Keele UNIVERSITY

Impact Accelerator Unit

Keele Critically Appraised Topic (CAT Form)

Clinical Question

What are the risks associated with adding intra-articular corticosteroid injection to usual physiotherapy care for patients with painful osteoarthritis (OA) in the knee and/or hip in a community musculoskeletal service?

Clinical bottom line

Based on limited evidence that directly addresses this clinical question (Table 3), adding intra-articular corticosteroid injection (ICSI) to usual physiotherapy rehabilitation may increase the risk of temporary worsening of joint pain in a high proportion of individuals and can occasionally be associated with allergic reaction for patients with OA knee pain (Table 4). No direct evidence was identified that addressed risks of adding ICSI to physiotherapy rehabilitation in people with OA hip pain.

In this extended CAT, broader evidence on risks of ICSI for OA hip and knee pain is summarised in Appendix 1 (page 7 – 20) with recommendations from this evidence provided in Appendix 2 (page 21). There remains ongoing controversy around the risks of ICSI (Appendix 3, page 22).

Why is this important?

Arthritis Research UK (2013) reports that 8% people aged 45 and over in the UK have sought treatment for OA hip and close to 1 in 5 have sought treatment for OA knee. In Leeds Community Healthcare Trust (LCHT) MSK Service, between 2,000 and 4,000 patients are treated each year for knee and hip pain associated with OA. In line with NICE guidance (2022) and other guideline recommendations (Table 1), patients may be offered ICSI alongside rehabilitation to help manage symptoms.

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	ICSI for OA knee	ICSI for OA hip
OARSI	Conditionally recommended	Not recommended
ACR	Recommended	Recommended with US guidance
EULAR	Recommended	Not recommended
AAOS	Inconclusive	Recommended
NICE	Could be considered if other treatments have not worked*	As for knee based on evidence for injections in OA knee*

OARSI - Osteoarthritis Research Society International; ACR - American College of Rheumatology; EULAR - European League Against Rheumatism; AAOS - American Association of Orthopedic Surgeons; NICE – National Institute for Health and Care Excellence; *recommends considering injections only if used to supplement and support people to participate in therapeutic exercise and only if person aware that the injection would only provide short term relief (2-10 weeks)

ICSIs are included as part of a package of care when appropriate, delivered by trained physiotherapists who work within the parameters set out in a local Patient Group Directive (PGD). This involves injection of up to 40mg triamcinolone acetonide (Kenalog) and up to 4ml Lidocaine sequentially through the same needle, using anatomical landmarks for guidance.

Before delivering injections, the trained physiotherapist assesses suitability for ICSI. This is based on clinical presentation and perceived risks and benefits which are discussed as part of a shared decision-making process with the patient. This shared decision-making enables a patient to make an informed choice about what is right for them. Local anecdotal evidence suggests that information shared by different clinicians about the risks or potential adverse effects associated with ICSIs may vary and that clinicians may not feel confident about what information to share.

Over 500 ICSIs are delivered for OA hip or knee pain each year in (LCHT) MSK service. During the last 5 years, there have been 12 Datix recording adverse events/ harms and potential harms/ risks associated with administration of ICSIs. These include 4 reported infections of which one was reported as septic arthritis, one case of anaphylactic shock, and one case of avascular necrosis following injection in a hip joint.

To reduce variation in clinical practice and optimise shared decision-making conversations, a review of the current evidence is required. Our search strategy is detailed in Tables 3 and 4, and summary of search results is presented in Figure 1.

Criteria for Critically Appraised Topic

Population: Adults with OA knee pain and/ or OA hip pain
Intervention: Intra-articular steroid injection in addition to usual rehabilitation
Comparator: Usual rehabilitation alone
Outcome(s): Risks, harms or adverse side effects

Search timeframe (e.g. 2013-2013)

- Search terms are listed in Table 2.

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- Search Timeframe: Databases searched from 2018 onwards:
- Databases searched:
    - CINAHL
    - Cochrane
    - Emcare
    - Medline
    - TRIP
    - NICE Guidelines
    - BMJ Best Practice
- Date of search: Search completed 8th November 2023.
- Additional studies were identified through backward/ forward searching

Table 2. Search terms used

Population	Intervention	Comparison	Outcomes
• Adults (don't want to limit by that in case some articles aren't indexed as such) AND • OA hip • OA knee • Knee arthritis • Hip arthritis • Coxarthrosis (Note for Helen – this is hip) • Gonarthrosis (Note for Helen – this is knee) • (osteoarthrotic or osteoarthros*) AND (knee or hip) • (degenerative adj2 arthritis) AND (knee or hip) • Tibiofemoral • Patellafemoral • Joint pain (AND knee or hip) *Working assumption - given that our population is adults with knee or hip joint pain. Clinically, pain would be the indication for these injections, so I don't think we need to specify in search.*	• Glucocorticoid • Corticosteroid • Steroid • lidocaine AND • Intra-articular • Joint AND • Injection • Ultrasound guided injection • Image guided injection • Sonographic guided injection • CSI	• Physiotherapy • Exercise • Activity • non-surgical • lifestyle change/ modification • Advice • Education • Analgesic/analgesia • Medical/ medication • Pain relief • no treatment • watchful wait(ing) • placebo • orthosis/ orthoses • orthotic devices • Mobilisation • Manipulation • walking aid • walker/rollator • cane/stick • Strengthening • Weight loss • NSAIDS • Pain killer/Painkiller • Acupuncture • Insoles • Brace • Rocker sole • Hyaluronic acid • Conservative management • Advice • Leaflets • Education • Heat • Ice • Cryotherapy • Hands-on	• Risk(s) • Harm(s) • Adverse event(s) • Side effect(s) • Infection • Pain • Swelling • Bruising • Damage • Cartilage • Health care utilisation • Complications • Safety • Risk • Pain function • Adverse effect • Uterine bleeding • irregular menstrual bleeding/menstrual irregularity • Facial flushing • Anaphylaxis • Impaired diabetic glycaemic control/elevated HbA1c. • thinning of the skin • Skin depigmentation/ hypopigmentation/discolouration • Fat atrophy/subcutaneous atrophy • Reduced lactating in breastfeeding women/reduction in milk supply • Bleeding/bruising – intra-articular bleed/ haemarthrosis • Post injection flare of pain • infection • Avascular necrosis (AVN) - • Rapidly progressive idiopathic arthritis of the hip (RPIA) • inferior (or non-superior) symptom relief

Population	Intervention	Comparison	Outcomes
		• Manual therapy • Stretches / stretching • Sham injection • Placebo injection	• joint degeneration • rapidly destructive hip disease (RDHD) • rapidly progressive osteoarthritis (RPOA) • rapidly destructive osteoarthritis (RDO)

Figure 1. Results of the search

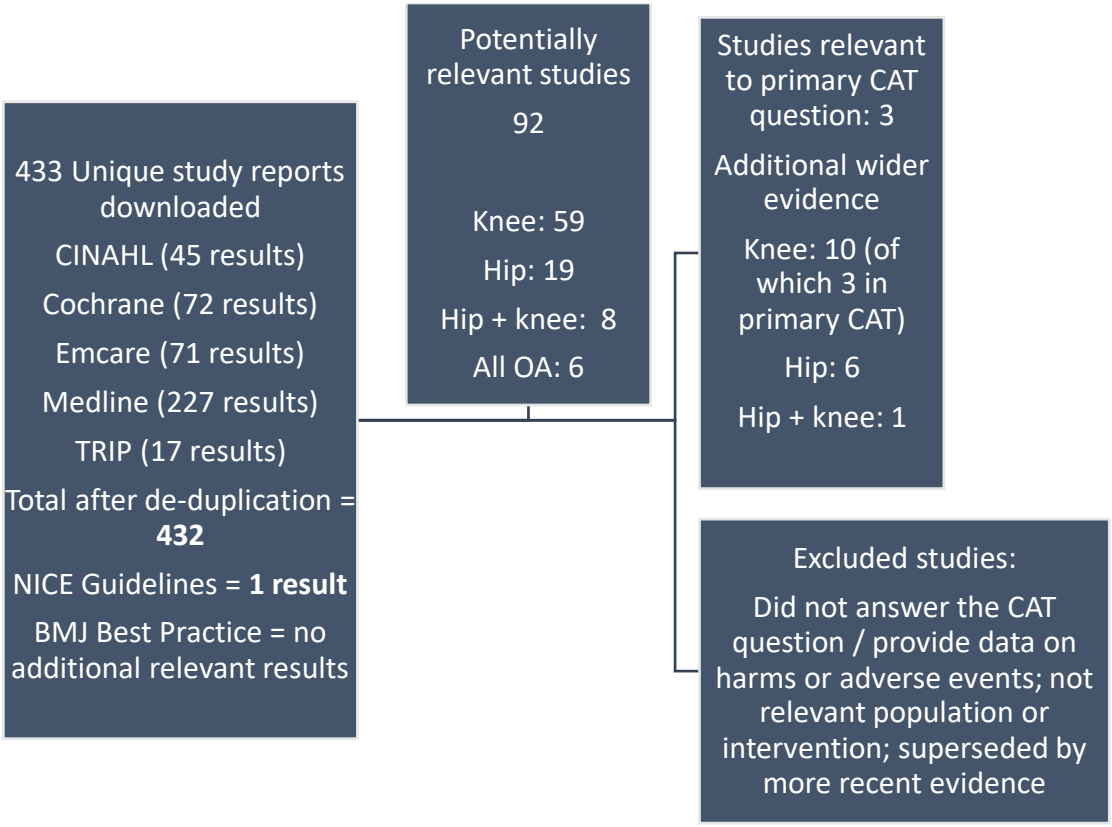

Table 3. Detail of included studies

First author, year and type of study	Population and setting	Intervention or exposure tested	Study results	Assessment of quality and comments

Liao C.D., 2023 Comparative Efficacy of Intra-Articular Injection, Physical Therapy, and Combined Treatments on Pain, Function, and Sarcopenia Indices in Knee Osteoarthritis: A Network Meta-Analysis of Randomized Controlled Trials. International journal of molecular sciences, 24(7), p.6078. Systematic Review and Network Meta-analysis (NMA) Deyle G.D; 2020: Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. New England	80 RCTs (up to January 2023) reporting the effects of ICSI+ Physiotherapy (PT)/exercise vs. ICSI or PT alone in participants with knee OA (6934 patients; ten studies were identified that included combined IAI+PT regimens) 156 Patients with osteoarthritis in one or both knees from US Military Health System primary care setting in US. 50 participants with OA knee who received steroid and placebo injection, exercise and had MRI follow-up data up to 26 weeks.	Interventions: intra-articular injections (any) combined with PT (any) alone or combined. Control: placebo injection or usual care Outcomes: pain, global function, and walking capability Interventions: ICSI = 78 Control: physical therapy (average of 11.8 sessions) Outcomes WOMAC, Alternate Step Test, Timed Up and Go test, Global Rating of Change scale, all at 1 year. Intervention: ICSI + exercise (12-week programme) Control: placebo (saline) injection + exercise (12-week programme) Outcomes: change in bone marrow lesion volume, KOOS score	ICSI+PT (SMD = -1.31; 95% CI: -2.14, -0.49) was more effective than PT alone for pain reduction. Adverse events: No serious adverse events. Minor adverse events as detailed in Table 4. Of the 78 individuals who received ICSI, one fainted whilst receiving the injection. No other adverse events were reported in either group. At 1 year, the mean between-group difference in WOMAC scores was 18.8 points (95% CI = 5.0 to 32.6) in favour of physical therapy A significant change in relative bone marrow lesion (BML) volume was observed between the ICSI group and placebo group after 14 weeks (reduced BML volume in ICSI group, increased BML volume in placebo group) [-1.1% vs 2.7%; between-group difference, 3.8% (95% CI 0.5 to 7.0)] but not after 26 weeks [0.8% vs 1.6%; between-group difference, 0.8% (95% CI -2.8 to 4.4)].	Although this well conducted and reported systematic review with NMA included studies directly addressing the CAT question, it also included a wide range of injection treatments other than ICSI. The NMA results did not provide a clear ranking for ICSI + physiotherapy treatment. Furthermore, adverse event findings were not analysed specifically in relation to ICSI combined with physio. Findings are limited by the low number and quality of included studies. This RCT compares ICSI to physiotherapy treatment but does not evaluate combined ICSI with physiotherapy. Information on adverse events is limited to one report of fainting at time of ICSI intervention. Whilst outcomes were significantly better in participants randomised to

Journal of Medicine, 382(15), pp.1420-1429. RCT Nielsen F.K.; 2018 The effect of intra-articular glucocorticosteroids and exercise on symptoms and bone marrow lesions in knee osteoarthritis: a secondary analysis of results from a randomized controlled trial Osteoarthritis and Cartilage, 26(7), pp.895-902. RCT retrospective secondary analysis			These changes did not correlate with changes in KOOS scores. Both groups had improved KOOS pain scores at 14 weeks, but there was no between group difference.	physiotherapy compared to ICSI, these results should be considered with some caution due to risk of bias through lack of blinding, potential recruitment bias, and potential attention bias (considerably greater number of consultations in physiotherapy participants). This study is a secondary analysis of RCT data and therefore not powered specifically to detect changes in bone marrow lesions. Well conducted RCT and analysis. Reduced volume of bone marrow lesions (ie improvement) was associated with the ICSI intervention versus saline placebo injection when administered as part of physio/injection package. However, this did not correlate with changes in KOOS so clinical relevance is unclear

Summary of evidence

Few studies directly explored the use of ICSI combined with physiotherapy: We identified one network meta-analysis (Liao 2023) that included 3 studies of moderate quality, comparing physiotherapy versus physiotherapy plus ICSI (two of which had samples of less than 50); and one secondary analysis from an RCT comparing ICSI to placebo injection, both combined with a physiotherapy programme. A narrative review (Samuels 2021) identified two additional studies not included in Liao's systematic review that reported no benefit from adding ICSI before a programme of exercise therapy but failing to report on adverse effects. These studies all involved people with OA knee pain. No studies were identified that explored ICSI combined with physiotherapy rehabilitation for OA hip pain.

The identified studies reported similar rates of adverse effects in both groups (Table 4), but physiotherapy plus ICSI was associated with different types of adverse effects (increased joint pain lasting less than 2 minutes, allergic reaction) compared to physiotherapy alone (gastrointestinal symptoms associated with oral medications, temporary increase in bone marrow lesion volume).

Table 4: Summary of results from included studies (adding ICSI to rehabilitation)

Study	Intervention and outcomes		Control and outcomes	
	Corticosteroid intervention (with/without PT) in patients with OA knee pain		Physiotherapy intervention alone in patients with OA knee pain	
Delgado—Enciso 2018*	ICSI + PT n = 8	Increased joint pain n = 8	PT n = 6	GI pain (related to NSAIDs) n = 6
Delgado-Enciso 2019*	ICSI + PT n = 119	Increased joint pain n=114 Allergic reaction n = 1	PT n = 118	78 GI pain (related to NSAIDs) n = 78
Subazwari 2020 *∓	*ICSI + PT (n = 22)*	*Not reported*	*PT (n = 22)*	*Not reported*
Nielsen 2018	ICSI + Exercise n = 50	Short term reduction in volume of bone marrow lesions -1.1%	Exercise (+ placebo injection of saline) n = 50	Short term increase in volume of bone marrow lesions +2.7%
Totals	**ICSI + PT/Exercise n = 177**	**Increased pain n = 122 Allergic reaction n = 1**	**PT/Exercise n = 174**	**GI pain (NSAID related) n=84 Volume of bone marrow lesions ↑ by +2.7%**

**relevant studies from Lliao 2023 systematic review;* ∓ Excluded from totals as adverse events not reported
CS = corticosteroid injection , PT = physiotherapy, GI = gastrointestinal, NSAIDs = Non-steroidal anti-inflammatories

Summary of broader evidence on risks of ICSI for OA hip and knee pain (see appendices)

• ICSI for OA hip or knee pain are frequently associated with minor/ transient adverse effects

• Serious/long-lasting complications appear to be uncommon but can be catastrophic

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• Infection risk is low but can potentially lead to joint replacement or death

• ICSI delivered within the 3 months prior to hip or knee arthroplasty surgery increases the risk of post-surgical infection. Risks diminishes with longer periods between ICSI and surgery. For OA hip, the risk may still be higher at 12 months than in those who have not had a ICSI

• Risks relating to structural damage (accelerated OA progression, subchondral insufficiency fractures, osteonecrosis and rapid joint destruction following ICSI particularly in the hip joint) are currently unclear due to inconsistent evidence

Implications for practice

Risks of transient joint pain and allergic reaction should be discussed with patients when considering adding ICSI to physiotherapy rehabilitation for OA knee pain. As there is insufficient evidence for a fully informed shared decision-making process, the broader evidence relating to risks of hip and knee ICSI outlined below should also be considered and discussed – see recommendations on Page 21.

These CAT findings will be shared with clinical teams locally and local patient information sheets and clinical pathways will be reviewed to ensure they reflect the findings. The CAT and accompanying resources such as a summary poster and/ or VLOG will be made available on the Keele CAT website.

Further randomised controlled trials (RCTs) and large observational studies are needed to better understand risks (including incidence and causality) of adding ICSI to physiotherapy rehabilitation for OA knee and hip pain.

What would you post on X (previously Twitter)?

Adverse effects from knee/ hip intra-articular steroid injections are poorly reported in research literature. Minor/transient side effects seem common. There remains uncertainty and debate around incidence of serious adverse events and their causal associations. Shared decision-making discussions with patients need to acknowledge this uncertainty.

Appendix 1. Broader evidence of risks associated with ICSI in OA hip/ knee

In an attempt to answer our CAT question more fully, we have drawn on broader evidence of risks from studies without a physiotherapy rehabilitation component that compared ICSI to placebo or to 'no-care' controls. This proved challenging because the primary focus of

most published studies on ICSI for OA hip/ knee is on efficacy rather than risks/ harms. Furthermore, studies commonly use image guidance for ICSI delivery (unlike our clinical practice) and often include mixed hip and knee pain populations that are not isolated to OA.

Table A1: Included studies providing broader evidence on risks of ICSI for OA hip and knee pain.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
Baums M. H., 2023 Risk analysis of periprosthetic knee joint infection (PJI) in total knee arthroplasty after preoperative corticosteroid injection: a systematic review: a study performed by the Early-Osteoarthritis group of ESSKA-European Knee Associates section. *Archives of Orthopaedic and Trauma Surgery*, *143*(5), pp.2683-2691. **Systematic Review**	Participants with periprosthetic joint infection following Total Knee Replacement (TKR) surgery. Original clinical studies, published in English up to July 2021. Six studies were included that involved 80,579 participants who received injections	**Intervention**: ICSI before TKR surgery **Control**: No ICSI before TKR **Outcomes:** Association between preoperative ICSI and Joint infection in TKR. Time point from which ICSIs could be applied without risking joint infection.	No statistical significance found in infection rate in ICSI group compared to control groups. However, the subgroup receiving ICSI within 3 months of TKR was found to be at significantly greater risk of infection (OR: 1.52, 95% CI 1.37–1.67, $p < 0.01$); this was not observed for those receiving ICSI in the 6-month period prior to TKR (OR: 1.05, 95% CI 0.80–1.39, $p = 0.72$).	Not directly relevant to CAT – evaluates risk of infection from ICSI before TKR surgery, no physio rehab involved. Comprehensive and well conducted systematic review. Provides clear and clinically meaningful outcome, relevant to our patient population if being referred for surgical opinion
Ibad H.A., 2023 Longitudinal MRI-defined cartilage loss and radiographic joint space narrowing following intra-articular corticosteroid injection for knee osteoarthritis: A systematic review and meta-analysis *Osteoarthritis Imaging*, p.100157. **Systematic Review & Meta-analysis**	Participants with Knee OA. RCTs and observational studies from inception to June 2022. Six studies were included that involved 1,437 participants	**Intervention**: ICSI Dosage included 40 mg of triamcinolone acetonide, 32 mg of FX006 (extended-release triamcinolone acetonide) and 12 and 18 mg of dexam- ethasone sodium phosphate	The estimated effect of ICSIs on cartilage structure revealed greater odds of cartilage structure worsening (OR: 2.01, 95% CI: 1.18,3.44).	Not directly relevant to CAT – evaluates risk of radiological cartilage loss following ICSI, no physio rehab involved. Well conducted systematic review that adds limited evidence minor relevance to

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
		Control: no injection and placebo injection. **Outcomes:** cartilage thickness changes (derived from MRI) or Joint space width (derived from X-ray).		our CAT question. Specifically, this review suggests that people who received ICSI were around twice as likely to experience adverse effects on knee cartilage structure than those who received placebo or no injection.
Kim Y.M., 2023 Preoperative intra-articular steroid injections within 3 months increase the risk of periprosthetic joint infection in total knee arthroplasty: a systematic review and meta-analysis *Journal of Orthopaedic Surgery and Research*, *18*(1), pp.1-7. **Systematic Review**	Participants diagnosed with periprosthetic joint infection following primary TKR surgery. Studies published up to October 2022 14 studies (113,032 participants received ICSI)	**Intervention**: ICSI before TKR surgery **Control**: No ICSI before TKR **Outcomes:** association between preoperative ICSI and Joint infection in TKR. Time point from which ICSIs could be applied without risking joint infection after surgery.	With the time interval < 3 months, the pooled odds ratio was 1.26 (95% CI 1.06–1.50, p < 0.01) indicating a significantly increased risk of infection. With the time interval < 6 months, the pooled odds ratio was 1.19 (95% CI 0.99–1.43, p = 0.06) indicating this is a safe time to inject. The time interval of 3–6 months has not been investigated enough	Not directly relevant to CAT – evaluates risk of infection from receiving ICSI before TKR surgery, no physio rehab involved. Comprehensive systematic review, providing clear and clinically meaningful outcomes, including risks associated with different time intervals between ICIS and TKR surgery, relevant to our patient population if being referred for surgical opinion.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
				Findings based on data from non RCTs, none of which were deemed high risk of bias.
Sabatini F.M; 2023 Incidence of Rapidly Progressive Osteoarthritis Following Intra-articular Hip Corticosteroid Injection: A Systematic Review and Meta-Analysis. Arthroplasty Today. **Systematic Review and Meta-Analysis**	OA hip participants. 10 studies (2 prospective and 8 retrospective) that were classified as able to detect Rapidly Progressive OA (RPOA) therefore were included for the meta-analytic estimate of RPOA incidence after hip ICSIs. 17 studies could not detect RPOA. Includes studies up to September 2022.	**Intervention:** ICSI hip **Control:** none **Outcomes**: comparison of pre- and post- ICSI imaging	The meta-analytic estimate of RPOA incidence was 6% (95% confidence interval, 3%-9%) based on 10 articles classified as able to detect RPOA. RPOA definitions varied from progression of OA within 6 months to the presence of destructive changes. These studies were subject to bias from excluding patients with missing post-ICSI radiographs. A large percentage of patients (up to 80% in 2 studies) were often excluded from the individual studies due to lack of follow-up imaging post ICSI. I^2 was 89%. The incidence of RPOA after ICSIs remains unknown due to variation in definitions and follow-up (2 months to 2 years). While RPOA following ICSIs may	Limitations of the included studies were acknowledged but impacts the result as bias within individual studies reflects in the reviews findings. Results need to be taken in context of limitations of the available evidence. The majority of prospective studies did not have follow-up imaging, which could have allowed cases of RPOA to go undetected. Conversely, retrospective studies may be overestimating the incidence of RPOA through selection bias. Exclusion of patients without a follow-up radiograph narrows the study

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			be 6%, many cases are not severe, and this may reflect selection bias. Whether clinically significant RPOA following ICSIs is common enough to limit use remains unknown.	population to those returning to clinic for a follow-up radiograph who may be more likely to have continued pain. This may artificially increase the estimated incidence.
Saracco, M., 2023 Do prior intra-articular injections impact on the risk of periprosthetic joint infection in patients undergoing total hip arthroplasty? A meta-analysis of the current evidences with a focus on the timing of injection before surgery. EFFORT Open Reviews, 8(6), 459-467. Retrieved Nov 22, 2023, from https://doi.org/10.1530/EOR-23-0028 **Literature review and meta-analysis**	Participants older than 18 years undergoing Total Hip Replacement (THR) surgery. 11 retrospective studies were included from 2005 to 2021 – 10 used for the meta-analysis. 6 adopted a matched cohort design, 5 were case–control studies. The studies reported outcomes for ICSIs in 6 cases for Hyaluronic Acid (HA) injections in 1 case and for ICSI or HA injection in the remaining 4 papers.	**Intervention:** intra-articular injections of any drugs performed before the THR surgical procedure. **Comparison:** a cohort of patients who did not undergo intra-articular injections prior to the THR surgical procedure. **Outcome:** diagnosis of Joint infection (according by any definition used in the included studies).	With all studies included, pooling of data revealed an increased risk of Joint infection in the injection group (RR: 1.38, 95% CI: 1.01, 2.72) that was statistically significative (t = 2.36, P = 0.0427), and this remained significant after removing two influential studies (RR: 1.20; 95% CI: 1.08, 1.35; t = 3.87; P = 0.0061) for sensitivity analysis Results regarding time from injection to THR seem to be done with all studies included, they report: the subgroup 0–3 months, have an increased risk of PJI after injection (RR: 1.64, 95% CI: 1.44, 1.86, < 0.01; I2 = 0%, P = 0.37).	Does not directly address CAT question - evaluates risks associated with both ICSI and HA injections, and no physio rehab element. Well conducted meta-analysis with sensitivity analysis evident. Subgrouping enables relevant ICSI component to be extrapolated which is the part relevant for this CAT. However, this subgrouping does not expand to evaluation of other risks (infections based on time

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			No significative increased risk was reported for the subgroup 3–6 months (RR: 1.12, 95% CI: 0.88, 1.41, P = 0.36; I2 = 56%, P = 0.10), while a significative increase in the risk of PJI after injection was identified in the <12 months group (RR: 1.20, 95% CI: 1.05, 1.36, P < 0.01; I2 = 0%, P = 0.76) *A subgroup analysis performed to investigate if the type of drug injected influenced risk of infection – for this, data from five studies using ICSI were pooled which revealed a significative increased relative risk of infection (RR: 1.64, 95% CI: 1.44, 1.88, P < 0.01; I2 = 0%, P = 0.73). In four studies, both ICSI and HA injections were used and the pooled results for this group were RR: 1.20, 95% CI: 1.05, 1.36, P < 0.01; I2 = 0%, P = 0.76.	from ICSI to THR) which is only presented for the results as a whole which includes HA injection data).

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
Serhal A., 2023 Rapidly Progressive Idiopathic Arthritis of the Hip After Intra-articular Steroid and Anesthetic Injection in Patients with Hip Osteoarthritis: Incidence and Risk Factors. *Advances in Clinical Radiology*, *5*(1), pp.99-106. **Retrospective study**	Hip injections participants – does not clearly define reason for injection in text, but title of article alludes to ICSI for OA "…Intra-articular Steroid and Anesthetic Injection in Patients with Hip Osteoarthritis" and all patients with history of inflammatory, septic or neuropathic arthropathy, or those with an early surgery or hardware on the injected hip were excluded.	**Intervention:** 163 fluoroscopic guided hip CSI's **Control:** none **Outcomes:** radiograph changes/ evaluation. All included participants had pre-injection radiographs within the last 3 months, and postinjection radiograph at least 1 year after the injection unless the participant developed Rapidly progressive Idiopathic arthritis (RPOA) on follow-up radiographs performed less than 1 year after the injection.	-Study demonstrates that RPOA developed in 13.5% of the injected hips. - 22 hips developed RPOA. Regarding the pre-injection Kellgren/Lawrence (KL) score, there was no statistically significant difference between the 2 groups when the scores are considered individually; however, when the scores are grouped in 2 groups: scores 0 to 2 for no or mild OA and groups 3 to 4 for moderate and severe OA, the RPOA group showed higher pre-injection K/L score ($P < .001$). -There was a significant difference in age between groups ($P < .05$); the mean age of the RPOA group at the time of injection was 65.9 years compared with 59.0 years for the non-RPIA group, but no difference in BMI, sex, race, laterality of	No control group. RPOA can occur without injection so query how 13.5% incidence compares to RPIA patients who haven't received an injection. There is likely selection bias because the cases without follow-up radiographs at least 12 months from the injection were excluded. These patients might have been lost to follow-up or might not have experienced worsening symptoms to warrant radiographic follow-up, which could lead to a higher percentage of positive cases in our population.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			injection, oral steroid use. -Regarding the cumulative number of hip injections, there was no significance difference between both groups with an average number of injections for the same hip of 2.22 for the RPOA group and 2.72 for the non-RPOA group.	
Streck L.E., 2023 How safe are intra-articular corticosteroid injections to the hip?. *BMC Musculoskeletal Disorders*, *24*(1), p.665. **Retrospective evaluation**	682 hips that underwent ICSI with 40 mg of Triamcinolone for primary OA of the hip. Doesn't state if guided ICSI – but were performed by surgeon	**Intervention:** ICSI with 40 mg of Triamcinolone **Control:** none **Outcomes:** Pre- and post-injection radiographs were compared to identify cases with RPOA. Native joint septic arthritis, surgical site infections and joint injections were identified by chart review	4 hips (0.6%) developed RPOA 2–4 months following ICSI. The current data suggests a relative safety of ICSI regarding the onset of RPOA, even in joints with repeated injections. The cumulative Triamcinolone dose was not associated with the development of RPIO (p = 0.281). 1 case was diagnosed with septic arthritis (The patient had several risk factors such as a history of rheumatoid arthritis and oral prednisone intake (10 mg	Limitations: the study design was retrospective, and did not include a control group so RPIO rates in patients without injections are not known.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			Prednisone/day at the time of ICSI). A prior diagnostic aspiration had been performed at an outside hospital and a history of joint pain with fever and chills was documented prior to the ICSI. Therefore, it cannot be ruled out nor proven whether the septic arthritis was caused by the ICSI or whether the patient developed and acute on chronic infection, that was preexisting.) There were 3 superficial surgical site infections/wound dehiscence and no Joint infection - 199 hips (41.2%) that underwent the last ICSI less than 3 months prior to THR and 181 patients (37.4% of the THR) that underwent 2–9 injections with cumulative Triamcinolone-doses up to 360 mg prior to surgery. None of these hips	

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			developed a joint infection.	
NICE 2022 Osteoarthritis in over 16s: diagnosis and management NICE Guideline NG226 **GUIDELINE - Evidence Review**	OA in people over age 16, excluding those with: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to OA, medical conditions presenting with joint inflammation and malignancy. 9 studies related to knee OA and ICSIs compared to placebo (1219 participants received steroid injection) 4 studies related to hip OA and image-guided ICSIs compared to placebo and 3 studies related to intra-articular hyaluronic acid (image guided) compared to ICSIs (image guided)	**Intervention:** intraarticular injection: ICSI/ HS injection / stem cell injection. **Control:** other injection substance or placebo injection **Outcomes**: Pain, physical function, QoL, OA flares, adverse events before 3 months and at 3 months or longer.	Risk Difference (RD) for Serious Adverse Events (SAEs) at ≤3 months after ICSI (image guided) vs placebo injection = 0.01 (-0.04 to 0.07) (data from 2 RCTs, 120 participants, mean follow-up = 10 weeks; total of one event associated with ICSI, none with placebo) Risk Difference (RD) for SAEs at ≤3 months ICSI (unguided) vs placebo = 0.00 (0.00 to 0.04) (data from 2 RCTs, 190 participants, mean follow-up 12 weeks; total of no events associated with ICSI or with placebo). Risk ratio (RR) for SAEs at >3 months ICSI (unguided) vs placebo = 1.19 (0.37 to 3.77) (data from 2 RCTs, 624 participants, mean follow-up 16 months; total of 9 events associated with ICSI, 4 with placebo). Context: -Low quality evidence of	Not directly addressing CAT question. Recognised national guideline. Evidence ranged from high to very low quality, with the majority of evidence being of moderate to low quality. Evidence quality was often downgraded due to risk of bias, inconsistency and imprecision…In general, evidence quality was poorer for important outcomes (OA flares and serious adverse events) where they were often downgraded because of risk of bias due to studies not reporting the definition for the outcome of interest. Apart from studies

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			improvement in pain at 3 months, but not for other outcomes and no longer-term benefits. -Current evidence is insufficient to fully understand risks The committee agreed that there were limitations in using RCTs for understanding the harms and adverse events associated with ICSI. The committee were aware of data which showed that ICSI were associated with a 0.08% risk of septic arthritis, which was not seen in this review. -There is also evidence to show an increased risk of periprosthetic joint infection if joint replacement is performed in the months following ICSI of a native joint.	conducted in people with knee OA, the analyses were based on data from a small number of participants.
Paskins Z. 2022 Clinical effectiveness of one ultrasound guided intra-articular corticosteroid and local anaesthetic injection in addition to advice and education for hip osteoarthritis (HIT trial): single blind, parallel group,	199 adults aged ≥40 years with hip OA and at least moderate pain.	**Intervention:** 66 randomly assigned to best current evidence (BCT) plus ultrasound guided ICSI of triamcinolone and lidocaine	- four (6%) of 66 participants reported thinning or whitening of the skin at the injection site and four (6%) of 66 had hot flushes (number needed to	Clear and comprehensive methodology description, participants were randomised, injectors, injectees and

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
three arm, randomised controlled trial. BMJ, *377*. **Single blind, parallel group, three arm, RCT**		**Control:** 67 were randomly assigned to receive advice and education and 66 to BCT plus ultrasound guided injection of lidocaine. **Outcome:** primary outcome was self-reported current intensity of hip pain (0-10 Numerical Rating Scale), secondary WOMAC, (SF-12 and EuroQoL Q-5D-5L),1 measures, Adverse events were self-reported and collected by participants' general practitioner. Adverse events to an injection were collected by clinical case report forms and questionnaires (at two weeks and two months).	harm 3.47 (95% confidence interval 2.39 to 6.54. - 7 serious adverse events were recorded. - a participant with a bioprosthetic aortic valve **died** from subacute bacterial endocarditis four months after receiving BCT plus ultrasound-triamcinolone-lidocaine. The possibility of a causal link could not be excluded. - the other 6 serious events/the remainder were judged unrelated to the trial treatment.	statisticians were blinded, P values, power calculations and CI's were used and sensitivity analysis conducted. Relevant paper reporting CSI harms. Relatively comparable population and intervention, although very limited ethnic diversity and study used US guidance for ICSI delivery unlike usual practice within LCHT MSK service.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
Latourte, A., 2022 Do glucocorticoid injections increase the risk of knee osteoarthritis progression over 5 years?. *Arthritis & Rheumatology*, *74*(8), pp.1343-1351. **Observational cohort study (multi-centre)**	564 patients with symptomatic knee OA form an OA hip and knee cohort in France with 5 year follow-up aged 40-75	**Intervention** No experimental intervention as observational study of Intra-articular injections (ICSI, HA, or no injection) **Comparators** were HA injection and/ or no injection **Outcomes** Radiographic changes / TKR surgery within 5 years	51 (9%) had ICSI, (17.5% had hyaluronic acid injection; 63.1% had no injection) Knees treated with ICSI had a similar risk of iTKR (hazard ratio [HR] 0.92 [95% CI 0.20, 4.14; P = 0.91) or K/L grade worsening (HR 1.33 [95% CI 0.64, 2.79; P = 0.44) Similar results were obtained for Joint space narrowing.	Does not directly address CAT question – evaluates risk of radiological deterioration following ICSI compared to no injection/ HA injection in moderate size cohort study. Results suggest no increased risk of TKR/ joint deterioration associated with ICSI, in contrast to other studies. Limitations include sample size, participant selection, participant reported injection details
Wang, Q., 2022 Effect of intramuscular vs intra-articular glucocorticoid injection on pain among adults with knee osteoarthritis: The KIS randomized clinical trial. *JAMA network open*, *5*(4), pp.e224852-e224852. **RCT**	Adults aged 45+ in Netherlands with clinical diagnosis of symptomatic OA knee (pain x 3 months or more, 3/10 or more on pain NRS, attending consultations in primary care. (71 participants randomised to IA injection, 67 received)	**Intervention:** ICSI **Control**: intramuscular steroid injection **Outcomes** Knee pain on Knee injury and OA Outcome Score (KOOS score) and Kellgren/Lawrence radiographic scores	The most frequently reported adverse events were hot flush (Intramuscular steroid injection, 7 [10%] vs ICSI, 14 [21%]) and headache (Intramuscular steroid injection, 10 [14%] vs ICSI, 12 [18%]), and all events were classified as nonserious.	Limited relevance to our patient population in that comparator is intramuscular injection. Incomplete data/ crossovers/ protocol deviations more prevalent in ICSI group, but are considered in

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			Overall, adverse events, although not serious, were relatively common (affecting 42% of those receiving ICSI)	sensitivity analyses. Lack of blinding of participants and of treatment delivery GPs (placebo effect linked to ICSI injection method), and participant preference (for Intramusculular injection) were considered as potential bias risks.
Ayub S., 2021 Efficacy and safety of multiple intra-articular corticosteroid injections for osteoarthritis—a systematic review and meta-analysis of randomized controlled trials and observational studies *Rheumatology*, *60*(4), pp.1629-1639. **Systematic Review & Meta-analysis**	Fourteen RCTs and 2 observational studies were assessed for the safety of multiple ICSIs compared to placebo/ no injection. Of these, 11 studies reported on 591 patients with OA knee pain undergoing multiple steroid injections.	**Intervention:** Between 1 and 8 ICSIs (various steroids, and with varying frequency ranging from 1 to 3 weekly injections, to 3-monthly injections over 2 years) **Outcomes**: Any adverse events reported (in addition to efficacy measured by pain intensity and duration of pain reduction)	Minor local adverse events were similar in both groups. One RCT found that regular ICSIs every 3 months for 2 years caused greater cartilage loss compared with saline injection (-0.21 vs 0.10 mm). One cohort study found that multiple ICSIs were associated with worsening of joint space narrowing (HR 3.02, 95% CI 2.25, 4.05) and increased risk of joint replacement (HR 2.54, 95% CI 1.81, 3.57).	Not directly addressing CAT question and looks at safety of ICSI for all OA joints (although majority are OA hip and knee). Adverse event/ safety data are presented narratively as authors unable to pool due to heterogeneity/ low incidence. Still of some relevance to broader shared decision making discussion
Cheok T., 2021 Safety of intraarticular corticosteroid injection	Studies that evaluate outcomes in participants with	**Intervention**: participants who received ipsilateral	- odds of PJI in patients receiving ICSI within 12	Good quality SR and meta-analysis.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
preceding hip and knee arthroplasty: a systematic review and meta-analysis amid resolving COVID-19 arthroplasty restrictions. *Journal of hip preservation surgery*, *8*(3), pp.215-224. **Systematic review and meta-analysis**	primary hip or knee arthroplasty	ICSI to their native joint within the preceding 12 months of arthroplasty **Control:** participants who had no ICSI **Outcome:** prosthetic joint infection (PJI)	months prior to ipsilateral hip arthroplasty - there was a significant difference in rates of PJI between the two arms [OR=1.17, 95% CI=1.01–1.36, *P*-value=0.04]. - There was a significantly increased rate of PJI in patients who received an ICSI in 3 months preceding hip arthroplasty [OR=1.45, 95% CI=1.15–1.83, *P*-value=0.002]. - In hip arthroplasty, there appeared to be a temporal relationship, whereby the odds of PJI decreased from 1.45 at 3 months prior to 1.17 within 12 months prior to their arthroplasty.	Provides relevant information for broader shared decision-making discussion.
Jurgensmeier, K, 2021 Intra-articular injections of the hip and knee with triamcinolone vs ketorolac: a randomized controlled trial. *The Journal of Arthroplasty*, *36*(2), pp.416-422. **RCT**	58 people with moderate to severe radiographic primary OA knee in orthopaedic clinic, Idaho	**Intervention**: US guided ICSI of triamcinolone **Control:** Ultrasound guided ICSI of Ketorolac **Outcomes**: patient reported outcomes of KOOS and VAS	The reported adverse effects of injected medications were minimal. In the triamcinolone group, 2/58 patients with diabetes reported an elevation in blood glucose during the first	There are concerns regarding quality for this study: Comparability between groups at baseline is unclear. Drop outs are not accounted for.

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
			week post-injection. Additionally, nausea, high blood pressure, and a flare of temporal arteritis were each recorded once among those who received steroids. it is unclear whether these additional reported effects were related to the triamcinolone injection	Data sets or patients with one or more missing measurement were not included in the analysis. The effect size for steroid injection compared to anti-inflammatory injection is not clear. The reporting of adverse effects adds to information that can be shared with patients in a shared decision-making process. However, it is unclear whether some of the adverse effects reported were related to the intervention, and participant selection was based on radioagraphic severity which does not reflect our clinical practice.
Samuels J. 2021 Critical appraisal of intra-articular glucocorticoid injections for symptomatic	Studies related to people with symptomatic OA knee.	**Intervention**: ICSI steroid injection for symptomatic OA knee	Reports that adverse events with ICSIs are rare (~1 per 3,000	Lack of robust methodology may lead to bias, but

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
osteoarthritis of the knee *Osteoarthritis and Cartilage*, *29*(1), pp.8-16. **Review**	No details about number of studies included, how searched/ selected, inclusion/exclusion criteria, quality of studies generating included evidence, etc	**Control**. N/A **Outcomes**: broad discussion of outcomes with a focus on clinical, molecular, and structural effects of ICSIs in knee OA	patients) (based on 2 studies. Reports that short-term increases in pain, mild headache, insomnia and facial flushing, may occur in as many as 40% (based on 1 study). Reports potential for transient (24e48 h) suppression of the hypothalamic-pituitary adrenal axis and elevated blood glucose (based on 1 study), increased risk of periprosthetic joint infection with injections given within 3 months of surgery (odds ratio 1.21; P= 0.014, based on 1 observational study of over 50,000 patients); and conflicting evidence about increased risk of TKR following injection from 3 studies.	includes some useful data/ references
Zhong, H.M., 2020 Intra-articular steroid injection for patients with hip osteoarthritis: a systematic review and meta-analysis. *BioMed Research International*, *2020*. **Systematic Review and meta-analysis**.	Patients with hip OA, which was diagnosed based on American College of Rheumatology criteria and/or radiographic evidence	**Intervention:** ICSI – all were image guided. **Control:** placebo groups in RCTs or different regimes of ICSI in noncontrolled trials **Outcomes:** reported usable	1504 pts - Of all 1504 patients, only a few participants were reported to withdraw for side effects. Lambert - One deep vein thrombosis at 3 months in the steroid group; one	Some databases were omitted form search such as Cochrane and BMJ best practice but well conducted review. Appropriate RCT results

Study (first author, year of publication, study type)	Population and setting	Intervention evaluated and outcomes measured	Study results (reported harms/ adverse events)	Quality
		pain reduction was primary outcome	patient in the placebo group and 3 patients in the steroid group reported rebound pain. Micu - Transient facial rash was present in 16 patients during the first 24–48 h after injection. Young - One episode of temporary hyperglycaemia in a type 1 diabetic, one facial flush, one patient reported soft-tissue swelling, and two patients reported a temporary increase in pain.	were pooled with good detail on how this was done and those studies not appropriate to be pooled by meta-analysis were summarized. Harms were reported within the text, no meta-analysis of harms as the primary outcome was pain reduction so limited data related to this CAT.

This broader literature indicates that adverse effects are not uncommon following intra-articular ICSI for OA hip and knee pain. These are, however, reported to be mostly minor or transient and include reports of vasovagal episodes (fainting), allergic reactions, bleeding, thinning or whitening of the skin at the injection site, and short-term flushing, headache, nausea/vomiting, insomnia, raised blood pressure, palpitations/tachycardia, hyperglycaemia in people with diabetes, and increased joint pain and joint/soft tissue swelling.

The overall incidence of adverse effects following intra-articular steroid injection is high (up to 42% for OA knee joint injections; overall rates for OA hip joint injections were not identified in the available literature). In summary of the evidence we reviewed:

- Samuels 2021 This narrative review reported that adverse events with ICSI are rare (~1 per 3,000 patients) based on evidence from two studies. However the review also states that short-term increases in pain, mild headache, insomnia and facial flushing, may occur in as many as 40% (based on 1 study). In addition, this review reports potential for transient (24-

48 hour) suppression of the hypothalamic-pituitary adrenal axis and elevated blood glucose (based on 1 study).

- Wang 2022 This RCT found that adverse events, although generally not serious, were relatively common (affecting 42% of those receiving ICSI). The most frequently reported adverse events (all classified as non-serious) were hot flush (Intramuscular injection, 7 [10%] vs ICSI, 14 [21%]) and headache (Intramuscular injection, 10 [14%] vs ICSI, 12 [18%]).
- Jurgensmeier 2021 This RCT reported an elevation in blood glucose during the first week post-injection in 2/58 patients with diabetes following injection with triamcinolone.
- Ayub 2021 This systematic review reported similar frequencies of local adverse events such as temporary joint pain, erythema, and itching when comparing multiple steroid injections to no/ placebo injections, and a single report of malaise, tachycardia and hypotension following ICSI. The majority of studies included in this review reported on ICSI for OA hip and knee pain, but studies of injections for other joints were also included.
- Deyle 2020 This RCT reported just a single adverse event in one participant in the ICSI group who fainted while receiving an injection, and no adverse events in the comparison group who had physiotherapy rehabilitation. The mean between-group difference in WOMAC scores was 18.8 points; (95% CI 5.0 to 32.6) in favour of physical therapy.

Serious adverse effects including infection (local infection/sepsis), bone/ joint deterioration, and systemic effects are reported to be rare but can be catastrophic.

- NICE 2022 This national guidance reports on Serious Adverse Events (what is included as an SAE is not clearly defined) associated with ICSI as follows:
    - Risk Difference (RD) at ≤3 months for image guided ICSI vs placebo = 0.01 (-0.04 to 0.07) (data from 2 RCTs, 120 participants, mean follow-up = 10 weeks; total of one event associated with ICSI, none associated with placebo)
    - Risk Difference (RD) at ≤3 months for unguided ICSI vs placebo = 0.00 (0.00 to 0.04) (data from 2 RCTs, 190 participants, mean follow-up 12 weeks; total of no events associated with steroid injection or with placebo).
    - Risk ratio (RR) for >3 months for unguided ICSI vs placebo = 1.19 (0.37 to 3.77) (data from 2 RCTs, 624 participants, mean follow-up 16 months; total of 9 events associated with steroid injection, 4 with placebo).

Infection

No systematic reviews, large cohort studies or RCTs were identified in our search evaluating infection rates associated with ICSI for OA hip/knee pain, and overall incidence of infection is not clear from the wider evidence that we reviewed. Rates of infection for knee joint injections cited in older literature range from 1 in 3,000 to 1 in 50,000 (McGarry 2011). More recently, a systematic review of studies involving multiple ICSIs for OA in any joint (Ayub 2021) found no reports of infections in the 16 included studies (of which the majority focused on knee or hip OA), whilst recent guidance (NICE 2022) highlighted data suggesting

that intra-articular injections (for any joint) are associated with a 0.08% risk of septic arthritis. Infections are usually treatable but they can potentially cause serious harm. In the evidence we reviewed, one case of septic arthritis resulted in a staged hip arthroplasty, and one case of bacterial endocarditis in a patient with bioprosthetic aortic valve resulted in death four months following a hip injection where a causal link could not be excluded. None of the other studies that we reviewed reported joint infections/ septic arthritis.

- Ayub 2021: This systematic review of multiple steroid injections for any OA joint compared to no injection/ placebo found no reports of infections in the 16 included studies.
- Uson 2021: This European guideline for ICSI for any joint condition reports septic arthritis risk to range from 0.0002 to up to 0.035%, the latter being 3 per 7900 procedures.
- Paskins 2022: In this RCT, of 199 participants with OA hip undergoing CSI, one participant with a bioprosthetic aortic valve died from subacute bacterial endocarditis four months later.
- Streck 2023: In this retrospective evaluation of 682 hips that underwent ICSI for osteoarthritis of the hip, 3 cases of superficial wound infections and one case of septic arthritis was reported.
- NICE 2022: The NICE committee highlighted data not included in their review that showed intra-articular injections to be associated with a 0.08% risk of septic arthritis.

Post-arthroplasty infection

There is convincing and consistent evidence that intra-articular steroid injections delivered within the 3 months prior to hip or knee arthroplasty surgery increases the risk of post-surgical infection. Whilst it has been reported that a window of 12 months between injection and knee arthroplasty seems to be safe, evidence suggests that for patients undergoing hip arthroplasty the risk is still higher at 12 months than in those who have not had a CSI in the previous 12 months. There appears to be a temporal relationship, whereby the odds of infection decrease from 1.45 at 3 months to 1.17 at 12 months prior to arthroplasty.

- Kim 2023: In this systematic review including 14 relevant studies of ICSI for OA knee, the pooled odds ratio was 1.26 (95% CI 1.06–1.50, $p < 0.01$) indicating a significantly increased risk of infection for ICSIs delivered within < 3 months before TKR surgery. For time interval < 6 months, the pooled odds ratio was 1.19 (95% CI 0.99–1.43, $p = 0.06$) indicating this to be a safe time to inject. The time interval of 3–6 months has not been sufficiently investigated to comment on safety.
- Baums 2023: In this systematic review, no statistical significance in intra-articular infection rate for OA knees is reported in ICSI group compared to control groups overall, but ICSI within 3 months prior to TKA were associated with a significantly increased risk of infection

(Odds Ratio: 1.52, 95% CI 1.37–1.67, p < 0.01); this was not observed in the 6-month period (Odds Ratio: 1.05, 95% CI 0.80–1.39, p = 0.72).

- Saracco 2023: In this review of various injection types, five studies used ICSIs for OA hip pain. For this subgroup, the pooling of data revealed a significative increased relative risk of joint infection post THR surgery (Risk Ratio: 1.64, 95% CI: 1.44, 1.88, P < 0.01; I2 = 0%, P = 0.73).
- Cheok 2021: In this systematic review, significantly increased infection rates in OA hip participants was reported for those who had ICSI within 12 months of arthroplasty [Odds Ratio: 1.17, 95% CI=1.01–1.36, P-value=0.04], and even greater increased risk in patients who received an ICSI in 3 months preceding hip arthroplasty [Odds Ratio: 1.45, 95% CI=1.15–1.83, P-value=0.002].

Structural deterioration

We found inconsistent evidence/ conflicting interpretation of findings related to structural joint damage following intra-articular steroid: Documented effects include accelerated osteoarthritis progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction with bone loss, occurring more commonly in the hip joint, and amongst women. However, causality is unclear, as is natural history, making interpretation of current evidence challenging. A systematic review published in 2023 suggests there may be a 6% incidence of rapidly progressive OA after ICSIs but cautioned that incidence remains unknown due heterogeneity and bias within studies. In two recently published studies (not included in the 2023 systematic review) an incidence of 0.6% of rapidly progressive osteoarthritis is reported in one study, and an incidence of 13.5% is reported in a second smaller study where older participants were identified at greater risk. Neither study includes controls for comparison with natural history and drop-outs before follow-up present a risk of bias in the second study.

- Sabatini 2023: This systematic review reported a meta-analytic estimate of Rapidly progressive OA incidence to be 6% (95% CI 3%-9%) however the studies were subject to bias from excluding patients with missing post-ICSI radiographs. Furthermore, definitions of Rapidly Progressive OA varied between studies as did the timing of follow-up imaging. I^2 of 89% reflects the inconsistency of findings.
- Ibad 2023: This systematic review reported greater odds of cartilage structure worsening (Odds Ratio: 2.01, 95% CI: 1.18,3.44) in participants with OA knee after ICSI compared to no injection/ placebo injection.
- Serhal 2023: In this retrospective study of OA hip, rapid progression of arthritis developed in 13.5% (n = 22) of the injected hips. Risk seemed greater in those with moderate to severe OA and older age, but risk was not associated with number of injections. No control data was collected for comparison with natural history.

- Streck 2023: In this retrospective observational study, of 682 participants with OA hip, 4 hips (0.6%) developed rapid progression of arthritis 2–4 months following ICSI. No control data was collected for comparison with natural history.
- Ayub 2021: This systematic review of repeated ICSIs for OA joints in which most studies focused on OA knee, conflicting evidence was reported from 2 RCTs [one reporting no difference between groups, and another reporting greater cartilage loss (mean change in cartilage volume loss on MRI -0.21 vs -0.10 mm), and a higher risk of cartilage damage over 2 years compared to placebo injection)] and from 2 observational studies [one reporting no difference between groups for radiographic degeneration, and the other reporting worsening of OA in 65 of 148 (44%) knees in the steroid injection group compared with 80 out of 536 (15%) knees in the control group (Kellgren–Lawrence grading)]. The Hazard Ratio for worsening OA was 4.67 (95% CI 2.92, 7.47). This study also reported 33 joint replacements over the 2-year observation period in the ICSI group (22.3%) compared with 29 in the placebo group (5.4%).
- Latourte 2022: In this observational cohort study (564 participants) reported (in contrast to above) that knees treated with steroid injection had a similar risk of total knee arthroplasty (hazard ratio 0.92 (95% CI 0.20, 4.14; P = 0.91)) or worsening osteoarthritic changes (Kellgren Lawrence) (hazard ratio 1.33 (95% CI 0.64, 2.79; P = 0.44)) when compared to hyaluronic acid injection or no injection.

Efficacy

Whilst this CAT did not focus on treatment effectiveness, it should be noted for context that systematic reviews show that the treatment effect for pain relief is modest compared with intra-articular saline placebo and lasts for 2-4 weeks on average (Guermazi 2023). Current NICE guidance advises that patients should be informed of short-term pain relief of between 2 and 10 weeks (NICE 2022).

Additional information on adverse effects related to steroid treatments for OA/joint conditions but not specifically related to OA hip or OA knee:

A systematic review of injections for OA (not specifically hip/ knee) published in 2022 concluded that current evidence is insufficient to detemine disease progression/ time to surgery (Donovan 2022) following injection.

Habib et al have published two systematic reviews (2009 and 2010) covering systemic side effects and local side effects of ICSIs for study populations with any rheumatological joint condition including OA, but primarily involving populations with rheumatoid arthritis and juvenile idiopathic arthritis.

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Local adverse effects include:

The risk of infection is higher among immunocompromised and incapacitated patients. The knee is the most common infected joint, as it is the most injected joint. However, relative to the frequency of injection, the hip is the most infectable joint. Fatalities are uncommon, one case of death from hip infection due to Staphylococcus aureus.
Avascular necrosis most commonly involves the hips, knees, and shoulders.
Rapid destruction of the femoral head is reported after just one injection and is usually seen in women with unilateral hip involvement 3–12 months following the injection.

Type of complication	Frequency
Infection	~1:1,000 to ~1:25,000
Intra-articular and periarticular calcifications	~4 to ~50%
Cutaneous atrophy	~8.3%
Cutaneous depigmentation	~5%
Avascular necrosis	Uncommon
Rapid destruction of the femoral head	Uncommon
Acute synovitis	Uncommon
Charcot's arthropathy	Rare
Tendinopathy	Rare
Nicolau's syndrome	Very rare
Joint dislocation	Very rare

Systemic adverse effects include:

HPA-Axis – cortisol suppression in serum, saliva, urine; ACTH suppression/ blunted response; Cushing syndrome
Metabolic – including hyperglycaemia; bone/ cartilage turnover/ formation
Haematological – including sickle cell crisis
Vascular – including flushing; increased blood pressure
Other – infection, allergy/ anaphylaxis; hiccups; hallucinations; psychological

Ayub 2020 undertook a systematic review and meta-analysis of effects and safety of repeated intra-articular steroid injections for OA (any joint), that included 14 RCTs and 2 observational studies. Eleven of these studies reported on 591 patients with OA knee and this paper has therefore been included in the broader evidence summarised above. This review found that local side effects such as temporary joint pain, erythema and itching were reported in some but not all RCTs and it was not appropriate to calculate hazard ratios for each trial due to the rarity of these events. They concluded that there is some evidence of potential detrimental effects on structural OA progression of multiple intra-articular corticosteroid injections which needs further investigation.

Stone 2021 published a review of the history, effectiveness and adverse effects of corticosteroids (injection and oral) in the treatment of joint pain. Their review outlines the literature for both local and systemic adverse effects. Minor pharmacological effects include elevated serum glucose (particularly in patients with diabetes), skin rash including erythema of the face/torso, post-injection flare, reduction in immunity, increased pain, and increased propensity to infection, citing and earlier review that calculated an incidence from

0% to 81% for minor adverse events (skin rash, flushing, increased pain, steroid flare) and 0% to 5.8% for major events (rupture, infection, atrophy, calcification). Skin hypopigmentation has been reported to occur in 1.3% to 4% of patients who underwent local corticosteroid injection, typically occurring 1 to 4 months after injection and most noticeable in dark-skinned patients. Subcutaneous fat atrophy typically lasts for 6 to 12 months after corticosteroid injections, land is generally reversible and resolved within one year. The risk of both skin hypopigmentation and subcutaneous fat atrophy can be reduced if steroids with suitable solubility and potency are used. Reported moderate to severe adverse effects included infection, nerve damage, Charcot arthropathy, osteonecrosis, avascular necrosis, cartilage damage, steroid arthropathy, tendon rupture, tissue arthropathy, fat necrosis, calcification, joint instability, and hypothalamic-pituitary-adrenal axis suppression.

Infections

Reported joint infection rates are low. A rate of 0.08% has been reported following intra-articular steroid injections for OA in one study (Peterson 2019) Of the 11 cases of septic arthritis in this study, one patient died from sepsis.

Hyperglycaemia

Intraarticular injection has been reported to increase blood glucose levels for a few days in controlled diabetic patients with knee osteoarthritis (Habib 2011). In a systematic review of steroid injection effects (Choudhry 2016), all studies reported a rise in blood glucose levels following injection. In some cases, peak levels occurred several days following injection. Diabetic patients should therefore be advised to regularly monitor their blood glucose levels for up to a week after injection and should seek medical advice if safe thresholds are breached.

Acute coronary syndrome

Data from 41,276 patients indicated that those who had received a musculoskeletal corticosteroid injection (joint/ site not reported) were twice as likely to be hospitalised with an acute coronary syndrome within a week, compared to those who had not received an injection. odds ratio (OR) = 1.95 (1.56–2.43) (Thomas 2023).

Appendix 2. Recommendations for Clinical Practice and Research from Broader Evidence

Hip injections should not be offered to patients considering hip arthroplasty surgery within 3 months (and possibly within 12 months) without a discussion of the increased risk of peri/ postoperative joint infection risk.

A candid and informed discussion and risk assessment should form part of a shared decision-making process with patients considering intra-articular steroid injection as part of a package of physiotherapy rehabilitation care for managing their OA hip and knee pain.

Information leaflets given to patients before undergoing steroid injections for hip and/ or knee OA should clearly describe the potential risks that include:

- minor / transient risks such as flare-up of pain and swelling, bleeding, local skin changes, tissue damage including potential nerve, blood vessel, allergic reactions/ anaphylaxis, temporary immunosuppression, and a range of further systemic effects including uterine bleeding in women, facial flushing (particularly in women), and hyperglycaemia in people with diabetes.
- risk of infection and sepsis, which although rare can be catastrophic
- ICSI delivered within the 3 months prior to hip or knee arthroplasty surgery increases the risk of post-surgical infection. Risks diminishes with longer periods between ICSI and surgery. For OA hip, the risk may still be higher at 12 months than in those who have not had a CSI.
- possible longer-term (or delayed) structural deterioration that may or may not be related to the steroid injection. These longer-term complications include potential accelerated OA progression, rapid joint destruction and bone loss, subchondral insufficiency fracture, osteonecrosis and articular collapse and older patients may be at greater risk.

The current LCHT patient information leaflet potentially requires updating to reflect the evidence, for example it currently does not detail any post-surgery/arthroplasty infection risk.

A shared decision-making process should be framed in the context of likely short-term benefits and with consideration of alternative treatment options appropriate for the individual patient. It is also important to advise patients to immediately seek clinical attention should they experience worsening joint pain after steroid injection, or signs of potential infection or sepsis.

Further research in this area is recommended to elucidate the true risk associated with ICSI for OA hip and knee pain (Guermazi 2020). Large, prospective studies are needed, but it is acknowledged that given the relatively rare incidence of some of these adverse outcomes, any clinical trial would be challenging in design and a large number of patients would need to be included.

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Appendix 3: Ongoing Controversy surrounding ICSIs for OA hip/knee

The ongoing debate and controversy around the risks associated with intra-articular steroid injections are highlighted in recent publications and discussions:

- Jennings, J.W., 2022. The Safety and Potential Harm of Intraarticular Steroid Injections: The Debate Continues. *Radiology*, *304*(2), pp.370-371.
- Guermazi, A., Hunter, D.J. and Kloppenburg, M., 2023. Debate: Intra-articular steroid injections for osteoarthritis–harmful or helpful?. *Osteoarthritis Imaging*, *3*(3), p.100163.
- Orchard, J.W., 2020. Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis?. *Bmj*, *368*.
- Orchard, J.W., 2023. Pay attention to the evidence: In the longer term, intraarticular corticosteroid injections offer only harm for knee osteoarthritis. *Osteoarthritis and Cartilage*, *31*(2), pp.142-143.
- Kompel, A.J., Roemer, F.W., Murakami, A.M., Diaz, L.E., Crema, M.D. and Guermazi, A., 2019. Intra-articular corticosteroid injections in the hip and knee: perhaps not as safe as we thought?. *Radiology*, *293*(3), pp.656-663.
- McAlindon, T.E., Harkey, M.S., Ward, R.J., Hochberg, M.C. and Driban, J.B., 2020. Intra-articular corticosteroid injections in the hip and knee: perhaps not as dangerous as they want you to believe? *Radiology*, *295*(1), pp.249-250.
- https://www.youtube.com/watch?v=t0Ie6j1UO4Y&t=6s.
- https://www.jointaction.info/podcast/episode/86654c05/steroid-injections-for-osteoarthritis-harmful-or-helpful
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CAT image	Evidence quality	Checkbox
	Good quality evidence to support use….	☐
	Insufficient or poor quality evidence OR substantial harms suggest intervention used with caution after discussion with patient…	☑
	No good quality evidence, do not use until further research is conducted OR Good quality evidence to indicate that harms outweigh the benefits….	☐

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