is not fully understood, but it is believed to result from a complex interplay between 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]

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.[10] Other features include crepitus, joint deformity or effusion. In early knee OA the pain is related to activity and becomes more constant over time, while in late stage OA the 'background pain' is interspersed with unpredictable intense pain.[11] Pain is typically activity-related and resolves with rest. Early morning stiffness is transient, lasting <30 minutes.[12] However, as the disease progresses, pain can become more continuous and begin to affect activities of daily living.[7] This can lead to functional decline, reduced participation in daily activities and quality of life, 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.[13]

Blood tests, such as complete blood count, erythrocyte sedimentation rate and rheumatoid factor are usually normal in OA patients, although these may be ordered 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] Magnetic resonance imaging (MRI) can also be used to examine cartilage and bony changes during disease progression.[14] Cartilage depth and quality can be used as a possible radiological indicator for worsening disease in OA patients; however, a clear association between how cartilage depth and quality translates to clinical progression has not been established.[15]

2.2 Prognosis

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 clinically worsen or even improve.[16] It is considered a life-long disease, and therefore 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.[17,18] Some studies have also suggested that serum hyaluronic acid and tumour necrosis factor-α are associated with knee OA progression.[17,19] 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.[19]

The clinical progression of hip OA has been found to be associated with comorbidities, a higher Kellgren–Lawrence grade (i.e. a classification of the severity of osteoarthritis), superior or lateral femoral head migration and subchondral sclerosis.[20] An evidence synthesis of cohort and case-control studies has indicated that clinical progression is not associated with gender, social support, baseline use of pain medication, baseline quality of life, or limited range of motion of internal or external hip rotation.[20]

2.3 Treatment pathway

IAGI is usually given as a pain management intervention for patients with hip and knee OA who have not responded to oral or topical analgesics. However, there is discordance in the recommendations from guidelines on the management of hip and knee OA by scientific organisations such as the American College of Rheumatology (ACR),[21] the American Academy of Orthopedic Surgeons (AAOS),[22] the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO),[23] the European Alliance of Associations for Rheumatology (EULAR)[24] and the Osteoarthritis Research Society International (OARSI).[25] 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 physical therapy), this HTA will focus on evaluating the efficacy of IAGI in relation to placebo (including oral placebo and sham injection) or no treatment.

3. Technology description

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 quality of life.[26,27] 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.[26,28]

3.1 Types of glucocorticoids for intra-articular injection

The various IAGI preparations publicly reimbursed in Switzerland are outlined in ***Table 4*** (***Appendix A***).[29-31] 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.[32,33] IAGI can be administered with an equal volume of 1% or 2% anaesthetic (lidocaine and ropivacaine are usually used, as they provide more rapid onset and longer-lasting effects) to reduce discomfort and provide some immediate relief;[33] however, current evidence suggests that multiple intra-articular local anaesthetic injections may be associated with an increased risk of chondrolysis.[28,34] There is a lack of consensus on the optimal dose for IAGI, which may depend on the size of the joint or body region, the severity of inflammation and the amount of articular fluid present.

3.2 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, gene suppression of leukocytes, production of protease and cytokine, and alteration of collagen synthesis.[29] 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.[35] Similar to gout or pseudogout, intra-articular application of glucocorticoids is a potent treatment of microcrystalline inflammation.[36,37]

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.[28,38]

4. Population, Intervention, Comparator, Outcome (PICO)

Population, intervention, comparator and outcomes (PICO) are defined as:

Table 1 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 period of time (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, Kellgren–Lawrence stage, EULAR or the National Institute for Health and Care Excellence (NICE). Studies that include patients with secondary OA, or mixed populations (i.e. hip and knee combined) will be excluded. The definition of 'primary OA' and 'secondary OA' will be taken as defined in the included trials.

4.2 Intervention

The intervention of interest is IAGI (intra-articular glucocorticoid injection). The pharmaceuticals used for IAGI will be 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 given 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.[39]

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 inactive substance such as starch or sugar.[40,41]

Sham injection and oral placebo can be grouped and subgroup analysis done to investigate the impact of the 2 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.[42]

Pain: Pain is a common symptom of OA. It is caused by the decreased ability of the cartilage to act as a shock absorber, synovitis and bone marrow oedema.[43] Pain from OA can lead to functional limitation and fatigue, which contributes to depressed mood and worsening pain and function.[44] Pain can be measured using several scales. Where a study reports more than one pain scale, data will be extracted preferentially for the first outcome listed according to the following hierarchy, based on Juni 2015:[27]

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.[45] 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 WOMAC, the knee injury and osteoarthritis outcome score (KOOS) and the hip injury and osteoarthritis outcome score (HOOS). Where a study reports more than one function scale, data will be extracted preferentially for the first outcome listed according to the following hierarchy, based on Juni 2015:[27]

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 osteoarthritis index global score
8. other algofunctional scale
9. participant's global assessment
10. physician's global assessment

Health-related quality of life (HRQoL): 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 QoL questionnaire (OAKHQOL).[46-48] 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).[49-51] No limitations will be placed on the type of HRQoL tools included. Where a study reports more than 1 HRQoL measure, data will be extracted preferentially

for the first outcome listed according to the following hierarchy, based on their relative ease and reliability for calculating quality-adjusted life years (QALYs) for the economic analysis:[52]

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.[53-55] 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).[54,56,57]

Treatment satisfaction: Treatment satisfaction is defined as the degree to which patients perceive that the treatment fulfils their health needs.[58] Patient satisfaction is an important indicator of the quality of care provided to patients with OA.[59] Patient-reported outcomes such as patient satisfaction are used to determine patients' experiences of the disease and can provide information to the physician for facilitating patient-centred care.[59] Treatment satisfaction measures include the treatment satisfaction questionnaire version 1.4 (TSQM-1.4) and the osteoarthritis 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.[60,61]

Serious adverse event (SAE): SAEs are negative experiences associated with a medical intervention that may be life-threatening at the time of occurrence. The incidents do not need to have a causal relationship with the medical intervention to be considered an SAE. Examples of SAEs associated with OA may include accelerated osteoarthritis 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.[27,62] In addition, discontinuation or study withdrawal due to an AE will also be considered an SAE.

5. HTA key questions

5.1 HTA research questions

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

1. Is IAGI efficacious compared to no treatment or placebo (incl. oral placebo and sham injection) for patients with primary OA of the hip or knee?
2. Is IAGI safe compared to no treatment or placebo (incl. oral placebo and sham injection) for patients with primary OA of the hip and knee?
3. What are the costs associated with IAGI compared to no treatment or placebo (incl. oral placebo and sham injection) for patients with primary OA of the hip or knee?
4. Is IAGI cost-effective compared to no treatment or placebo (incl. oral placebo and sham injection) for patients with primary OA of the hip or knee?
5. What is the budget impact of IAGI compared to no treatment or placebo (incl. oral placebo and sham injection) for patients with primary OA of the hip or knee?
6. Are there ethical, legal, social or organisational issues related to the use of IAGI for patients with primary OA of the hip or knee?

6. Clinical evaluation methodology

The proposed methods have been developed with reference to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3)[63] and presented in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[64] Clinical outcomes for hip and knee OA will be analysed separately.

6.1 Databases, search strategy and study selection

6.1.1 Databases and search strategy

Systematic literature searches will be conducted in 5 biomedical databases – Ovid (Embase, MEDLINE), the Cochrane Library, the INAHTA database and EconLit. Preliminary search strings are presented in ***Appendix B***. During the HTA phase of this project, the Ovid search strategy detailed in ***Table 5, Appendix B*** will be adapted to the Cochrane Library, the INAHTA database, and EconLit. Search filters to exclude specific publication types (i.e. editorials, letters to the editor, news articles and conference abstracts) will be utilised in all searches. The searches will be limited to English, French, German and Italian publications. No date limit will be applied. Grey literature searches will be limited to HTA and specialist websites (***Table 6***, ***Appendix B***). The International Clinical Trials Registry Platform (ICTRP) will be searched to identify relevant unpublished and/or ongoing clinical trials. Preliminary search strategies for clinical trial registries are listed in ***Table 7***, ***Appendix B***.

6.1.2 Study selection

All results from systematic literature searches will be imported into Rayyan (Rayyan Systems Inc, United States) for study selection.[65] Rayyan allows for blinded title and abstract screening of citations between independent reviewers and resolution of study inclusion conflicts.[65] Screening will be performed to include studies that meet the pre-defined study selection criteria (***Table 2***). Only studies published in World Health Organization (WHO) Mortality Stratum A countries will be included.[66] This limitation will ensure that all included studies have a comparable disease burden and cause of death to Switzerland.[66] Exclusion criteria will also be based on publication type (e.g. case notes, case reports, opinion pieces).

Table 2 Study selection criteria

	Inclusion criteria	Exclusion criteria
Population(s)	Adult patients (≥18 years of age) with primary OA of the knee or hip	OA in other joints (e.g. shoulder, wrist, neck, spine), 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)*	Other interventions
Comparator(s)	• No treatment • Sham injection (e.g. saline injection) • Oral placebo	Other comparators
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 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 Swiss healthcare payer	Inadequate data (no measures of variance, incongruous data reported between figures and text etc), incomplete reporting, unclear follow-up duration, any other outcomes
Design / publication type	Clinical evidence • Systematic reviews and meta-analyses • Randomised controlled trials • Non-randomised studies of interventions Economic evidence • Full economic evaluations (CEA or CUA only) • Cost analyses • Other economic analyses (i.e. CCA or CMA) • Budget impact analyses	• 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; CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; CMA: cost-minimisation analysis; CUA: cost-utility analysis; 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: Numeric rating scale; NSAIDs: Non-steroidal anti-inflammatory drugs; OA: osteoarthritis; QALY: quality-adjusted life years; SAE: serious adverse event; SF-12: 12-Item Short Form Health Survey; VAS: Visual Analogue Scale; VR-12: Veterans RAND 12 Item Health Survey; UK: United Kingdom; USA: United States of America; WHO: world health organisation; 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.

All search results will be screened by title and abstract by 2 independent reviewers. At the completion of title and abstract screening, full-text publications will be independently reviewed by each reviewer. Conflicts regarding final study inclusion will be settled by a third reviewer. The inclusion and exclusion decisions will be detailed in a PRISMA flow chart.[64]

6.1.2.1 Study design

Various study designs will be considered for inclusion. Systematic reviews and meta-analyses that meet the PICO criteria (***Section 4***) will be included to assess the clinical outcomes associated with IAGI compared to no treatment or placebo (incl. oral placebo and sham injection). Randomised controlled trial (RCT) evidence will be included in the absence of, or to update, existing systematic reviews and meta-analyses. If there is limited evidence for AEs associated with IAGI reported in the RCTs, non-randomised studies of interventions (NRSI) meeting the PICO criteria (***Section 4***) will be included to evaluate this outcome specifically.

6.2 Data extraction, analysis and synthesis

6.2.1 Data extraction

Data will be 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 will be performed against the original publication by a second reviewer. Any conflicts will be resolved by consensus and if consensus cannot be reached, a third independent reviewer will be consulted.

Data to be extracted include:

- **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, 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 joint in question (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), if IAGI was administered 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 deviations for any outcome of interest. Information on the continuous outcome measures used in the included studies (scale and direction of effect) and the corresponding timepoints (up to 1 month, 3 months, 6 months, 12 months) will also be collected. Information on AEs, SAEs and joint replacement surgery will be collected 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.

6.2.2 Risk of bias appraisal

Different appraisal criteria will be used to assess the risk of bias of the included evidence base. Critical appraisal will be performed by a single reviewer and checked by a second reviewer. Any differences between reviewers will be settled via consensus and if consensus cannot be reached, a third reviewer will be consulted.

Risk of bias tools used to appraise the included studies will depend on the study design. Systematic reviews will be evaluated against the AMSTAR-II appraisal criteria.[67] RCTs will be evaluated with the Cochrane Risk of Bias (RoB) 2.0 tool.[68] The Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool will be applied for NRSIs.[69]

6.2.3 Data analysis of efficacy, effectiveness and safety outcomes

6.2.3.1 Meta-analysis of dichotomous outcomes

For the dichotomous outcomes of AEs, SAEs and joint replacement surgery, the primary endpoint will be longest follow-up. Dichotomous outcomes will be meta-analysed using pairwise random-effects models, where there are sufficient data from the primary studies.[70-73] The inverse-variance method will be used to estimate primary study weights.[63] The Mantel-Haenszel (MH) method will be used to estimate primary study weights when data are sparse, such as when event rates are low or when the study sizes are small.[63] Results will be reported as risk ratios (RR) with 95% confidence intervals (CI). A RR greater than one will indicate an increased probability of the event occurring in the intervention group relative to the comparator group. A RR less than one will indicate a reduced probability of the event occurring in the intervention group relative to the comparator group.

For outcomes reported by fewer than 2 RCTs, or where it is inappropriate to pool trials, the results will be described narratively.

6.2.3.2 Meta-analysis of continuous outcomes

For the continuous outcomes of pain, function, HRQoL, care utilisation and treatment satisfaction, the primary endpoint will be analysed at 3 months. Secondary timepoints of up to 1 month, 6 months and 12 months will also be assessed. Mixed-effect meta-regression models, incorporating time of follow-up as a covariate factor, will be used to analyse the continuous outcomes. The mixed effect model will estimate 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 will be conducted in R utilising the metafor package with two-stage analysis multivariate function for longitudinal data (rma.rv). The longitudinal meta-analysis takes a first-order heteroscedastic autoregression covariance structure (AR_1) to account for the within-study longitudinal effect. Within-study covariance will be calculated for each study using a method adapted from Horváth (2009).[74] A point estimate (mean difference and/or standardised mean difference [SMD]) with the corresponding 95% CI will be generated for the selected timepoints for each outcome of interest. Various random effects will be tested and compared using both AR_1 and unstructured variance-covariance structure, where model-fitting criteria will be used to select the best model. Outcomes reported with multiple measurement scales (e.g. pain, function) will be evaluated using SMDs. Each study will be included in the analysis once per outcome. Where a study reports multiple scales for the same outcome, scales will be selected preferentially based on the hierarchy described in ***Section 4***.

6.2.3.3 Assessment of heterogeneity

Heterogeneity of continuous and dichotomous outcomes will be assessed statistically using Tau^2 and I^2. Tau^2 will be calculated to quantify the extent of heterogeneity among the included studies. I^2 will be used to assess the percentage of the variability in effect estimates that is due to heterogeneity. The significance of I^2 will depend on the strength of the evidence for heterogeneity (i.e. Tau^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 will account for the correlation between timepoints at the individual study level, and then consider their variation from different timepoints as well as across different studies to derive total heterogeneity. The level of heterogeneity will be 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.[63]

6.2.4 Imputation methods for dealing with missing values

Missing values will be obtained using formulae detailed in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3).[63] For studies reporting outcomes graphically, WebPlotDigitizer will be used to convert graph points to numerical values.[75]

6.2.5 Assessment of publication bias

The influence of small-trial effects and their potential association with publication bias will be investigated using Egger's test of funnel plot asymmetry.[63] The ability to detect and assess publication bias may be limited by the number of included studies in the review. The inclusion of a large number of studies (i.e. at least 10) generally provides a more robust result in the evaluation of publication bias.[63] Analyses of SMDs will be conducted according to the method proposed by Harbord and colleagues.[76] It is worth noting that both of these methods have limitations regarding their ability to detect publication bias.

6.2.6 Subgroup and sensitivity analyses

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

A two-tailed Z-test will be used to determine if the difference between the 2 groups is statistically significant (considered statistically significant if <5% of the difference occurs by chance alone i.e. $p < 0.05$). If there are only 10 trials in the subgroup analyses Tau^2 will be calculated using trials in both subgroups. If the subgroup analyses include more than 10 trials, a separate Tau^2 will be calculated for each individual subgroup.

The sensitivity analyses will also follow the parameters listed in the paragraph above. Possible sources of uncertainty include risk of bias and imputed SD.[63]

Subgroup analysis will be 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)
- effusion present or not
- removal of joint fluid before treatment or not.

Sensitivity analyses will be conducted to investigate the impact of methodological factors on the reported results of the clinical evaluation of RCTs as follows:[27]

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

It is important to note that the effect modifiers investigated may change during the analysis phase for the full HTA and will be reported as protocol amendments.

6.2.7 Overall quality of evidence appraisal

The overall quality of the evidence will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The 5 domains (imprecision, inconsistency, indirectness, risk of bias and publication bias) of the GRADE framework will be scored (high, moderate, low, very low) according to a decision algorithm developed by Pollock et al.[77] The GRADEpro guideline development tool will be used to construct the summary of findings tables, which will feature 6 of the included outcomes (i.e. pain, function, HRQoL, treatment satisfaction, AEs, SAEs).

7. Economic evaluation methods

7.1 Literature review

7.1.1 Study selection

The systematic literature searches outlined in ***Section 6.1.1*** will be used to identify studies relevant to the cost or cost-effectiveness of IAGI for OA of the hip and knee. Criteria outlined in ***Table 2*** (***Section 6.1.2***) will guide the selection of relevant economic evidence.

7.1.2 Data extraction, analysis and synthesis

Data pertaining to the following domains will be extracted from the included studies: country, perspective, intervention and comparators, population characteristics, type of analysis, analysis methods, time horizon, discount rate, included cost items, currency and costing year, outcome measure(s) used, key sources of evidence, assumptions, results, uncertainty analysis, additional comments (e.g. author conclusions) and conflicts of interest. Data extraction will be completed by one reviewer and checked by a second reviewer.

Full economic evaluations will be assessed against the applicability checklist items outlined by NICE (***Table 8***, ***Appendix C***).[78] Studies will be judged as directly applicable, partially applicable or not applicable to the HTA key questions. Directly and partially applicable studies will be further assessed against the study limitations checklist items and rated as having minor limitations, potentially serious limitations or very serious limitations (***Table 9***, ***Appendix C***).[78] Only Swiss-specific evaluations will be judged as directly applicable.

Results of the included studies will be tabulated and synthesised narratively. Data extracted on the approaches taken by existing models (e.g. model structure, how treatment effects are modelled, how impacts on HRQoL are captured) will be used to guide de novo modelling if required (***Section 7.2***).

7.2 Modelling considerations

Should available evidence be insufficient to address the research question within the Swiss healthcare context, de novo modelling will be undertaken due to the limitations of translating evaluation results across healthcare settings.

Initial scoping suggests a de novo evaluation will likely be required. A systematic review of economic evaluations of pharmacological treatments for OA covering articles published up to November 2021, identified one economic evaluation conducted within the USA healthcare context that included IAGI.[79] The need for de novo modelling will be re-evaluated following the systematic

literature searches and will be confirmed during preparation of the ***Economic Analysis Plan***, to be drafted during the HTA phase.

A high-level overview of the proposed evaluation is provided in ***Table 3***, with individual components subsequently discussed. The proposed approach has been guided by the PICO criteria (***Section 4***), the needs of the decision-maker and the reference case for economic evaluations in OA published by Hiligsmann et al (2014).[80]

Table 3 Summary of the proposed economic evaluation

Population	• Patients ≥18 years of age with osteoarthritis of the knee • Patients ≥18 years of age with osteoarthritis of the hip
Intervention	Intra-articular glucocorticoid injections
Comparator	Standard care without intra-articular glucocorticoid injections
Perspective on costs	Swiss healthcare payer
Perspective on outcomes	Personal health of person receiving the intervention
Type of analysis	CUA (CEA, CCA or CMA if a CUA is inappropriate/not feasible)
Time horizon	Sufficient to capture all important differences in costs and outcomes between the intervention and the comparator
Source of effectiveness inputs	Systemic review detailed in *Section 6*
Measuring and valuing health effects	QALYs (or if transformation to QALYs is not feasible, an outcome measure that captures the overall health of the patient from the patient perspective)
Evidence of resource use and costs	Combination of sources including peer-reviewed literature, clinical care guidelines, the Spezialitätenliste, the Analysenliste, TARMED, the uniform tariff structure for physiotherapy services, Swiss DRGs
Discount rate	Annual rate of 3% for both costs and outcomes (0% and 5% in sensitivity analyses)
Sensitivity analyses	• Parameter uncertainty will be explored using DSA (univariate) and PSA • Translational and structural uncertainty will be addressed using scenario analysis

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; CMA: cost-minimisation analysis; CUA: cost-utility analysis; DRG: diagnosis-related group; DSA: deterministic sensitivity analysis; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

The cost-effectiveness of IAGI for patients with OA of the knee or hip relative to standard care without IAGIs will be assessed. The definition of standard care will be guided by the care permitted in the comparator arms of included trials (i.e. any other intervention used in addition to placebo/sham in both treatment arms). The applicability of such care to the Swiss healthcare context will be assessed. For any pooled effect estimates, heterogeneity between trials will also be considered as there may be differences in what standard care entails across trials. Separate

assessments depending on the location of the OA (knee or hip) will be performed. Hiligsmann et al (2014) propose separate reference cases for OA of the hand, knee or hip.[80]

Hiligsmann et al (2014) specify that subgroups of interest may be defined according to demographic criteria such as age and gender, or according to comorbidity factors including obesity or risks relating to gastrointestinal or cardiovascular events.[80] Where supported by the availability of clinical evidence, subgroup analyses defined by such criteria will be presented.

The analysis will be conducted from a Swiss healthcare payer perspective, as this is the relevant perspective for the decision-maker. Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement.[81]

7.2.1 Model conceptualisation

Structural and analytical approaches taken by previous economic evaluations of OA, along with Swiss clinical management pathways for patients with OA of the knee or hip, will guide the model conceptualisation process. Clinical expert advice may also be sought.

A conceptual model reflecting the disease process and including all clinically-relevant and significant health states and events will be constructed. This conceptual model will be reviewed within the context of available input data and modified as necessary to produce the final model. All structural assumptions will be documented and justified.

In the context of OA, Zhao et al (2021) recommend use of a lifetime state-transition (Markov) model that can incorporate repetitive health events, with the integration of memory to capture the dependence of AEs and time to events (e.g. decision for joint replacement) on patient history.[82] The chosen model type (decision tree, state-transition model etc.), modelling technique (i.e. cohort or individual simulation) and final model structure will be presented in the ***Economic Analysis Plan***.

The time horizon of an economic evaluation should be sufficient to capture in full the differences in cost and effect of the options being compared.[83] Hiligsmann et al (2014) specify a lifetime horizon as being, generally, the most appropriate time horizon, given that OA is a chronic disease.[80] The authors 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.[80] The choice of time horizon will be finalised during model conceptualisation. A stepped presentation of results will be considered, whereby results over the time horizon of the trial and over longer time periods are both presented.

7.2.2 Parameter estimation

Results of the clinical evaluation will inform the clinical input parameters of the economic model. Where data are unavailable, these figures will be supplemented by data from the peer-reviewed literature or expert opinion.

Costs (resource use and unit costs) will be estimated using peer-reviewed literature, clinical care guidelines, Swiss diagnosis-related group (DRG) costs, TARMED positions, the uniform tariff structure for physiotherapy services and the Spezialitätenliste. Resource use will be identified, measured and valued in 2023 Swiss francs (CHF) as part of the HTA.

The preferred approach is a cost-utility analysis (CUA), with effectiveness expressed using QALYs. Hiligsmann et al (2014) specify use of QALYs and application of the CUA as the recommended approach for economic evaluations of OA.[80] The feasibility of CUA depends on the availability of reliable HRQoL data. If transformation to QALYs as the final health outcome is impractical, an alternate analysis (i.e. cost-effectiveness analysis and/or cost-consequence analysis) will be considered. Should the clinical evidence indicate non-inferior safety and effectiveness between IAGI and the comparator(s), cost-minimisation analysis may be considered.

Health state utilities may be informed by HRQoL data captured in the clinical review or sourced from other peer-reviewed literature. If HRQoL outcomes data are available from the clinical evaluation, these will be assessed for relevance to the economic evaluation. Where HRQoL is expressed using a non-preference-based instrument, the availability of a mapping algorithm to transform the data into utilities will be considered, noting the additional uncertainty this could introduce.

Externally-sourced utility weights may also be required. These would likely be applied to time spent in different health states of a model to estimate QALYs gained. A systematic review and meta-analysis of OA-related health state utility values for different affected joint sites before and after various treatments was recently published.[84] This provides a database of OA-related health state utility values and may provide a valuable source of HRQoL data should literature-based values be required.

7.2.3 Addressing uncertainty

Uncertainties in base case parameter values will be explored using one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). One-way DSAs will allow identification of the key model drivers of each pairwise comparison. DSA results will be tabulated as well as presented visually using tornado diagrams. PSA captures the joint uncertainty across model parameters, giving decision-makers information on the overall certainty of the economic outcomes. Results of PSAs will be presented as 95% confidence ellipses on the cost-effectiveness

plane. Cost-effectiveness acceptability curves (CEAC) will also be produced. Consistency between the ranges used in DSAs and the distributions used in PSAs will be maintained.

Scenario analyses will be undertaken to explore how changes in modelling assumptions (time horizon, source of utility estimates etc.) affect economic outcomes.

There is no accepted willingness-to-pay (WTP) threshold in Switzerland. Using CEAC curves produced via PSAs, the probability of cost-effectiveness will be expressed as a function of WTP.

7.2.4 Model transparency and validation

The model structure, parameter values and assumptions will be documented in the ***HTA report***. Validation methods used to assess the model's accuracy in predicting the clinical course of the target population will also be documented in the report. These methods may include steps to assess the following:[85]

- face validity (extent to which the model corresponds to current science and evidence)
- internal validity/verification (extent to which the model behaves as intended)
- cross validity (i.e. comparison with other published models)
- external validity (comparison of predicted outcomes with real-world outcomes).

7.3 Budget impact analysis

The annual number of Swiss patients receiving IAGI will be estimated using data from the Spezialitätenliste, supplemented with additional sources to help define utilisation specific to knee or hip OA. This estimate will be extrapolated over 5 years to project expected utilisation of the intervention for OA of the knee or hip from 2024 to 2028 under current policy conditions. The annual cost (CHF) of IAGI will then be calculated using annual per patient costs estimated as part of the economic analysis.

Depending on the findings of the clinical and cost-effectiveness evaluations, the financial implications of certain policy changes may also be modelled. Should this be required, the policy changes to be considered will be described in the ***HTA report***. In these scenarios, the impact of restricting IAGI use on patient utilisation of other healthcare resources (NSAIDs, physiotherapy etc.) will be modelled. This modelling will only be undertaken should the clinical or economic findings support such a substitution.

A healthcare payer perspective will be adopted for the analysis. All major assumptions will be tabulated, as will all input parameters and their data sources. Scenario analyses will be used to explore the impact of certain assumptions on the results, while one-way sensitivity analysis will be undertaken to identify key drivers of the budget impact analysis.

8. Legal, social, ethical and organisational evaluation methods

The systematic literature searches detailed in ***Section 6.1.1*** will be used to identify literature relevant to any legal, social, ethical and organisational issues related to IAGI for OA of the hip and knee. Additional targeted, non-systematic keyword searches for literature addressing these domains will also be conducted. Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies will all be considered for inclusion. The included literature will be arranged in tables describing the study characteristics and key findings. The results will be synthesised narratively.

9. Summary and Outlook

9.1 Summary

As the clinical analysis will compare IAGI with no treatment and placebo/sham, this includes the potential for introducing heterogeneity when the oral placebo and sham injection are subject to placebo effects compared to no treatment. As such, the main analysis will evaluate sham/placebo and no treatment separately.

Certain challenges arise within the economic evaluation:

- A comprehensive literature search will be performed when developing the ***Economic Analysis Plan***; however, scoping searches point towards a lack of economic data for IAGI within the Swiss healthcare context. De novo modelling is expected to be required.
- While a lifetime horizon is recommended for economic evaluations of OA, clinical studies of OA are often not long enough to fully assess all relevant outcomes.[80,82] Several assumptions may be required when extrapolating over a lifetime horizon and evidence on longer-term outcomes may need to be sourced from observational studies, rather than from RCTs.[80] In any case, the appropriateness of a lifetime horizon itself will first need to be considered in light of the clinical evidence on the duration of effect of IAGIs.
- The choice of mapping algorithm to transfer outcomes reported in the clinical studies into QALYs, represents a potential challenge. Previous economic evaluations have mapped WOMAC domain scores to either EQ-5D or Health Utility Index 3 (HUI 3) utility scores.[86,87]
- Indications for glucocorticoid injections in Switzerland can vary, so defining utilisation specific to OA of the knee and hip from Spezialitätenliste data may pose a challenge.

9.2 Outlook

The HTA protocol is followed by production of an HTA report. The objective of the HTA report is to generate a focused assessment of various aspects of the health technology in question. The applied analytic methods, their execution and the results are described. The analytical process is comparative, systematic and transparent. The external review group consulted during the protocol phase is consulted once again during the HTA phase. Subsequently, the HTA draft report is presented to the stakeholders for consultation. Communication with the reviewers and stakeholders is coordinated by the FOPH.

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11. Appendices

11.1 Appendix A: Glucocorticoid preparations available in Switzerland

Table 4 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

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
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	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 showed 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.

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
		and hypersensitivity reactions to drugs or insect bites. • in severe and disabling allergic conditions that do 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			

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
		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 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 the 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

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
					• poliomyelitis with the exception of bulbar encephalitic form • lymphomas after BCG vaccination • osteoporosis, narrow • wide-angle glaucoma
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-sized 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

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
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 sized 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

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
					• lymphadenitis after BCG vaccination • Narrow- and wide-angle glaucoma
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 adjunctive 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.
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	As short-term adjunctive 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	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.	• Intrathecal, intranasal, intraocular or epidural administration. • Intravascular (e.g. intravenous) administration. • intramuscular administration • systemic fungal infections • severe conduction disorders • acute decompensated heart failure

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
	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		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.	Monoethylglycine xylidide and glycine xylidide are pharmacologically active, but their activity is weaker than that of the parent compound.	• 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.
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

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
					• 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.
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

Drug: brand name/manufacturer	Dosage, frequency of administration	Indications	Half life	Metabolism	Contraindications
					additional causal therapy is contraindicated.
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 vaccine; CYP1A2: Cytochrome P450 Family 1 Subfamily A Member 2; CYP3A4: Cytochrome P450 3A4; CYP450: Cytochrome P450; OA: osteoarthritis.
Source: Spezialitätenliste and Swiss Medic.[5,88]

11.2 Appendix B: Search strategy

Table 5 Search strategy – Ovid (MEDLINE and Embase)

Domain	Query	Search term(s)
Population	1	exp osteoarthritis/
	2	osteoarthritis.tw.
	3	exp osteoarthritis, knee/
	4	exp osteoarthritis, hip/
	5	OA.tw.
	6	exp arthritis/
	7	(("osteo.tw." AND "arthritis.tw.") OR "osteo arthritis.tw.")
	8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
Intervention	9	exp injections/
	10	injection.tw.
	11	injectable.tw.
	12	exp Injections, Intra-Articular/
	13	(("intra.tw" AND "articular.tw.") OR "intra articular.tw.")
	14	IA.tw.
	15	9 OR 10 OR 11 OR 12 OR 13 OR 14
	16	corticosteroid.tw.
	17	corticosteroids.tw.
	18	glucocorticoid.tw.
	19	glucocorticoids.tw.
	20	triamcinolone.tw.
	21	prednisolone.tw.
	22	steroid.tw.
	23	steroids.tw.
	24	hydrocortisone.tw.
	25	dexamethasone.tw.
	26	methylprednisolone.tw.
	27	exp glucocorticoids/
	28	betamethasone.tw.
	29	cortisone.tw.
	30	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
Comparator	31	placebo.tw.
	32	exp placebo/
	33	sham.tw.
	34	sham treatment.tw.
	35	31 OR 32 OR 33 OR 34
Limits	36	English.lg.
	37	French.lg.

Domain	Query	Search term(s)
	38	German.lg.
	39	Italian.lg.
	40	36 OR 37 OR 38 OR 39
	41	Editorial.pt.
	42	Letter.pt.
	43	News.pt.
	44	Congress.pt.
	45	41 OR 42 OR 43 OR 44
Combined string	46	15 AND 30 (intervention)
	47	46 AND 35 (intervention and comparator)
	48	47 AND 40 (language restriction)
	49	48 NOT 45 (publication type restriction)

Table 6 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
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

Source	Website
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	
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

Source	Website
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	
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/

Source	Website
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

Abbreviations: HTA: health technology assessment; INAHTA: International Network of Agencies for Health Technology Assessment.

Table 7 Search strategy – International Clinical Trials Registry Platform

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

11.3 Appendix C: Economic resources

Table 8 Applicability section (section 1) of the NICE checklist for economic evaluations

Checklist Item	Rating (yes, partly, no, unclear or NA)	Comments
1.1 Is the study population appropriate for the review question?		
1.2 Are the interventions appropriate for the review question?		
1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?		
1.4 Is the perspective for costs appropriate for the review question?		
1.5 Is the perspective for outcomes appropriate for the review question?		
1.6 Are all future costs and outcomes discounted appropriately?		
1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken.		
Overall judgement: Directly applicable, partially applicable or not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Other comments:		

Abbreviations: NA: not applicable; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year.
Notes: This checklist can be used to determine whether an economic evaluation provides evidence that is useful to inform decision-making. It judges the applicability of the study and the limitations. Section 1 (Applicability) is used first, to filter out irrelevant studies.
Source: Developing NICE Guidelines, the Manual; Appendix H – Checklists.[78]

Table 9 Study limitations section (section 2) of the NICE checklist for economic evaluations

Checklist Item	Rating (yes, partly, no, unclear or NA)	Comments
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?		
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?		
2.3 Are all important and relevant outcomes included?		
2.4 Are the estimates of baseline outcomes from the best available source?		
2.5 Are the estimates of relative intervention effects from the best available source?		
2.6 Are all important and relevant costs included?		
2.7 Are the estimates of resource use from the best available source?		
2.8 Are the unit costs of resources from the best available source?		
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?		
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?		
2.11 Has no potential financial conflict of interest been declared?		
Overall assessment: minor limitations, potentially serious limitations or very serious limitations		
Other comments:		

Abbreviations: NA: not applicable; NICE: National Institute for Health and Care Excellence.
Notes: This checklist can be used to determine whether an economic evaluation provides evidence that is useful to inform decision-making. It judges the applicability of the study and the limitations. Section 2 (Study Limitations) should be used once it has been decided that the study is sufficiently applicable to the context of the guideline.
Source: Developing NICE Guidelines, the Manual; Appendix H – Checklists.[78]