National Institute for Health and Care Excellence

Final

Osteoarthritis in over 16s: diagnosis and management

[J] Evidence review for the clinical and cost-effectiveness of intra-articular injections for the management of osteoarthritis

NICE guideline NG226

Evidence reviews underpinning recommendations 1.4.9 and 1.4.10 and research recommendations in the NICE guideline

October 2022

Final

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1.1 Review question

What is the clinical and cost-effectiveness of intra-articular injections for the management of osteoarthritis?

1.1.1 Introduction

Intra-articular injections are sometimes used to relieve pain for people with osteoarthritis. These include injections with corticosteroids, hyaluronan and stem cells. Corticosteroid injections are undertaken to deliver this high dose anti-inflammatory agent within the joint to reduce inflammation of the joint lining (synovium), however, they may not work for everyone in the short term and in some people, repeated injections may be required to sustain symptom control. Hyaluronan injections have been developed to replicate the natural lubricant within the joint with reported benefits, however, its mechanism of action for osteoarthritis is contentious and it can be associated with increased pain in the short term. Stem cells are cells that are capable of developing into different types of tissue. These can be injected into an osteoarthritic joint and this type of therapy has been developed to stimulate regeneration of the tissues, such as cartilage, which consequently can improve symptoms and function and may reduce the need for future joint replacement.

Current practice for people with osteoarthritis is to be offered an intra-articular injection when analgesia is not adequately controlling pain or improving function, when surgery is not about to take place in the affected joint or when the patient has an immediate need for reduced pain or symptoms. Joint injections are delivered in both the generalist and specialist settings, depending on the context and the joint, joint injections may be delivered under imaging guidance or “blind”. It is not clear what benefit these joint injections deliver over time and the extent to which these balance potential harms. Stem cell therapy is the newest intra-articular treatment approach for osteoarthritis which is currently only used under experimental conditions within the NHS.

This review aims to evaluate the clinical and cost-effectiveness of intra-articular injections of corticosteroids, hyaluronic acid and stem cell therapy for the management of osteoarthritis.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Stratify by site of osteoarthritis: • Hip • Knee • Ankle • Foot • Toe • Shoulder • Elbow • Wrist • Hand

	• Thumb • Finger • Temporomandibular joint (TMJ) To note that where evidence for other rare forms of osteoarthritis is identified the committee will stratify into a group they are most similar to. Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies in people with meniscal injury without osteoarthritis • Studies with an unclear population (e,g, type of arthritis, proportion of participants with osteoarthritis) • Spinal osteoarthritis
Interventions	Stratify interventions by image guided versus non-image guided: • Intra-articular hyaluronic acid (of any formulation) • Intra-articular corticosteroids (of any type) • Intra-articular stem cell therapy
Comparisons	• Compared to each other • Placebo
Outcomes	Primary outcomes: • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Physical function [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Pain [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months Secondary outcomes: • Psychological distress [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Osteoarthritis flares [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Number of serious adverse events [dichotomous] at ≤3 months and >3 months
Study design	RCTs and systematic reviews of RCTs

For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

92 studies (101 papers) were included in the review;[9, 11, 12, 16, 19, 22, 26, 32, 45, 47-49, 54, 56, 59, 72, 73, 75, 81, 85, 90, 94, 102, 108-110, 122, 123, 126, 130, 151-153, 159, 162, 179, 183, 192, 195, 198, 199, 201, 225, 226, 237, 240, 242, 257, 259-262, 265, 268, 273, 276, 287, 291, 292, 301, 303, 310, 311, 315, 323, 329, 330, 336, 338, 369, 373, 374, 377, 381, 383, 391, 398, 407, 416, 417, 430, 438, 441, 445, 446, 452, 454, 455, 460, 462, 466, 467, 469, 470, 473, 475, 485, 494, 496, 503, 529] these are summarised in Tables 2-9 below. Evidence from these studies is summarised in the summary matrices (Tables 10-25) and in more detail in the clinical evidence summary tables below (Tables 26-45).

Evidence was available for the following strata and comparisons:

- Hip osteoarthritis[22, 54, 260, 262, 315, 383, 398, 452]
  - Intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided) [22, 383, 452]
  - Intra-articular hyaluronic acid (image guided) compared to placebo[22, 54, 315, 383, 398]
  - Intra-articular corticosteroids (image guided) compared to placebo[22, 260, 262, 383]
- Knee osteoarthritis[9, 11, 12, 16, 19, 32, 45, 49, 56, 59, 72, 73, 75, 85, 90, 102, 109, 122, 123, 126, 130, 151, 153, 162, 179, 183, 195, 198, 199, 201, 225, 226, 237, 240, 257, 259, 268, 273, 276, 287, 291, 292, 301, 303, 311, 336, 338, 369, 373, 374, 391, 407, 430, 438, 441, 445, 446, 460, 469, 470, 473, 475, 485, 494, 496, 503, 529]
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)[19, 45, 59, 151, 195, 199, 276, 438, 445, 446, 470, 473, 475, 485, 494]
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo[9, 11, 12, 16, 49, 56, 75, 90, 102, 122, 123, 126, 162, 179, 183, 198, 201, 225, 226, 237, 240, 242, 259, 287, 291, 336, 338, 369, 373, 374, 407, 430, 460, 469, 496]
  - Intra-articular corticosteroids (non-image guided) compared to placebo[72, 85, 153, 292, 303, 311, 391, 441, 529]
  - Intra-articular stem cell therapy (image guided) compared to placebo[257, 273]
  - Intra-articular stem cell therapy (non-image guided) compared to intra-articular hyaluronic acid (non-image guided)[73, 301, 503]
  - Intra-articular stem cell therapy (non-image guided) compared to intra-articular corticosteroids (non-image guided)[32]
  - Intra-articular stem cell therapy (non-image guided) compared to placebo[130, 242, 268]
- Ankle osteoarthritis[81, 110, 416]
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo[81, 110, 416]
- Toe osteoarthritis[330, 377]
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)[377]
  - Intra-articular hyaluronic acid (image guided) compared to placebo[330]
- Shoulder osteoarthritis[48, 261]
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo[48, 261]
- Thumb osteoarthritis[26, 152, 192, 310, 323, 455]
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)[26, 152, 192, 323, 455]
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo[192]
  - Intra-articular corticosteroids (non-image guided) compared to placebo[192, 310]
- Finger osteoarthritis[454]
  - Intra-articular corticosteroids (non-image guided) compared to placebo[454]
- Temporomandibular joint osteoarthritis[47, 159]

- Intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)[159]
- Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)[47]

There were no relevant clinical studies for the foot, wrist and hand osteoarthritis strata. Additionally, there were no relevant clinical studies comparing image guided and non-image guided injections.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

Five Cochrane reviews were identified in the review. Vasiliadis 2010[502] and Wasiak 2006[512] did not include the same population and comparisons as those agreed in the protocol. De 2012[107] did not include the same population as that agreed in the protocol. Witteveen 2015[515] and Jüni 2015[227] included comparisons that were not included in the protocol for this review. Where relevant comparisons were reported, references were checked.

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

1.1.5.1 Hip osteoarthritis

Table 2: Summary of studies included in the evidence review including people with hip osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Atchia 2011[22]	**Intra-articular hyaluronic acid (image guided)** (n=19) 3mL non-animal stabilised hyaluronic acid (Durolane, 60mg) given as 1 ultrasound guided injection. **Intra-articular corticosteroid (image guided)** (n=19) 3mL methylprednisolone acetate (depomedrone, 120mg) given as 1 ultrasound guided injection. **Placebo** (n=19) 3mL normal saline given as 1 ultrasound guided injection. **"Standard care"** (n=20) No restrictions regarding medication usage. Was not used as a comparator in this review. **Concomitant therapy:** There were no restrictions regarding medication use, but participants were requested to notify changes in medication during follow up.	**Hip osteoarthritis** Mean age (SD): 69 (8) years N = 77 Definition: People with primary hip osteoarthritis fulfilling the American College of Rheumatology criteria for hip osteoarthritis Severity: Moderate-to-severe Duration of symptoms (mean [SD]): 36 (32) months Presence of multimorbidities: Not stated/unclear	Osteoarthritis flares at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Brander 2019[54]	**Intra-articular hyaluronic acid (image guided)** (n=182) 6mL hyaluronic acid (Hylan G-F 20, 48mg) given as 1 injection under fluoroscopy or ultrasound guidance **Placebo** (n=175) 6mL phosphate buffered saline given as 1 injection under fluoroscopy or ultrasound guidance **Concomitant therapy:** Paracetamol was the only allowable medication for target hip osteoarthritis pain. Short-acting NSAIDs and paracetamol for pain or for reasons other than pain in the target hip joint were allowed but needed to be recorded and weren't allowed to be used within 2 days of each study visit.	**Hip osteoarthritis** Mean age (SD): 60.3 (9.4) years N = 357 Definition: Hip OA (radiographically confirmed Kellgren Lawrence grade 2 or 3) per American College of Rheumatology criteria (hip pain at baseline plus at least 2 of the following 3 features - erythrocyte sedimentation rate <20mm/h, radiographic femoral and acetabular osteophytes, or radiographic joint space narrowing) Severity: Majority grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	
Kullenberg 2004[260]	**Intra-articular corticosteroids (image guided)** (n=40) 2mL triamcinolone acetonide (80mg) given in 1 injection **Placebo** (n=40) 2mL mepivacaine 1% given in 1 injection **Concomitant therapy:** People were discharged after a short rest and advised to rest for the remainder of the day and start	**Hip osteoarthritis** Mean age (SD): 70.0 (7.6) years N = 80 Definition: People with hip pain recruited from a waiting list for hip replacement and with hip osteoarthritis that was radiologically graded (by the Ahlback criteria) as grade 2 or worse.	Pain at ≤3 months Physical function at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	normal activities from the next day	Severity: Ahlback grade 2 or worse Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Lambert 2007[262]	**Intra-articular corticosteroids (image guided)** (n=31) Up to 5mL of triamcinolone hexacetonide (40mg) and bupivacaine (10mg) given as 1 injection under fluoroscopic guidance **Placebo** (n=21) Up to 5mL of bupivacaine (10mg) and normal saline (2mL) given as 1 injection under fluoroscopic guidance **Concomitant therapy:** All people were advised to rest (preferably in the form of bed rest) for 3 days and to maintain minimal activity. After this period they were advised to refrain from active exercise and (if possible) work for 1 week.	**Hip osteoarthritis** Mean age (SD): 62.1 (11.8) years N = 52 Definition: Primary osteoarthritis of the hip according to the American College of Rheumatology criteria, including radiologic evidence of osteoarthritis Severity: Kellgren Lawrence grade 1-4 Duration of symptoms (mean [SD]): 51 (46.6) months Presence of multimorbidities: Not stated/unclear	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	
Migliore 2009[315]	**Intra-articular hyaluronic acid (image guided)** (n=22) 4mL hyaluronic acid (Hyalubrix, 60mg) given as 2 injections over 1 month by ultrasound guidance **Placebo** (n=20)	**Hip osteoarthritis** Mean age (SD): 70 (8.9) years N = 42 Definition: Hip osteoarthritis as defined by the American College of Rheumatology radiographic criteria	Pain at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	4mL 2% mepivacaine given as 2 injections over 1 month by ultrasound guidance **Concomitant therapy:** Not explicitly stated. However, NSAIDs were permitted as NSAID usage was an outcome.	Severity: Radiological grade 2-4 Duration of symptoms (mean [SD]): 4.71 (3.93) years Presence of multimorbidities: Not stated/unclear		
Qvistgaard 2006[383]	**Intra-articular hyaluronic acid (image guided)** (n=33) 2mL hyaluronic acid (Hyalgan) given with 1mL lidocaine given as 3 injections with 14 day intervals between each injection **Intra-articular corticosteroid (image guided)** (n=32) 1mL methylprednisolone (40mg Depo-medrol) given with 1mL lidocaine given as 3 injections with 14 day intervals between each injection **Placebo** (n=36) 2mL saline given with 1mL lidocaine given as 3 injections with 14 day intervals between each injection **Concomitant therapy:** People were asked to continue their usual analgesic consumption throughout the study. If the pain demanded change in therapy, the person was secondarily excluded.	**Hip osteoarthritis** Mean age (SD): 66 (12) years N = 101 Definition: Hip osteoarthritis as defined by the American College of Rheumatology criteria, with radiological changes of hip osteoarthritis Severity: Kellgren Lawrence grade 1-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Osteoarthritis flares at ≤3 months Serious adverse events at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Richette 2009[398]	**Intra-articular hyaluronic acid (image guided)** (n=42) 2.5mL hyaluronic acid (Adant) after arthrocentesis given in 1 injection under fluoroscopic guidance **Placebo** (n=43) 2.5mL saline after arthrocentesis given in 1 injection under fluoroscopic guidance **Concomitant therapy:** Paracetamol was allowed throughout the study. Use of NSAIDs or step 2 analgesics for the affected hip was only permitted if symptoms did not respond to optimal doses of paracetamol. Washout was not performed before any assessment.	**Hip osteoarthritis** Mean age (SD): 60.1 (11.5) years N = 85 Definition: People fulfilling the American College of Rheumatology criteria for the diagnosis of hip osteoarthritis Severity: Kellgren Lawrence grade 2-3 Duration of symptoms (mean [SD]): 4.4 (5.4) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Osteoarthritis flares at ≤3 months Serious adverse events at ≤3 months	
Spitzer 2010[452]	**Intra-articular hyaluronic acid (image guided)** (n=150) 2mL hyaluronic acid (Hylan G-F 20) given as two injections over 2 weeks under fluoroscopic guidance **Intra-articular corticosteroids (image guided)** (n=155) 2mL methylprednisolone (40mg) 1 injection under fluoroscopic guidance followed by a sham injection (deep tissue injection of lidocaine) 2 weeks later	**Hip osteoarthritis** Mean age (SD): 59 (11.5) years N = 305 Definition: Primarily unilateral, primary, symptomatic osteoarthritis of the hip radiographically confirmed Kellgren Lawrence grade 2 or Kellgren Lawrence grade 3 disease	Pain at >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional analgesia during injection. Paracetamol use of <4000mg/day was allowed for breakthrough pain or post injection pain. Any medications had to be discontinued 48 hours prior to each study visit. Other analgesics or NSAIDs, systemic corticosteroids, IA viscosupplementation or corticosteroid injections in any nontarget joint (other than the intervention in the trial), other investigational treatments and chronic narcotics were not allowed.	Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		

1.1.5.2 Knee osteoarthritis

Table 3: Summary of studies included in the evidence review including people with knee osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Altman 1998[11] Subsidiary paper: Punzi 2001[381]	**Intra-articular hyaluronic acid (non-image guided)** (n=164) 2mL (20mg) hyaluronic acid in a saline vehicle given as 5 injections over 5 weeks. **Placebo** (n=168) Saline (no hyaluronic acid) given as 5 injections over 5 weeks.	**Knee osteoarthritis** Mean age (SD): 63.6 (10.1) years N = 495 Definition: Clinically diagnosed osteoarthritis according to the American College of Rheumatology criteria with knee radiography	Pain at >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	A third intervention arm, that received oral naproxen (n=163) were included in the study. This group did not fulfil the criteria stated in the protocol so were not included in the analysis for this review. **Concomitant therapy:** Joint aspiration was conducted as required. 500mg acetaminophen tablets were permitted up to 4000mg/day for escape analgesia as needed for knee pain. People were instructed not to take products containing aspirin, NSAIDs, other non-narcotic or narcotic analgesics, or corticosteroids.	showing at least 1 osteophyte and a KL grade 2 or 3. Severity: Moderate Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Altman 2004[9]	**Intra-articular hyaluronic acid (non-image guided)** (n=172) 3mL non-animal hyaluronic acid (Durolane, 60mg hyaluronic acid in a saline vehicle) given as 1 injection. **Placebo** (n=174) 3mL buffered sodium chloride (0.9%, pH7) given as 1 injection. **Concomitant therapy:** Paracetamol (maximum daily dose, 4g) was permitted as rescue medication excepting during the 48-hour period prior to each study visit.	**Knee osteoarthritis** Mean age (range): 63.1 (18.4-61.1) years N = 346 Definition: OA of the knee as defined by the American College of Rheumatology criteria - clinical diagnosis (with potential imaging) Severity: Kellgren-Lawrence grade 2-4 Duration of symptoms (mean [range]): 5.75 (0-50.5) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Altman 2009[12]	**Intra-articular hyaluronic acid (non-image guided)** (n=293) 2mL 1% sodium hyaluronate (IA-BioHa, 20mg) given as 3 injections over 3 weeks **Placebo** (n=295) 2mL phosphate buffered saline given as 3 injections over 3 weeks **Concomitant therapy:** Aspirin to a maximum of 325mg a day was allowed for cardiovascular protection. Nonprescription neutraceuticals (e.g. glucosamine, chondroitin), topical analgesics, and nasal or inhaled corticosteroids were allowed if the dosage had been stable for at least 1 month and the identical regimen was to be continued throughout the study period. Nonpharmacologic treatments (physical therapy, acupuncture, osteopathic, and chiropractic manipulations) were allowed if treatment had been stable for at least 1 month and there was no plan to change frequency throughout the course of the study. The following had to be discontinued: NSAIDs, opioid narcotics, local corticosteroid knee injections, systemic corticosteroids, IA-HA in the past 6 months.	**Knee osteoarthritis** Mean age (SD): 61.64 (10.54) years N = 588 Definition: Osteoarthritis of the knee by the American College of Rheumatology criteria Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms: Not explicitly stated Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events at >3 months	FLEXX trial

Study	Intervention and comparison	Population	Outcomes	Comments
Arden 2014[16]	**Intra-articular hyaluronic acid (non-image guided)** (n=108) 3mL non-animal hyaluronic acid (Durolane, 60mg) given as 1 injection **Placebo** (n=110) 3mL phosphate buffered saline given as 1 injection **Concomitant therapy:** Rescue medication with paracetamol up to 4g per day was allowed throughout the study except during the 48 hour period preceding each study visit. NSAIDs, including topical agents for the knee, were not permitted.	**Knee osteoarthritis** Median age (range): 64.5 (29-84) years N = 218 Definition: Knee pain meeting the American College of Rheumatology criteria for the diagnosis of osteoarthritis provided that the osteoarthritis was confirmed in the study knee radiographically (Kellgren-Lawrence grades 2-3) and by a WOMAC pain score of 7-17 at their baseline visit Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms (median [range]): Hyaluronic acid group: 2.2 (0-21.2) years Placebo group: 3.1 (0-44.1) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	
Askari 2016[19]	**Intra-articular hyaluronic acid (non-image guided)** (n=71) 2mL hyaluronic acid (Hylan) given as 1 injection **Intra-articular corticosteroids (non-image guided)** (n=69) 40mg corticosteroid (type not specified)	**Knee osteoarthritis** Mean age (SD): 57.8 (6.1) years N = 140 Definition: Clinical and radiographic osteoarthritis - symptoms for at least 3 months, along with radiographic grade 2-3	Pain at ≤3 months Physical function at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information	(according to Kellgren and Lawrence grading scale). Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Bastos 2020[32]	**Intra-articular stem cell therapy (non-image guided)** (n=16) Intra-articular injection of MSCs was performed between 2 and 3 weeks after the bone marrow aspiration procedure. **Intra-articular corticosteroids (non-image guided)** (n=17) Intra-articular corticosteroid injections. **Concomitant therapy:** The use of dipyrone 1 g every 6 h (analgesic non-anti-inflammatory) was allowed in case of severe pain.	**Knee osteoarthritis** Mean age (SD): 57.3 (10.7) years N = 47 Definition: knee radiography (standing anterior–posterior and lateral views), knee magnetic resonance imaging (MRI) Severity: Mix of people with Kellgren–Lawrence grade 1–4 severity. Duration of symptoms: Not reported/unclear Presence of multimorbidities: People with multimorbidities excluded	Quality of life at >3 months Pain at >3 months Physical function at >3 months	
Bisicchia 2016[45]	**Intra-articular hyaluronic acid (non-image guided)** (n=75) Hyaluronic acid (HYADD 4) given as 2 injections over 2 weeks **Intra-articular corticosteroids (non-image guided)** (n=75)	**Knee osteoarthritis** Mean age (SD): 70.1 (10.4) years N = 150 Definition: People presenting for unilateral primary knee osteoarthritis (based on	Quality of life at ≤3 months and >3 months Pain at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	6-methylprednisolone acetate (40mg) given as 2 injections over 2 weeks **Concomitant therapy:** People were encouraged to refrain from strenuous activity for a day following the intra-articular injections. No formal physical therapy was prescribed. Furthermore, NSAIDs and paracetamol consumption were the only pain medications allowed.	American College of Rheumatology criteria) included if they had a Kellgren-Lawrence grade 2-3 knee osteoarthritis and a VAS for pain ≥3 Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Blanco 2008[49]	**Intra-articular hyaluronic acid (non-image guided)** (n=26) 2 cycles of 5 injections of 2.5mL hyaluronic acid (25mg) in saline given over 5 weeks with 24 weeks between each cycle. **Placebo** (n=26) Same as for hyaluronic acid. However, only saline was given. **Concomitant therapy:** Rescue analgesia with paracetamol 4000mg/day or diclofenac 150mg/day was permitted in all.	**Knee osteoarthritis** Mean age (SD): 67.9 (8.6) years N = 52 Definition: Symptomatic osteoarthritis evidenced by pain according to the American College of Rheumatology criteria without joint inflammation but with grade 4 Kellgren-Lawrence radiographic changes Severity: Kellgren Lawrence grade 4 Duration of symptoms (mean [SD]): 10.5 (9.1) years Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events at >3 months	
Brandt 2001[56]	**Intra-articular hyaluronic acid (non-image guided)** (n=114)	**Knee osteoarthritis** Mean age (SD): 65.99 (8.459) years	Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	2mL sodium hyaluronate (Orthovisc, 15mg) given as 3 injections over 2 weeks **Placebo** (n=112) 2mL saline given as 3 injections over 2 weeks **Concomitant therapy:** Paracetamol (to a maximum of 4g daily) was allowed for rescue analgesia. No other pain medication was allowed.	N = 226 Definition: Idiopathic osteoarthritis according to the American College of Rheumatology cirteria, with Kellgren-Lawrence Grade II or III radiographic evidence of knee osteoarthritis Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Caborn 2004[59]	**Intra-articular hyaluronic acid (non-image guided)** (n=113) 2mL hyaluronic acid (Hylan G-F 20, Synvisc) given as three injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=105) 2mL triamcinolone hexacetonide (Aristospan, 40mg) given as 1 injection **Concomitant therapy:** The following oral pain medications were allowed except for within 24 hours of a study visit: paracetamol (up to 4g per day), analgesics or short-acting NSAIDs with a washout period of at least 24 hours for pain other than in the target	**Knee osteoarthritis** Mean age (SD): 63.07 (11.88) years N = 218 Definition: criteria of the American College of Rheumatology Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	knee, but not for more than 3 consecutive days or 1- days per month, and low dose aspirin (≤325mg/day) for antithrombotic prophylaxis. NSAIDs with once-daily dose regimens were prohibited.			
Chao 2010[72]	**Intra-articular corticosteroids (non-image guided)** (n=40) 1mL triamcinolone acetonide (40mg) given as 1 injection **Placebo** (n=39) 1mL of 0.9% sodium chloride given as 1 injection **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 64.3 (11.9) years N = 79 Definition: Radiographically proven osteoarthritis of the knee with knee pain who met the American College of Rheumatology criteria Severity: Not stated Duration of symptoms (mean [range]): 14 (0.3-51) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months	
Chen 2021[73]	**Intra-articular stem cell therapy** (n=49) ELIXCYTE stem cells injected into the knee, ranging from 16 million cells to 64 million cells. One injection, followed up for 96 weeks in total. **Intra-articular hyaluronic acid** (n=8) Active control with Hya Joint Plus Synovial fluid supplement 3mL. One injection, followed up for 96 weeks in total.	**Knee osteoarthritis** Mean age (SD): 67.6 (6.60) years N = 57 Definition: Knee osteoarthritis as determined by the American College of Rheumatology (with radiographic evidence) Severity: Kellgren Lawrence grade II-III (median grade II).	Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: People were allowed to use paracetamol and NSAIDs during the study.	Duration of symptoms (mean [SD]): 2.96 (4.164) years Presence of multimorbidities: Not stated/unclear		
Chevalier 2010[75]	**Intra-articular hyaluronic acid (non-image guided)** (n=124) 6mL hyaluronic acid (Hylang G-F 20) with arthrocentesis given as 1 injection **Placebo** (n=129) 6mL phosphate buffered saline with arthrocentesis given as 1 injection **Concomitant therapy:** Paracetamol (≤4000mg/day) was permitted as rescue medication for the target knee. Other permitted medications were analgesics/non-steroidal anti-inflammatory drugs with a half-life of 5 hours or less for indications other than osteoarthritis pain (not to be taken for more than five consecutive days or >10 days/month) and aspirin (≤325mg/day). However, for 48 hours before a study visit, people were required to abstain from any paracetamol, pain or osteoarthritis medications.	**Knee osteoarthritis** Mean age (SD): 63.0 (9.4) years N = 253 Definition: People meeting the American College of Rheumatology criteria for osteoarthritis (knee pain for most days of the previous month and osteophyte(s) at the joint margin visible on x-ray) Severity: Majority Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 73.6 (70.7) months Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events at >3 months	
Conaghan 2018[85] Subsidiary paper: Langworthy 2019[265]	**Intra-articular corticosteroids (non-image guided)** (n=161)	**Knee osteoarthritis** Mean age (SD): 62.07 (9.516) years	Quality of life at ≤3 months and >3 months	The two corticosteroid groups were combined to produce the outcome values.

Study	Intervention and comparison	Population	Outcomes	Comments
	5mL FX006 (a microsphere formulate of triamcinolone acetonide, 32mg) given as 1 injection **Intra-articular corticosteroids (non-image guided)** (n=162) 1mL triamcinolone acetonide immediate release (40mg) given as 1 injection **Placebo** (n=163) 5mL saline given as 1 injection **Concomitant therapy:** People were allowed to use paracetamol (≤3g/day by 500mg tablets provided) for rescue treatment. Otherwise analgesic medications were withdrawn.	N = 486 Definition: Radiographic knee osteoarthritis and presence of knee pain Severity: Kellgren-Lawrence grade 2-3. Duration of symptoms (mean [SD]): 7.2 (6.37) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	
Corrado 1995[90]	**Intra-articular hyaluronic acid (non-image guided)** (n=21) Sodium hyaluronate (20mg in 2mL phosphate buffer) given after arthrocentesis as 5 injections over 5 weeks **Placebo** (n=19) 2mL water containing 17mg sodium chloride, 0.1mg of monobasic sodium phosphate, 1.2mg of bibasic sodium phosphate given after arthrocentesis as 5 injections over 5 weeks	**Knee osteoarthritis** Mean age (SD): 61.3 (11.14) years N = 40 Definition: Clinically and radiologically ascertained mono- or bilateral osteoarthritis of the knee (Altman criteria) of at least 6 months duration Severity: Not stated Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information			
Day 2004[102]	**Intra-articular hyaluronic acid (non-image guided)** (n=116) 2.5mL sodium hyaluronate (ARTZ, 25mg) given as 1 injection **Placebo** (n=124) 2.5mL phosphate buffered saline given as 1 injection **Concomitant therapy:** People were provided with instruction on a set of physiotherapy exercises to be performed throughout the study and with paracetamol for breakthrough pain.	**Knee osteoarthritis** Mean age (range): 62 (33-79) N = 240 Definition: People with a diagnosis of mild to moderate, idiopathic, painful femorotibial OA of the knee as defined by: knee pain while standing, walking, and/or in motion, of at least 3 month duration; and evidence of femorotibial osteophytes and/or joint space narrowing based on standing (extended knee) anteroposterior and lateral knee radiographs taken during the previous 6 months. Severity: Mild-to-moderate Duration of symptoms (median): 2-5 years Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months	
DeCaria 2012[109] Subsidiary paper: Decaria 2011[108]	**Intra-articular hyaluronic acid (non-image guided)** (n=15) 2mL hyaluronic acid (40mg) given as 3 injections over 3 weeks **Placebo** (n=15) 1.2mL of 0.001mg/mL hyaluronic acid given as 3 injections over 3 weeks	**Knee osteoarthritis** Mean age (SD): 72.4 (6.2) years N = 30 Definition: Radiographically diagnosed mild-moderate knee OA Severity: Mild-to-moderate	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: All participants were given rescue medication (500mg paracetamol, 4g/day maximum) that could be used up to 8 hours before their next study visit and information on a home exercise program specifically designed for people with knee osteoarthritis (consisted of joint unloading, as well as knee range of motion and isotonic strength training activities).	Duration of symptoms: Not stated Presence of multimorbidities: High comorbidity score (Number of co-morbidities hyaluronic acid: 2.07 (1.98). Number of co-morbidities placebo: 1.94 (1.03).).		
Diracoglu 2009 [122]	**Intra-articular hyaluronic acid (non-image guided)** (n=42) Hyaluronic acid (Hylan G-F 20, Synvisc) given as 3 injections to both knees over 3 weeks **Placebo** (n=21) Sterile physiological saline (0.9% sodium chloride) given as 3 injections to both knees over 3 weeks **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 58.3 (9.2) years N = 63 Definition: Bilateral knee osteoarthritis according to the criteria of the American College of Rheumatology and at stage 2 and 3 according to the Kellgren Lawrence scale Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	
Dixon 1988[123]	**Intra-articular hyaluronic acid (non-image guided)** (n=30) Sodium hyaluronate (20mg) given as 11 injections over 23 weeks	**Knee osteoarthritis** Mean age (range): 68.5 (43-85) years N = 63	Serious adverse events as >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=33) Sodium hyaluronate (0.2mg) given as 11 injections over 23 weeks **Concomitant therapy:** Treatment with corticosteroids, non-steroidal anti-inflammatory agents and strong analgesics were not permitted during the trial period but there were no other restrictions regarding concomitant therapy. People were permitted to take paracetamol tablets, up to a total dose of 1g 3 times daily, for the treatment of their knee pain.	Definition: Symptomatic osteoarthritis in one or both knees Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Dougados 1993[126]	**Intra-articular hyaluronic acid (non-image guided)** (n=55) 2mL hyaluronic acid (Hyalectin, 20mg) given as 3 injections over 3 weeks **Placebo** (n=55) 2mL saline given as 3 injections over 3 weeks **Concomitant therapy:** They were allowed to use 'basic' therapy for osteoarthritis as long as the dose had been stable during the previous 3 months - including physiotherapy, NSAIDs and/or other analgesics.	**Knee osteoarthritis** Mean age (SD): 68.0 (10.2) years N = 110 Definition: American college of Rheumatology criteria for osteoarthritis of the knee Severity: Not stated Duration of symptoms: 68.5 (61.8) months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Serious adverse events at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Emadedin 2018[130]	**Intra-articular stem cell therapy (non-image guided)** (n=24) $40x10^6$ autologous bone-marrow derived mesenchymal stem cells given in 5mL saline supplemented with 2% human serum albumin. Given as 1 injection. **Placebo** (n=25) 5mL normal saline supplemented with 2% human serum albumin given as 1 injection **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 53.4 (7.4) years N = 49 Definition: People fulfilling the clinical and radiological criteria for knee osteoarthritis according to the American College of Rheumatology Severity: Kellgren-Lawrence grade 2-4. Duration of symptoms (mean [SD]): 13.1 (7.9) months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	
Frizziero 2002[151]	**Intra-articular hyaluronic acid (non-image guided)** (n=52) 2mL hyaluronic acid (Hyalgan, 20mg) given as 5 injections over 5 weeks. **Intra-articular corticosteroids (non-image guided)** (n=47) Methylprednisolone given as 3 injections over 3 weeks **Concomitant therapy:** Not allowed other intraarticular injections or concomitant treatment with NSAIDs	**Knee osteoarthritis** Mean age (SD): 49.5 (14.5) years N = 99 Definition: People with primary OA (n=50) or secondary OA due to trauma (n=49) with Kellgren-Lawrence grades 1-3 and fulfilling the clinical and radiological criteria of the American College of Rheumatology. Diagnosis confirmed by arthroscopy. Severity: Majority moderate Duration of symptoms (mean [SD]): 25.1 (24.1) months	Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multimorbidities: Not stated/unclear		
Gaffney 1995[153]	**Intra-articular corticosteroids (non-image guided)** (n=42) 1mL triamcinolone hexacetonide (20mg) given as 1 injection **Placebo** (n=42) 1mL 0.9% sodium chloride given as 1 injection **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 67.0 (9.2) years N = 84 Definition: People with clinical and radiographic evidence of knee OA who presented to a general rheumatology clinic with knee pain and functional impairment (modified Health Assessment Questionnaire >0) during a six month period. Those with bilateral knee OA had the most painful knee studied. Severity: Not stated Duration of symptoms (mean [SD]): 6.9 (6.5) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	
Gomoll 2021[162]	**Intra-articular hyaluronic acid (non-image guided)** (n=64) 4 ml HA intra articular injection. Duration 12 months. **Placebo** (n=68) 4 ml saline intra articular injection. **Concomitant therapy:** Not stated/unclear	**Knee osteoarthritis** Mean age (SD): ASA group 55.9 (12.3), HA 55.4 (11), saline 54.9 (9.8) years N = 200 Definition: Radiographs to confirm Kellgren-Lawrence (KL) grade of 2 or 3 Severity: Kellgren-Lawrence (KL) grade of 2 or 3. Duration: not reported	Quality of life at >3 months Pain at >3 months Physical function at >3 months Serious adverse events a >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multimorbidities: People with multimorbidities excluded		
Hangody 2018[179]	**Intra-articular hyaluronic acid (non-image guided)** (n=150) 4mL hyaluronic acid (Monovisc, 88mg) given as 1 injection **Placebo** (n=69) 4mL 0.9% sodium chloride given as 1 injection A third intervention arm (n=149) was given an injection of a combination of hyaluronic acid and corticosteroid. This was not included in the analysis. **Concomitant therapy:** People were not allowed to use medication that would interfere with the trial (what constituted this was not stated).	**Knee osteoarthritis** Mean age (SD): 58.3 (8.6) years N = 368 Definition: Radiologically confirmed osteoarthritis of the knee Severity: Kellgren-Lawrence grade 2 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Serious adverse events at >3 months	
Henderson 1994[183]	**Intra-articular hyaluronic acid (non-image guided)** (n=45) Hyaluronic acid (Hyalgan) in phosphate buffered saline given as 5 injections over 5 weeks **Placebo** (n=46) Phosphate buffered saline only given as 5 injections over 5 weeks **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 66.5 (4.9) years N = 91 Definition: Clinical history and radiological evidence of osteoarthritis of the knee Severity: Median radiological grade 3 Duration of symptoms: Not stated	Pain at ≤3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multimorbidities: Not stated/unclear		
Housman 2014[195]	**Intra-articular hyaluronic acid (non-image guided)** (n=259) 4mL hyaluronic acid (Hylastan) given as 1 or 2 injections. If only having 1 injection had arthrocentesis only for the second injection (these groups were reported separately and combined). Completed over 2 weeks. **Intra-articular corticosteroids (non-image guided)** (n=132) 1mL methylprednisolone acetate (40mg) given as 1 injection, followed up by a second session of arthrocentesis. Completed over 2 weeks. **Concomitant therapy:** Paracetamol 500mg was provided as rescue medication (with 1-2 to be taken every 4-6 hours as needed, not exceeding 8 tablets in 24 hours) except within 48 hour prior to a study visit	**Knee osteoarthritis** Mean age (SD): 60.9 (9.7) years N = 391 Definition: Fulfilling the American College of Rheumatology criteria for osteoarthritis with Kellgren-Lawrence Grade 1 to 3 disease. Severity: Majority Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 35.8 (40.9) months Presence of multimorbidities: Not stated/unclear	Pain at >3 months Serious adverse events at >3 months	
Huang 2011[198]	**Intra-articular hyaluronic acid (non-image guided)** (n=100) 2mL sodium hyaluronate (Hyalgan, 20mg) given as 5 injections over 5 weeks **Placebo** (n=100)	**Knee osteoarthritis** Mean age (SD): 65.0 (8.3) years N = 200 Definition: Diagnosis of osteoarthritis of the knee according to the American	Pain at ≤3 months and >3 months Physical function at >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	2mL saline given as 5 injections over 5 weeks **Concomitant therapy:** Paracetamol could be taken for further pain relief, but not exceeding 3g per day. People were not permitted to take paracetamol on the day before the study visit. Oral and parenteral corticosteroids, IA corticosteroid injections, NSAIDs or analgesics other than paracetamol, topical analgesic preparations, rehabilitation, physical therapy and acupuncture were not permitted.	College of Rheumatology criteria. Eligible patients also had radiographic evidence of osteoarthritis with Kellgren-Lawrence scores of II to III on X-ray with predominance in the tibio-femoral compartment Severity: Mild-to-moderate Duration of symptoms (mean [SD]): 427.0 (1022.5) days Presence of multimorbidities: Not stated/unclear		
Huang 2019[199]	**Intra-articular hyaluronic acid (non-image guided)** (n=40) 2mL hyaluronic acid given as 3 injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=40) 1mL corticosteroid (type and dose not specified) given as 1 injection **Other (intra-articular plasma-rich platelets)** (n=40) Plasma-rich platelets. Not included in this review. **Concomitant therapy:** After injection, people were allowed weight bearing and local ice	**Knee osteoarthritis** Mean age (SD): 54.5 (1.3) years N = 120 Definition: Symptomatic knee osteoarthritis with Kellgren-Lawrence grade 1-2 changes on radiography Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	application was recommended for 20 minutes every 2-4 hours for 24 hours. Vigorous activities of the knee were not recommended for 48 hours			
Huskisson 1999[201]	**Intra-articular hyaluronic acid (non-image guided)** (n=50) 2mL hyaluronic acid (Hyalgan, 20mg) given as 5 injections over 5 weeks **Placebo** (n=50) Buffered aqueous solution given as 5 injections over 5 weeks **Concomitant therapy:** All people were permitted to continue with existing analgesic or anti-inflammatory therapy.	**Knee osteoarthritis** Mean age (SD): 65.3 (9.1) years N = 100 Definition: People with a diagnosis of osteoarthritis of one or both knees according to the Australian Rheumatology Association criteria. All people had radiographic changes consistent with Kellgren and Lawrence grade II or III on an X-ray taken within the 6 months prior to the study. Severity: Not stated Duration of symptoms: Between 7-24 months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Osteoarthritis flares at >3 months Serious adverse events at >3 months	
Jorgensen 2010[225]	**Intra-articular hyaluronic acid (non-image guided)** (n=167) 2mL hyaluronic acid (Hyalgan, 20mg) given as 5 injections over 5 weeks **Placebo** (n=170) 2mL saline given as 5 injections over 5 weeks	**Knee osteoarthritis** Mean age (SD): 62.0 (11.3) years N = 337 Definition: Fulfilling the clinical and laboratory American College of Rheumatology criteria for primary osteoarthritis of the knee.	Pain at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Synovial fluid was aspirated before injection. Paracetamol was used as escape medication (maximum of 4g daily) during the 2 week washout period and throughout the entire study, but not on the days of examination.	Includes radiographic measures. Severity: Not stated Duration of symptoms (mean [SD]): 6.4 (7.5) years Presence of multimorbidities: Not stated/unclear		
Jubb 2003[226]	**Intra-articular hyaluronic acid (non-image guided)** (n=208) 2mL hyaluronic acid (Hyalgan, 20mg) given as 3 injections over 3 weeks repeated twice at 4 monthly intervals **Placebo** (n=200) 2mL saline given as 3 injections over 3 weeks repeated twice at 4 monthly intervals **Concomitant therapy:** Free concurrent use of analgesics and NSAIDs, except indomethacin, was allowed. Although in patients taking these treatments the regimens were required to be stable for at least one month before study entry.	**Knee osteoarthritis** Mean age (SD): 64.2 (9.3) years N = 408 Definition: Primary osteoarthritis of the Knee as defined by the American College of Rheumatology criteria and radiographic involvement of the medial tibio-femoral compartment associated with grade II or III severity (Kellgren-Lawrence scoring system). Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 8.19 (7.3) years Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Karlsson 2002[237]	**Intra-articular hyaluronic acid (non-image guided)** (n=180) 2.5mL 1% hyaluronan (Artzal) or 2mL 0.8% hyaluronan (Synvisc) given as 3 injections over 3 weeks. Is a combined group of	**Knee osteoarthritis** Mean age (SD): 71.4 (6.8) years N = 246 Definition: Dominant pain in one knee due to	Pain at ≤3 months and >3 months Serious adverse events at >3 months	The hyaluronic acid intervention was a combination of two groups in the paper receiving two different types of hyaluronic acid.

Study	Intervention and comparison	Population	Outcomes	Comments
	two different types of hyaluronic acid. **Placebo** (n=66) 3m: phosphate buffered saline given as 3 injections over 3 weeks. **Concomitant therapy:** Analgesic and antiinflammatory medications were discontinued prior to the start of treatment with the test drug (washout period of 2 weeks). During the washout period people were allowed to use paracetamol (up to 4g/day) as rescue medication. This was allowed during the trial but had to be discontinued at least 12 hours prior to the time of clinical assessment. Additional analgesics that were considered necessary were allowed to be given at the discretion of the investigator.	osteoarthritis, which was radiologically verified of grade I or II according to Ahlbäck criteria (either between 50%-99% loss of joint space or complete loss of joint space) estimated by an anteroposterior weight-bearing radiograph with a knee flexion angle of 10-15 degrees. Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Ke 2021[240]	**Intra-articular hyaluronic acid (non-image guided)** (n=218) Hylan G-F 20 (6mL injection, 48mg hylan polymer) injected into the knee joint. . Duration: one injection. **Placebo** (n=220) One placebo injection into the knee (6mL phosphate buffer saline, pH 7.2). Duration One injection	**Knee osteoarthritis** Mean age (SD): 61.6 (7.9) years N = 440 Definition: Grade I to III Kellgren Lawrence osteoarthritis of the knee, confirmed by standard X-ray up to three months before screening; people meeting the American College of	Pain at >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: On an as-needed basis in a tiered manner, the following therapies were allowed as rescue medication in case of unbearable pain (eg, worsening of osteoarthritis symptoms in the target knee) during the study period: 1) Paracetamol (500mg, up to 3000mg/day), paracetamol (325mg)/oxycodone (5mg, up to 1 tablet 4 times daily); paracetamol (325mg)/tramadol (37.5mg, up to 1 tablet 6 times daily). However, rescue medication was not to be taken within 48 hours prior to any study visit.	Rheumatology criteria for knee osteoarthritis Severity: Kellgren Lawrence grades I-III, median grade II. Duration of symptoms: Not stated/unclear. Presence of multimorbidities: Not stated / Unclear		
Khalifeh soltani 2019[242]	**Intra-articular stem cell therapy (non-image guided)** (n=10) 10mL allogenic placental mesenchymal stem cells (0.5-0.6x10^8 cells) given in 1 injection **Placebo** (n=10) 10mL normal saline given in 1 injection **Concomitant therapy:** All people were allowed to use paracetamol for breakthrough pain.	**Knee osteoarthritis** Mean age: 56.7 years N = 20 Definition: People with knee OA (grades 2-4 based on the Kellgren Lawrence criteria in knee standing anteroposterior and lateral radiographs) Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Kuah 2018[257]	**Intra-articular stem cell therapy (image guided)** (n=16)	**Knee osteoarthritis** Mean age (SD): 53.3 (7.6) years	Pain at >3 months Serious adverse events at >3 months	The two stem cell therapy groups (different doses of stem cells) were

Study	Intervention and comparison	Population	Outcomes	Comments
	Expanded allogenic mesenchymal stem cells from human adipose tissue (Progenza) 3.9 million and 6.7 million cells (combined groups) given as 1 injection. **Placebo** (n=4) 2mL cell culture medium and cryopreservative given as 1 injection. **Concomitant therapy:** No additional information	N = 20 Definition: Kellgren Lawrence grade 1-3 knee osteoarthritis with moderate-severe pain in the study knee Severity: Kellgren Lawrence grades 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		combined to produce the outcome results
Kul-panza 2010[259]	**Intra-articular hyaluronic acid (non-image guided)** (n=25) 2mL 1.5% hyaluronic acid (Orthovisc) given in 3 injections over 1 week **Placebo** (n=23) 2mL 0.9% saline solution given as 3 injections over 1 week **Concomitant therapy:** All people received instruction on quadriceps isometric exercises and range of motion exercises and were advised to practice them regularly at home. People were told not to use any drug for knee pain except paracetamol if required (500mg up to four times a day).	**Knee osteoarthritis** Mean age (SD): 61.1 (8.5) years N = 48 Definition: Knee pain and a diagnosis of osteoarthritis. Have radiographic grades stated in the baseline characteristics. Severity: Mean radiological grade = 2 (range 1-4) Duration of symptoms (mean [SD]): 7.2 (7.1) years Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events at >3 months	
Lee 2020[268]	**Intra-articular stem cell therapy (non-image guided)** (n=67)	**Knee osteoarthritis** Mean age (range): 56.7 (25-71) years	Pain at ≤3 months and >3 months	In Forest plots, this study is referred to as Lee 2019A

Study	Intervention and comparison	Population	Outcomes	Comments
	2mL of a 3:1 mixture of nontransduced allogenic human chondrocytes and transduced allogenic human chondrocytes expressing TGF-β given as 1 injection **Placebo** (n=35) 2mL of normal saline (0.9%) given as 1 injection **Concomitant therapy:** No additional information	N = 102 Definition: Kellgren-Lawrence grade 3 osteoarthritis of the knee Severity: Kellgren-Lawrence grade 3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Lee 2019[273]	**Intra-articular stem cell therapy (image guided)** (n=12) 3mL adipose-derived mesenchymal stem cells ($1x10^8$ cells) given in 1 injection **Placebo** (n=12) 3mL of saline given in 1 injection **Concomitant therapy:** The rescue analgesic was paracetamol at 4000mg or less per day. Other analgesics were not permitted, and any medications were recorded.	**Knee osteoarthritis** Mean age (SD): 62.7 (5.5) years N = 24 Definition: Osteoarthritis of the knee joint (Kellgren-Lawrence grade 2-4) Severity: Majority Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	In Forest plots, this study is referred to as Lee 2019B
Leighton 2014[276]	**Intra-articular hyaluronic acid (non-image guided)** (n=221) 3mL non-animal derived hyaluronic acid (Durolane, 60mg) given as 1 injection **Intra-articular corticosteroids (non-image guided)** (n=221)	**Knee osteoarthritis** Mean age (SD): 61.7 (9.8) years N = 442 Definition: Unilateral knee pain meeting the American College of Rheumatology criteria for the diagnosis of	Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	1mL methylprednisolone acetate (40mg) given as 1 injection **Concomitant therapy:** Synovial fluid was aspirated as needed and an IA injection of lidocaine was performed. Rescue medication with paracetamol was allowed up to 3g per day.	OA with radiographically verified OA of the study knee Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 4.8 (5.9) years Presence of multimorbidities: Not stated/unclear		
Lohmander 1996[287]	**Intra-articular hyaluronic acid (non-image guided)** (n=120) 2.5mL hyaluronan (25mg) in 1% phosphate buffered saline given as 1 injection **Placebo** (n=120) 2.5mL 1% phosphate buffered saline given as 1 injection **Concomitant therapy:** Concurrent and escape medication in the form of simple analgesics (for example, paracetamol) in addition to NSAIDs, was allowed during the trial	**Knee osteoarthritis** Mean age (SD): 58.3 (8.4) years N = 240 Definition: A clinical history of symptomatic, radiologically verified unilateral osteoarthritis of the knee (50-100% obliteration of the medial tibiofemoral joint space without bony erosion on anteroposterior standing films at 10-15 degrees flexion, taken within 6 months of the start of the study). Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Lundsgaard 2008[291]	**Intra-articular hyaluronic acid (non-image guided)** (n=84) 2mL sodium hyaluronate (Hyalgan 20.6mg) given as 4 injections over 4 weeks	**Knee osteoarthritis** Mean age (SD): 69.4 (6.8) years N = 251	Quality of life at >3 months Pain at >3 months Physical function at >3 months Osteoarthritis flares at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=84) 2mL physiological saline given as 4 injections over 4 weeks This study had a third intervention arm (n=83) where people received 20mL of saline per injection. This was not included in the analysis. **Concomitant therapy:** All people were permitted analgesics of the acetaminophen, aspirin, NSAID (inclusive COX-2 selective inhibitors), codeine and tramadol.	Definition: Daily knee pain with radiographic evidence of mild or severe change Severity: Majority Kellgren Lawrence grade 3-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Lyons 2005[292]	**Intra-articular corticosteroids (non-image guided)** (n=10) 2mL methylpednisolone (60mg) with 8mL 1% lignocaine given as 1 injection **Placebo** (n=10) 10mL 1% lignocaine given as 1 injection **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age: 59.7 years N = 20 Definition: A clinical diagnosis of osteoarthritis using the criteria of: in the absence of an alternative rheumatological diagnosis, three of the follow six being present: age >50 years; morning stiffness of less than 30 minutes duration; crepitus; bony tenderness; bony enlargement; no palpable warmth. Non-radiological. Severity: Not stated Duration of symptoms: At least 6 weeks	Pain at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multimorbidities: Not stated/unclear		
Matas 2019[301]	**Intra-articular stem cell therapy (non-image guided)** (n=20) A combination of two groups. One group received umbilical cord mesenchymal stem cells ($20x10^6$) given in two injections over 6 months. The second received one injection of mesenchymal stem cells and one of placebo (3mL of saline with 5% AB plasma) over 6 months. **Intra-articular hyaluronic acid (non-image guided)** (n=9) 3mL hyaluronic acid (Durolane) given as 2 injections over 6 months. **Concomitant therapy:** Paracetamol (1g every 8 hours) was allowed as needed in case of pain.	**Knee osteoarthritis** Mean age (SD): 55.9 (5.4) years N = 29 Definition: Symptomatic knee osteoarthritis (defined by daily pain at the affected joint for at least 3 months before inclusion) with grade 1-3 Kellgren Lawrence radiographic changes in the targeted knee, without meniscal rupture Severity: Majority Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events at >3 months	
McAlindon 2017[303]	**Intra-articular corticosteroids (non-image guided)** (n=70) 1mL triamcinolone (40mg) given as 8 injections over 2 years (every 12 weeks). **Placebo** (n=70) 1mL 0.9% sodium chloride given as 8 injections over 2 years (every 12 weeks).	**Knee osteoarthritis** Mean age (SD): 58.2 (8.0) years N = 140 Definition: Knee osteoarthritis defined by the American College of Rheumatology through standardised questions and tibiofemoral osteoarthritis evident on	Pain at >3 months Physical function at >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Synovial fluid was aspirated prior to injection. Participants were asked to discontinue concomitant analgesics 2 days before each assessment to avoid masking symptoms of pain. Participants were advised to take paracetamol only if needed.	posteroanterior weight0bearing semi-flexed radiographs. Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: People with multimorbidities excluded		
Mendes 2019[311]	**Intra-articular corticosteroids (non-image guided)** (n=35) 2mL triamcinolone acetonide (40mg) given as 1 injection **Placebo** (n=35) 2mL sterile saline (0.9%) given as 1 injection This study had a third intervention arm (n=35) where people received intraarticular Botulinum toxin type A. This was not included in the analysis. **Concomitant therapy:** In all groups, people were advised to rest for 48 hours and to use 750mg of paracetamol every 8 hours as needed.	**Knee osteoarthritis** Mean age (SD): 64.2 (6.9) years N = 105 Definition: Primary knee osteoarthritis as defined by the American College of Rheumatology. Mild to moderate OA according to the Kellgren-Lawrence classification (grades II or III). Severity: Mild-to-moderate Duration of symptoms: 6.3 (7.1) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	
Navarro-sarabia 2011[336]	**Intra-articular hyaluronic acid (non-image guided)** (n=153) 2.5mL 1% sodium hyaluronate. 4 treatment cycles of 5 injections over 5 weeks (followed by two 6 month follow	**Knee osteoarthritis** Mean age (SD): 63.5 (8.6) years N = 306	Serious adverse events at >3 months	AMELIA trial

Study	Intervention and comparison	Population	Outcomes	Comments
	up periods, then two 1 year follow up periods). **Placebo** (n=153) 2.5mL saline injections (same method as intra-articular hyaluronic acid). **Concomitant therapy:** Acetylsalicylic acid (maximum 300mg/day) for vascular protection, paracetamol up to 4g/day as rescue medication as well as short cycles of NSAID were permitted (however for 1 day to 1 week prior to the study involvement respectively, the medication had to be stopped). During the whole study period intraarticular corticosteroid was not permitted in the target knee. Only two injections were allowed in the contralateral knee, and no more than two injections per year in any other joint than the knee.	Definition: Knee osteoarthritis in the medial tibialfemoral compartment according to the American College of Rheumatology with grade 2 to 3 radiographic stage osteoarthritis Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 7.5 (7.7) years Presence of multimorbidities: Not stated/unclear		
Neustadt 2005[338]	**Intra-articular hyaluronic acid (non-image guided)** (n=248) Two groups combined. One had 2mL hyaluronic acid (Orthovisc, 30mg) given as 4 injections over 4 weeks. The other had 2mL hyaluronic acid (Orthovisc, 30mg) given as 3 injection and one sessions of arthrocentesis only conducted over 4 weeks.	**Knee osteoarthritis** Mean age (SD): 58.8 (8.7) years N = 372 Definition: Diagnosis of knee osteoarthritis according to the American College of Rheumatology criteria, a Kellgren Lawrence grade of 1-3 in accord with radiographic	Pain at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=124) Arthrocentesis only with the needle left in for enough time to simulate injection, conducted over 4 sessions over 4 weeks **Concomitant therapy:** Paracetamol up to 4g/day was the only rescue medication allowed. Paracetamol was not permitted for at least 24 hours prior to each study assessment session.	evidence of knee osteoarthritis, and a summed WOMAC pain score ≥200mm and <400mm (maximum possible score 500mm) in the index (treated) knee and <150mm in the contralateral (untreated) knee Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Petrella 2002[369] Subsidiary paper: Cubbage 2002[94]	**Intra-articular hyaluronic acid (non-image guided)** (n=30) 2mL of sodium hyaluronate (Synplasyn, 20mg) given as 3 injections over 3 weeks with oral placebo twice daily **Placebo** (n=30) 2mL of isotonic sodium chloride solution given as 3 injections over 3 weeks with oral placebo twice daily There were two additional groups (one receiving hyaluronic acid injections [n=30], one receiving placebo injections [n=30]) that also received oral NSAIDs. These were not included in the analysis. **Concomitant therapy:**	**Knee osteoarthritis** Mean age (SD): 65.5 (9.0) years N = 120 Definition: Radiographic evidence of medial compartment unilateral knee osteoarthritis Severity: Radiographic grade (mean [SD]): 2.2 (0.3) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	People were also given 325mg acetaminophen as rescue medications to be taken as needed up to 650mg four times a day			
Petterson 2019[373]	**Intra-articular hyaluronic acid (non-image guided)** (n=184) 4mL hyaluronic acid (Monovisc) given as 1 injection **Placebo** (n=185) 4mL 0.9% saline given as 1 injection **Concomitant therapy:** Oral glucosamine and chondroitin sulphate were permitted if subjects maintained a constant dosage throughout the duration of the study. Daily paracetamol consumption of up to 4g (8-500mg tablets) was permitted as rescue medication starting 7 days prior to the randomisation visit). People were not allowed to take paracetamol 24 hours prior to each follow up appointment	**Knee osteoarthritis** Mean age (SD): 59.1 (8.6) years N = 369 Definition: Diagnosis of idiopathic knee osteoarthritis defined by the American College of Rheumatology with Kellgren Lawrence grade 2 or 3 changes in the index knee Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	Physical function at ≤3 months and >3 months Serious adverse events at >3 months	
Pham 2004[374]	**Intra-articular hyaluronic acid (non-image guided)** (n=131) 2.5mL hyaluronic acid (NRD 101) given as 3 courses of 3 injections over 3 weeks with daily placebo capsules **Placebo** (n=85)	**Knee osteoarthritis** Mean age (SD): 64.8 (8.0) years N = 301 Definition: Symptomatic medial femorotibial knee osteoarthritis with radiographic evidence of	Pain at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	2.5mL saline injections given as 3 courses of 3 injections over 3 weeks with daily placebo capsules There was one additional group (n=85) that received placebo injections with daily diacerein capsules. They were not included in the analysis. **Concomitant therapy:** People were allowed to take analgesics as rescue drugs. However, before each evaluation visit, they were required to undergo a 2 day washout period. Aspirin at an antiplatelet dose (<500mg/day) was allowed. If NSAIDs were required, the drugs used were those with an equivalent dosage available, and a 7 day washout period was required before each evaluation visit. No systemic corticosteroid, IA treatment (lavage, HA, corticosteroid), or any potential symptom modifying drug was allowed during the study	medial joint space width >2mm. Severity: Majority Kellgren Lawrence grade 3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Raynauld 2003[391]	**Intra-articular corticosteroids (non-image guided)** (n=34) 1mL triamcinolone acetonide (40mg) given in 8 injections over 24 months (every 3 months) **Placebo** (n=34)	**Knee osteoarthritis** Mean age (SD): 63.2 (9.1) years N = 68 Definition: Clinical and radiological diagnosis fulfilled by the American College of	Pain at >3 months Physical function at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	1mL saline given in 8 injections over 24 months (every 3 months) **Concomitant therapy:** People in both treatment groups were permitted to receive simple analgesics and NSAIDs, and analgesic regimens could be changed according to the rheumatologist's preferences and the patient's clinical course. The use of indomethacin was not permitted.	Rheumatology criteria for knee osteoarthritis Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 9.3 (7.0) years Presence of multimorbidities: Not stated/unclear		
Rolf 2005[407]	**Intra-articular hyaluronic acid (non-image guided)** (n=181) Two groups combined. One group received 2mL hyaluronic acid (Synvisc) while the other received 2.5mL hyaluronic acid (Artzal). Both were administered as 3 injections over 3 weeks. **Placebo** (n=91) 2mL of sterile physiological buffered saline given as 3 injections over 3 weeks. **Concomitant therapy:** Paracetamol (500-2000mg/day) was the only oral treatment allowed for knee pain up to the 26 week visit.	**Knee osteoarthritis** Mean age (SD): 53.8 (9.4) years N = 272 Definition: Osteoarthritis of the knee, primarily affecting one knee with grade 1-3 chondral changes (as assessed by the Outerbridge criteria and verified by arthroscopy) Severity: Alhback grade 0-3. Duration of symptoms (mean [SD]): 7.8 (6.5) years Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Sezgin 2005[430]	**Intra-articular hyaluronic acid (non-image guided)** (n=22)	**Knee osteoarthritis** Mean age (SD): 59.7 (10.0) years N = 41	Pain at ≤3 months Physical function at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	2mL hyaluronic acid (30mg) given after arthrocentesis in 3 injections over 3 weeks **Placebo** (n=19) 2mL 0.9% sodium chloride given after arthrocentesis in 3 injections over 3 weeks **Concomitant therapy:** All people were instructed to do isometric quadriceps exercises. They were not given any analgesics or NSAIDs except for paracetamol.	Definition: Diagnosis of primary gonarthrosis based on the modified American College of Rheumatology criteria with grade 2 or 3 disease on plain X-ray of the knee according to Kellgren-Lawrence grading Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Presence of multimorbidities:		
Shimizu 2010[438]	**Intra-articular hyaluronic acid (non-image guided)** (n=32) Sodium hyaluronate (25mg) given as 5 injections over 5 weeks. **Intra-articular corticosteroids (non-image guided)** (n=29) Corticosteroid (type not specified, 4mg) given as 1 injection (with the option for an additional injection dependent on symptoms). **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 75.6 (5.4) years N = 61 Definition: Tibiofemoral and/or patellofemoral joint pain with osteoarthritis findings on radiography (Kellgren Lawrence grade 2 or 3) Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months	
Shrestha 2018[441]	**Intra-articular corticosteroids (non-image guided)** (n=57) Triamcinolone acetonide (no additional information) given as 1 injection.	**Knee osteoarthritis** Mean age (SD): 67.3 (5.3) years N = 117	Pain at ≤3 months Physical function at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=60) Normal saline given as 1 injection **Concomitant therapy:** All people were given 1 week of oral aceclofenac 100mg once a day and had physiotherapy with a trained physiotherapist.	Definition: Clinically diagnosed osteoarthritis of the knees by the criteria of the American College of Rheumatology (unclear if radiography was used) Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Skwara 2009[445]	**Intra-articular hyaluronic acid (non-image guided)** (n=21) 2mL hyaluronic acid (Ostenil, 20mg) given as 5 injections over 5 weeks **Intra-articular corticosteroids (non-image guided)** (n=21) 1mL triamcinolone acetonide (10mg) given as 5 injections over 5 weeks **Concomitant therapy:** People are allowed to use paracetamol up to 2g per day and 100mg/day acetylsalicylic acid (for people with cardiovascular diseases).	**Knee osteoarthritis** Mean age (SD): 61.1 (6.9) years N = 42 Definition: Radiographically verified unilateral degenerative osteoarthritis of the knee grade 2 or 3 according to the Kellgren and Lawrence classification Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	
Skwara 2009[446]	**Intra-articular hyaluronic acid (non-image guided)** (n=30) 2mL hyaluronic acid (Durolane, 60mg) in buffered physiological sodium chloride solution given as 1 injection	**Knee osteoarthritis** Mean age (SD): 61.4 (10.5) years N = 60 Definition: Radiographically verified degenerative	Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	In Forest plots, this study is referred to as Skwara 2009B

Study	Intervention and comparison	Population	Outcomes	Comments
	Intra-articular corticosteroids (non-image guided) (n=30) 1mL triamcinolone acetonide (10mg) given as 1 injection **Concomitant therapy:** Other intraarticular therapy was not permitted, and regular antithrombotic or NSAIDs/psychiatric pharmaceuticals were not permitted	osteoarthritis of the knee (grade II or III according to the Kellgren and Lawrence classification) Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear		
Strand 2012[460] Subsidiary papers: Strand 2016[462] Takamura 2018[466] Takamura 2019[467]	**Intra-articular hyaluronic acid (non-image guided)** (n=251) 3mL cross-linked hyaluronic acid (Gel-200, 30mg) given as 1 injection **Placebo** (n=128) Phosphate buffered injection given as 1 injection **Concomitant therapy:** NSAIDs, nonprescription herbal therapies, and chondroprotective agents (e.g. oral HA, glucosamine, chondroitin sulfate, minocycline) were allowed if people did not change their treatment regimen and continued regular administration at stable doses from 4 weeks prior to randomization throughout the protocol participation. Intermittent use of short-acting oral opiates was also permitted	**Knee osteoarthritis** Mean age (SD): 60.7 (10.2) N = 379 Definition: Knee osteoarthritis with pain and Kellgren-Lawrence grade 1-3 changes seen by X-ray Severity: Kellgren Lawrence grade 1-3 Duration of symptoms (mean [SD]): 38.3 (48.4) months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Tamir 2001[469]	**Intra-articular hyaluronic acid (non-image guided)** (n=25) 2mL sodium hyaluronate (BioHy, 20mg) in a sterile 1% saline solution given as 5 injections over 5 weeks. **Placebo** (n=24) A sterile 1% saline solution given as 5 injections over 5 weeks. **Concomitant therapy:** Analgesic or NSAID medications were not deprived before or during the trial	**Knee osteoarthritis** Mean age: 71 years N = 49 Definition: Idiopathic symptomatic clinical osteoarthritis of the knee as classified according to the Altman criteria and radiologically verified osteoarthritis of the knee (stages 2-4) according to the Kellgren and Lawrence grading system. Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Tammachote 2016[470]	**Intra-articular hyaluronic acid (non-image guided)** (n=55) 6mL hyaluronic acid (Hylan G-F 20) given as 1 injection **Intra-articular corticosteroids (non-image guided)** (n=55) 1mL triamcinolone acetonide (40mg) plus 5mL of 1% lidocaine with epinephrine given as 1 injection **Concomitant therapy:** All people with post-infection pain were provided with a prescription of 35mg	**Knee osteoarthritis** Mean age: 61.8 years N =110 Definition: A diagnosis of knee osteoarthritis by clinical and radiographic evaluations at an orthopaedic clinic Severity: Kellgren Lawrence grade 1-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	orphenadrine citrate and 500mg paracetamol. They were advised to not take any other medication relevant to the treatment of osteoarthritis.			
Tasciotaoglu 2003[473]	**Intra-articular hyaluronic acid (non-image guided)** (n=30) 2mL sodium hyaluronate (Orthovisc, 30mg) given as 3 injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=30) 1mL 6-methylprednisolone acetate (40mg) given as 3 injections over 3 weeks **Concomitant therapy:** People were allowed to use paracetamol (to a maximum of 3 grams daily) during the study period. None was permitted for at least 48 hours before each injection and clinical assessment.	**Knee osteoarthritis** Mean age (SD): 58.8 (7.8) years N = 60 Definition: Idiopathic osteoarthritis according to the American College of Rheumatology criteria with grade II to III radiographic changes according to the Kellgren-Lawrence grading system Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms (mean [SD]): 6.4 (4.4) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Serious adverse events at >3 months	
Tekeoglu 1998[475]	**Intra-articular hyaluronic acid (non-image guided)** (n=20) Sodium hyaluronate (Orthovisc, 20mg) given in a phosphate buffer as 3 injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=20) Betamethasone (Celestone chronodose, 3mg/mL) given as 3 injections over 3 weeks	**Knee osteoarthritis** Mean age (SD): 58 (5.8) years N = 40 Definition: Kellgren Lawrence stage 1-4 and presence of knee pain Severity: Moderate-to-severe Duration of symptoms (mean [SD]): 54.0 (24.9) weeks	Serious adverse events at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information	Presence of multimorbidities: Not stated/unclear		
Trueba davalillo 2015[485]	**Intra-articular hyaluronic acid (non-image guided)** (n=100) 2.5mL 1% hyaluronic acid given as 5 injections over 5 weeks **Intra-articular corticosteroids (non-image guided)** (n=100) 1mL betamethasone diproprionate (5mg) and betamethasone sodium phosphate (2mg) (Diprospan Hypack) given as 2 injections over 4 weeks **Concomitant therapy:** Concomitant treatment with glucosamine sulfate 1500mg and meloxicam 15mg for 1 month. Once completed people were prescribed glucosamine 1500mg and chondroitin sulfate 1200mg for an additional month. In case of continued pain during follow up, paracetamol was allowed for up to 3g/day	**Knee osteoarthritis** Mean age (SD): 62.8 (0.6) years N = 200 Definition: Knee osteoarthritis diagnosed with an applicable medical history and proven on radiography Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	
Vaishya 2017[494]	**Intra-articular hyaluronic acid (non-image guided)** (n=42) 6mL hyaluronate (Synvisc-one, 48mg) given as 1 injection **Intra-articular corticosteroids (non-image guided)** (n=40) Triamcinolone hexacetate (30mg) given as 1 injection	**Knee osteoarthritis** Mean age: Not stated. People >80 years were excluded. N = 82 Definition: Moderate OA knee with Kellgren Lawrence grade 2-3 changes	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information	Severity: Moderate Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Van der Weegen 2015[496]	**Intra-articular hyaluronic acid (non-image guided)** (n=99) 2mL 1.5% sodium hyaluronate (Fermathron plus, 15mg sodium hyaluronate, 8.5mg sodium chloride, 0.25mg disodium hydrogen orthophosphate dihydrate, 0.044mg sodium dihydrogen phosphate dihydrate and water for injection) given as 3 injections over 3 weeks **Placebo** (n=97) Placebo (8.5mg sodium chloride, 0.25mg disodium hydrogen orthophosphate dihydrate, 0.044mg sodium dihydrogen phosphate dihydrate and water for injection) given as 3 injections over 3 weeks **Concomitant therapy:** Rescue medication in the form of paracetamol only	**Knee osteoarthritis** Mean age (SD): 59.4 (9.9) years N = 196 Definition: Mild to moderate knee osteoarthritis according to the American College of Rheumatology diagnostic criteria. Confirmed by a standard anteroposterior radiograph. Severity: Mild-to-moderate Duration of symptoms (mean [SD]): 65.3 (90.4) months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	
Vega 2015[503]	**Intra-articular stem cell therapy (non-image guided)** (n=15) Bone marrow mesenchymal stem cells (40x10^6 cells/knee) given as 1 injection	**Knee osteoarthritis** Mean age (range): 57.0 (36-73) N = 30 Definition: Kellgren Lawrence grade 2-4 chronic knee osteoarthritis that was	Quality of life at ≤3 and >3 months Pain at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Intra-articular hyaluronic acid (non-image guided) (n=15) 3mL hyaluronic acid (Durolane, 60mg) given as 1 injection **Concomitant therapy:** No additional information	unresponsive to conventional treatments Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Yavuz 2012[529]	**Intra-articular corticosteroids (non-image guided)** (n=90) Combination of 3 groups. A group received 1mL betamethasone disodium phosphate (3mg) in 1 injection. Another group received 1mL triamcinolone acetonide (40mg) given as 1 injection. A third group received 1mL methylprednisolone acetate (40mg) given as 1 injection. **Placebo** (n=30) 1mL physiological 0.09% serum given as 1 injection. **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 60.3 (6.2) years N = 120 Definition: People with knee pain who met the American College of Rheumatology criteria with radiological grade 2 or other changed by the Kellgren and Lawrence classification Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Serious adverse events at ≤3 months	

1.1.5.3 Ankle osteoarthritis

Table 4: Summary of studies included in the evidence review including people with ankle osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Cohen 2008[81]	**Intra-articular hyaluronic acid (non-image guided)** (n=16) 2mL hyaluronic acid (Hyalgan) given as 5 injections over 5 weeks **Placebo** (n=14) 2mL phosphate buffered saline given as 5 injections over 5 weeks **Concomitant therapy:** Paracetamol (up to 4g/day) as rescue medication. Otherwise no anti-inflammatory drugs	**Ankle osteoarthritis** Mean age (SD): 50.3 (16.3) years N = 30 Definition: Ankle osteoarthritis with pain associated with X-ray changes Severity: Kellgren-Lawrence grade 2-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Osteoarthritis flares at >3 months	
Degroot 2012[110]	**Intra-articular hyaluronic acid (image guided)** (n=39) 2.5mL sodium hyaluronic (Supartz, 25mg) given as 1 injection **Placebo** (n=25) 2.5mL normal saline given as 1 injection **Concomitant therapy:** No additional information	**Ankle osteoarthritis** Mean age (SD): 57.2 (14.8) years N = 64 Definition: Ankle arthritis classified on radiographs as Kellgren and Lawrence grade 2 or higher Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Serious adverse events at ≤3 months	
Salk 2005[416] Subsidiary paper:	**Intra-articular hyaluronic acid (non-image guided)** (n=10)	**Ankle osteoarthritis**	Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Salk 2006[417]	1mL sodium hyaluronate (10mg) given as 5 injections over 5 weeks **Placebo** (n=10) 1mL phosphate buffered saline given as 5 injections over 5 weeks **Concomitant therapy:** All were supplied 500mg paracetamol tablets and were allowed to take up to 4000mg/day for rescue analgesia. People were instructed to not take other NSAIDs, narcotic analgesics, non-narcotic analgesics, or corticosteroids.	Mean age (SD): 58.8 (14.4) years N = 20 Definition: Clinically diagnosed osteoarthritis of the ankle by clinical examination and radiographic procedures Severity: Kellgren Lawrence grades 2-4 Duration of symptoms: At least 3 months but less than 5 months Presence of multimorbidities: Not stated/unclear		

1.1.5.4 Toe osteoarthritis

Table 5: Summary of studies included in the evidence review including people with toe osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Munteanu 2011[330] Subsidiary paper: Munteanu 2009[329]	**Intra-articular hyaluronic acid (image guided)** (n=75) 1mL hyaluronic acid (hylan GF-20, Synvisc) given as 1 injection into the first metatarsal phalangeal joint under fluoroscopic guidance (with the option for an additional injection if symptoms persisted). **Placebo** (n=76)	**Toe osteoarthritis** Mean age (SD): 54.5 (11.3) years N = 151 Definition: Pain during motion or rest and stiffness of the first metatarsophalangeal joint with radiographic evidence (score of 1 or 2 for either	Quality of life at ≤3 and >3 months Pain at ≤3 and >3 months Physical function at ≤3 and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	1mL sterile saline (0.9%) given as 1 injection into the first metatarsal phalangeal joint under fluoroscopic guidance (with the option for an additional injection if symptoms persisted). **Concomitant therapy:** No additional information	osteophytes or joint space narrowing) of osteoarthritis Severity: Severe Duration of symptoms (mean [SD]): 42.9 (48.9) months Presence of multimorbidities: Not stated/unclear		
Pons 2007[377]	**Intra-articular hyaluronic acid (non-image guided)** (n=17) 1mL sodium hyaluronate (Ostenil mini) given as 1 injection **Intra-articular corticosteroids (non-image guided)** (n=19) 1mL triamcinolone acetonide given as 1 injection **Concomitant therapy:** People were encouraged to refrain from strenuous activity for a day after the injections. As rescue medications people were permitted to take only paracetamol tablets (500mg) for severe pain or symptomatic deterioration (not more than 2 grams per day).	**Toe osteoarthritis** Mean age (SD): 62.0 (12.1) years N = 36 Definition: Painful osteoarthritis of the first metatarsophalangeal joint with or without deviation diagnosed by clinical examination and radiography (grade 1 according to the classification of Karasick and Wapner) Severity: Grade 1 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	

1.1.5.5 Shoulder osteoarthritis

Table 6: Summary of studies included in the evidence review including people with shoulder osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Blaine 2008[48]	**Intra-articular hyaluronic acid (non-image guided)** (n=129) 2mL hyaluronic acid (20mg) given as 5 injections over 5 weeks **Intra-articular hyaluronic acid (non-image guided)** (n=136) 2mL hyaluronic acid (20mg) given as 3 injections, and 2mL phosphate buffered saline given as 2 injections. Together, 5 injections over 5 weeks. **Placebo** (n=133) 2mL phosphate buffered saline given as 5 injections over 5 weeks. **Concomitant therapy:** No additional information	**Shoulder osteoarthritis** Mean age (SD): 63.1 (12.5) years N = 398 (660 including people who do not have osteoarthritis) Definition: The study included people with persistent shoulder pain associated with limitation of motion due to glenohumeral joint osteoarthritis, rotator cuff tear (partial or complete), and/or primary or secondary adhesive capsulitis. They report the people with osteoarthritis separately. Severity: Less than stage 4 Kellgren and Lawrence changes Duration of symptoms: At least 6 months but less than 5 years Presence of multimorbidities:	Pain at >3 months	The two hyaluronic acid groups were combined to produce the outcome values. This paper included people without osteoarthritis. It was possible to extract results from the cohort with osteoarthritis separately.
Kwon 2013[261]	**Intra-articular hyaluronic acid (non-image guided)** (n=150) Hyaluronic acid given as 3 injections over 3 weeks **Placebo** (n=150)	**Shoulder osteoarthritis** Mean age (SD): 66.1 (11.2) years N = 300 Definition: People with shoulder pain primarily due to	Pain at >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Phosphate buffered saline given as 3 injections over 3 weeks **Concomitant therapy:** No additional information	glenohumeral osteoarthritis determined by the investigator and confirmed by standard shoulder radiography. This can be supported by MRI, but was not required in all people. Severity: Not stated Duration of symptoms: More than 6 months but less than 3 years Presence of multimorbidities: Not stated/unclear		

1.1.5.6 Thumb osteoarthritis

Table 7: Summary of studies included in the evidence review including people with thumb osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Bahadir 2009[26]	**Intra-articular hyaluronic acid (non-image guided)** (n=20) 0.5mL sodium hyaluronate (5mg) given as 3 injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=20) 0.5mL triamcinolone acetonide (20mg) given as 1 injection **Concomitant therapy:** People were not allowed to receive simple analgesics, NSAIDs, and any other kind of analgesic drugs. They did not	**Thumb osteoarthritis** Mean age (SD): 60.9 (8.3) years N = 40 Definition: Trapeziometacarpal joint osteoarthritis according to clinical and radiological findings Severity: Stage 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	use any kind of splint during the study period.			
Fuchs 2006[152]	**Intra-articular hyaluronic acid (image guided)** (n=28) 1mL 1% sodium hyaluronate (Ostenil mini) given as 3 injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=28) 1mL triamcinolone acetonide (10mg) given as 3 injections over 3 weeks **Concomitant therapy:** Paracetamol was allowed as rescue analgesia, otherwise other treatments were stopped.	**Thumb osteoarthritis** Age range: 44-80 years N = 56 Definition: Symptomatic osteoarthritis of the carpometacarpal joint of the thumb associated with radiographic evidence according to the Kellgren score Severity: Not stated Duration of symptoms: Pain for at least 6 months Presence of multimorbidities: Not stated/unclear	Serious adverse events at >3 months	
Heyworth 2008[192]	**Intra-articular hyaluronic acid (non-image guided)** (n=20) 1mL hyaluronic acid (Hylgan GF-20) given as 2 injections over 1 week **Intra-articular corticosteroids (non-image guided)** (n=22) 1mL saline followed by 1mL sodium betamethasone sodium phosphate-betamethasone acetate given over 1 week **Placebo** (n=18) 1mL saline given as 2 injections over 1 week	**Thumb osteoarthritis** Mean age (SD): 61 (1) years N = 60 Definition: Diagnosed using standard radiographic and clinical criteria: basal joint tenderness, thumb or wrist pain at rest or with activity, joint stiffness, decreased mobility, deformity, instability and decreased manual function Severity: Not stated Duration of symptoms: Not stated	Serious adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: People were given access to splints to wear as needed and standard doses of NSAIDs (ibuprofen 400mg every 4-6 hours as required)	Presence of multimorbidities: Not stated/unclear		
Meenagh 2004[310]	**Intra-articular corticosteroids (non-image guided)** (n=20) 0.25mL triamcinolone hexacetonide (5mg) given in 1 injection **Placebo** (n=20) 0.25mL sterile 0.9% saline given in 1 injection **Concomitant therapy:** The injected joint was immobilised in a thumb spica splint for 48 hours after injection	**Thumb osteoarthritis** Mean age (range): 60.0 (41-71) N = 40 Definition: Symptomatic carpometacarpal joint osteoarthritis (of the thumb) satisfying the American College of Rheumatology criteria for hand osteoarthritis Severity: Not stated Duration of symptoms (mean): 7.8 years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months	Results reported as median (interquartile range). Cannot be combined with the GRADE analysis, but is reported separately due to limited evidence for this stratum.
Monfort 2015[323]	**Intra-articular hyaluronic acid (non-image guided)** (n=48) 0.5mL hyaluronic acid (Suplasyn, 5mg) given as 3 injections over 3 weeks **Intra-articular corticosteroids (non-image guided)** (n=40) 0.5mL betamethasone disodium phosphate (1.5mg) and betamethasone acetate (1.5mg) given as 3 injections over 3 weeks	**Thumb osteoarthritis** Mean age (SD): 62.8 (8.7) years N = 88 Definition: A previous diagnosis of thumb carpometacarpal joint osteoarthritis as defined by criteria of the American College of Rheumatology provided they had clinical symptoms in the affected thumb for at least 90 days	Quality of life at ≤3 and >3 months Pain at ≤3 and >3 months Physical function at ≤3 and >3 months	Physical function reported as a median (interquartile range). Cannot be combined with the GRADE analysis, but is reported separately due to limited evidence for this stratum.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Instructed to discontinue any systemic or topical treatment. Paracetamol (maximum 3g/day) was allowed but all medication use during the trial needed to be recorded.	prior to the study, required treatment with analgesics or NSAIDs on a routine basis, and had an available confirmatory X-ray diagnosis (Kellgren-Lawrence grade I-III) within the previous 6 months. Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: At least 90 days Presence of multimorbidities: Not stated/unclear		
Stahl 2005[455]	**Intra-articular corticosteroids (non-image guided)** (n=25) 1mL methylprednisolone acetate (40mg) given as 1 injection **Intra-articular hyaluronic acid (non-image guided)** (n=27) 1mL sodium hyaluronate (Orthovisc, 15mg) given as 1 injection **Concomitant therapy:** No additional information	**Thumb osteoarthritis** Mean age (range): 62 (37-91) years N = 52 Definition: Symptomatic trapeziometacarpal joint grade 2 arthritis, that was diagnosed by clinical presentation and radiographic evaluation of the first carpometacarpal joint Severity: Eaton and Littler grade 2 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at >3 months	

1.1.5.7 Finger osteoarthritis

Table 8: Summary of studies included in the evidence review including people with finger osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Spolidoro paschoal nde 2015[454]	**Intra-articular corticosteroids (non-image guided)** (n=30) 0.2-0.3mL triamcinolone hexacetonide (4mg for distal interphalangeal joint, 6mg for proximal interphalangeal joint) given with 2% lidocaine without epinephrine given as 1 injection to the most symptomatic joint **Placebo** (n=30) 0.1mL 2% lidocaine without epinephrine given as 1 injection to the most symptomatic joint **Concomitant therapy:** Paracetamol (750mg per tablet) were used if required during the follow up period (up to three tablets per day.	**Finger osteoarthritis** Mean age (SD): 60.7 (8.25) years N = 60 Definition: A diagnosis of hand osteoarthritis involving the proximal interphalangeal joints or distal interphalangeal joints according to the American College of Rheumatology criteria Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	

1.1.5.8 Temporomandibular joint osteoarthritis

Table 9: Summary of studies included in the evidence review including people with temporomandibular joint osteoarthritis

Study	Intervention and comparison	Population	Outcomes	Comments
Bjornland 2007[47]	**Intra-articular hyaluronic acid (non-image guided)** (n=20) 0.7-1mL of the sodium salt of hyaluronic acid (Hylan G-F 20)	**Temporomandibular joint osteoarthritis** Mean age (SD): 51.7 (13.2) years N = 40	Pain at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	given as 2 injections over 2 weeks **Intra-articular corticosteroids (non-image guided)** (n=20) 0.7-1mL of betamethasone sodium phosphate betamethasone acetate given as 2 injections over 2 weeks **Concomitant therapy:** No additional information	Definition: People who fulfilled the criteria for osteoarthritis of the TMJ and myofascial pain according to the Research Diagnostic Criteria for temporomandibular disorders by Dworkin and LeResche Severity: Not stated Duration of symptoms (mean [SD]): 5.9 (9.3) years Presence of multimorbidities: Not stated/unclear		
Gencer 2014[159]	**Intra-articular hyaluronic acid (image guided)** (n=25) 2mL hyaluronic acid (Hyalgan, 20mg) given as 1 injection under ultrasound guidance **Intra-articular corticosteroids (image guided)** (n=25) 0.5mL betamethasone (3.5mg) given as 1 injection under ultrasound guidance Two additional groups were included in the study. One received intraarticular tenoxicam (n=25), the other received intraarticular saline (n=25). The latter cohort was not randomised (being selected as they had less severe disease). Therefore, these groups did not fulfil the protocol and so were not included in the analysis.	**Temporomandibular joint osteoarthritis** Mean age (SD): 42.5 (10.2) years N = 100 Definition: TMJ derangement present on CT. People were evaluated according to the Wilkes classification. Late intermediate or late stage people were included in the study group (stage 4-5). These had radiological evidence of significant degenerative changes. Severity: Wilkes grade 4-5 Duration of symptoms: Not stated Presence of multimorbidities:	Pain at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: An ice pack was applied immediately after injection. Five minutes after the injection, the person was examined for signs of facial palsy, and manual mobilisation of the jaw was performed to improve mouth opening			

See Appendix D for full evidence tables.

1.1.5.9 Summary matrices

Table 10: Matrix of comparisons for the hip osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	1 study, N=67, low quality	1 study, N=312, low quality	No evidence identified	2 studies, N=103, very low quality	1 study, N=67, very low quality
	Placebo	No evidence identified	4 studies, N=545, low to low quality	2 studies, N=442, moderate quality	No evidence identified	3 studies, N=190, low quality	2 studies, N=154, very low quality
Intra-articular corticosteroids (image guided)	Placebo	1 study, N=52, very low quality	3 studies, N=212, low-very low quality	2 studies, N=132, very low quality	No evidence identified	2 studies, N=107, very low quality	2 studies, N=122, very low quality

Table 11: Matrix of comparisons for the hip osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	1 study, N=312, moderate quality	1 study, N=312, moderate quality	No evidence identified	No evidence identified	1 study, N=305, very low quality
	Placebo	No evidence identified	2 studies, N=391, low to very low quality	1 study, N=357, low quality	No evidence identified	No evidence identified	2 studies, N=396, very low quality
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 12: Matrix of comparisons for the knee osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	1 study, N=150, very low quality	10 studies, N=1072, very low quality	5 studies, N=502, very low quality	No evidence identified	No evidence identified	3 studies, N=142, very low quality
	Intra-articular stem cell therapy (non-image guided)	1 study, N=30, moderate quality	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	17 studies, N=2873, moderate to low quality	9 studies, N=1354, high to low quality	No evidence identified	No evidence identified	2 studies, N=271, very low quality
Intra-articular corticosteroids (non-image guided)	Intra-articular stem cell therapy	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	1 study, N=414, moderate quality	7 studies, N=938, very low quality	4 studies, N=737, low to very low quality	No evidence identified	No evidence identified	2 studies, N=190, low quality
Intra-articular stem cell therapy (non-image guided)	Placebo	No evidence identified	2 studies, N=151, low quality	1 study, N=43, low quality	No evidence identified	No evidence identified	No evidence identified

Table 13: Matrix of comparisons for the knee osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	1 study, N=136, very low quality	9 studies, N=1308, very low quality	2 studies, N=277, very low quality	No evidence identified	No evidence identified	8 studies, N=1586, very low quality
	Intra-articular stem cell therapy (non-image guided)	1 study, N=30, moderate quality*	2 studies, N=57, moderate quality	1 study, N=27, low quality	No evidence identified	No evidence identified	3 studies, N=114, very low quality
	Placebo	2 studies, N=197, moderate quality	19 studies, N=3928, moderate to low quality	12 studies, N=2820, high to very low quality	No evidence identified	2 studies, N=262, very low quality	28 studies, N=6503, very low quality
Intra-articular corticosteroids (non-image guided)	Intra-articular stem cell therapy (non-image guided)	1 study, N=31, moderate quality	1 study, N=31, low quality	1 study, N=31, low quality	No evidence identified	No evidence identified	No evidence identified
	Placebo	1 study, N=414, high quality	3 studies, N=654, low quality	3 studies, N=549, moderate quality	No evidence identified	No evidence identified	2 studies, N=624, very low quality
Intra-articular stem cell therapy (image guided)	Placebo	No evidence identified	1 study, N=20, moderate quality	No evidence identified	No evidence identified	No evidence identified	2 studies, N=44, very low quality
Intra-articular stem cell	Placebo	No evidence identified	2 studies, N=151, low quality	1 study, N=43, low quality	No evidence identified	No evidence identified	3 studies, N=163, very low quality

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
therapy (non-image guided)							

** One study (N=30) reports multiple components of SF-12.*

Table 14: Matrix of comparisons for the ankle osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	2 studies, N=84, low quality	1 study, N=28, very low quality	No evidence identified	No evidence identified	1 study, N=64, low quality
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 15: Matrix of comparisons for the ankle osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	1 study, N=28, very low quality	1 study, N=28, very low quality	No evidence identified	1 study, N=28, very low quality	1 study, N=17, very low quality

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 16: Matrix of comparisons for the toe osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	1 study, N=151, moderate-low quality*	1 study, N=151, moderate quality	1 study, N=151, high quality	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	1 study, N=36, very low quality	1 study, N=34, very low quality	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

** One study (N=151) reports multiple subscales of SF-36. Due to variations in precision, outcomes were either of moderate or low quality.*

Table 17: Matrix of comparisons for the toe osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	1 study, N=151, moderate to low quality*	1 study, N=151, high quality	1 study, N=151, high quality	No evidence identified	No evidence identified	1 study, N=151, moderate quality
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

** One study (N=151) reports multiple subscales of SF-36. Due to variations in precision, outcomes were either of moderate or low quality.*

Table 18: Matrix of comparisons for the shoulder osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 19: Matrix of comparisons for the shoulder osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
	Placebo	No evidence identified	2 studies, N=562, very low quality	No evidence identified	No evidence identified	No evidence identified	1 study, N=300, very low quality
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 20: Matrix of comparisons for the thumb osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	1 study, N=88, very low quality*	3 studies, N=180, very low quality	1 study, N=40, very low quality	No evidence identified	No evidence identified	No evidence identified
	Intra-articular stem cell therapy	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

** One study (N=88) reports two subdomains of SF-36.*

Table 21: Matrix of comparisons for the thumb osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	1 study, N=88, very low quality*	3 studies, N=180, very low quality	1 study, N=40, very low quality	No evidence identified	No evidence identified	4 studies, N=190, very low quality
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 study, N=38, very low quality
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 study, N=40, very low quality

** Study reports two subdomains of SF-36. Due to variations in precision, outcomes were either of low or very low quality*

Table 22: Matrix of comparisons for the finger osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	1 study, N=60, moderate quality	1 study, N=60, moderate quality	No evidence identified	No evidence identified	No evidence identified

Table 23: Matrix of comparisons for the finger osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 24: Matrix of comparisons for the temporomandibular joint osteoarthritis stratum at ≤3 months

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	1 study, N=50, very low quality	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	1 study, N=40, low quality	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Intervention	Control	Quality of life at ≤3 months	Pain at ≤3 months	Physical function at ≤3 months	Psychological distress at ≤3 months	Osteoarthritis flares at ≤3 months	Serious adverse events at ≤3 months
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 25: Matrix of comparisons for the temporomandibular joint osteoarthritis stratum at >3 months

Intervention	Control	Quality of life at >3 months	Pain at >3 months	Physical function at >3 months	Psychological distress at >3 months	Osteoarthritis flares at >3 months	Serious adverse events at >3 months
Intra-articular hyaluronic acid (image guided)	Intra-articular corticosteroids (image guided)	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular hyaluronic acid (non-image guided)	Intra-articular corticosteroids (non-image guided)	No evidence identified	1 study, N=40, low quality	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Intra-articular corticosteroids (non-image guided)	Placebo	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Hip osteoarthritis

Table 26: Clinical evidence summary: intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (image guided)	Risk difference with intra-articular hyaluronic acid (image guided)	
Pain (VAS, 0-100, high is poor, change score) at ≤3 months	65 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean pain was -9	MD **2 lower** (13.5 lower to 9.5 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-100, high is poor, change score) at >3 months	312 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [b]	-	The mean pain was -13.59	MD **3.03 lower** (9.65 lower to 3.59 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months	312 (1 RCT) follow up: 4 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean physical function was -26.58	MD **8.39 higher** (3.51 higher to 13.27 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-100, high is poor, change score) at >3 months	312 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean physical function was -11.53	MD **2.27 lower** (8.67 lower to 4.13 higher)	MID = 0.5 SD (SMD)
Osteoarthritis flares at ≤3 months	101 (2 RCTs) follow up: mean 10 weeks	⊕◯◯◯ VERY LOW [a,b]	Peto OR 8.53 (1.60 to 43.60)	0 per 1,000	**120 more per 1000** (from 20 more to 220 more) [d]	MID (precision) = Peto OR 0.8-1.25.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (image guided)	Risk difference with intra-articular hyaluronic acid (image guided)	
Serious adverse events at ≤3 months	65 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,c]	RD 0.00 (-0.06 to 0.06)	0 per 1,000	**0 fewer per 1000** (from 60 fewer to 60 more) [d]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.
Serious adverse events at >3 months	305 (1 RCT) follow up: 4 weeks	⊕◯◯◯ VERY LOW [a,b]	RR 1.29 (0.35 to 4.72)	26 per 1,000	**7 more per 1,000** (17 fewer to 96 more)	MID (precision) = RR 0.8-1.25.

[a.] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b.] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[c.] Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

[d.] Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 27: Clinical evidence summary: intra-articular hyaluronic acid (image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Pain (VAS, 0-10, high is poor, final value) at ≤3 months	34 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean pain was 4.5	MD **0.2 lower** (1.95 lower to 1.55 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months	511 (3 RCTs) follow up: mean 12 weeks	⊕⊕◯◯ LOW [a]	-	-	SMD **0.02 SD lower** (0.19 lower to 0.16 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Pain (VAS, 0-10, high is poor, final value) at >3 months	34 (1 RCT) follow up: 24 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean pain was 5	MD **0.5 lower** (1.98 lower to 0.98 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-11, high is poor, change score) at >3 months	357 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean pain was -2.3	MD **0.07 higher** (0.53 lower to 0.67 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months	442 (2 RCTs) follow up: mean 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	-	SMD **0.1 SD higher** (0.09 lower to 0.29 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-11, high is poor, change score) at >3 months	357 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean physical function was -2.13	MD **0.04 higher** (0.54 lower to 0.62 higher)	MID = 0.5 SD (SMD)
Osteoarthritis flares at ≤3 months	190 (3 RCTs) follow up: mean 11 weeks	⊕⊕◯◯ LOW [a]	Peto OR 8.44 (2.21 to 32.26)	0 per 1,000	**100 fewer per 1,000** (160 fewer to 30 fewer) [c]	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events at ≤3 months	154 (2 RCTs) follow up: mean 12 weeks	⊕◯◯◯ VERY LOW [a,d,e]	RD 0.00 (-0.03 to 0.06)	0 per 1,000	**10 fewer per 1,000** (60 fewer to 30 more) [c]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Serious adverse events at >3 months	396 (2 RCTs) follow up: mean 25 weeks	⊕◯◯◯ VERY LOW [a,d,e]	RD -0.03 (-0.08 to 0.02)	78 per 1,000	**30 fewer per 1,000** (20 fewer to 80 more) [c]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Absolute effect calculated by risk difference due to zero events in at least one study arm
d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)
e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Table 28: Clinical evidence summary: intra-articular corticosteroids (image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular corticosteroids (image guided)	
Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months	52 (1 RCT) follow up: 8 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 26.58	MD **4.43 higher** (0.24 higher to 8.62 higher)	MID = 2
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months	52 (1 RCT) follow up: 8 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 53.57	MD **13.37 higher** (1.06 lower to 27.8 higher)	MID = 3
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	132 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **2.09 SD lower** (3.88 lower to 0.29 lower)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular corticosteroids (image guided)	
	follow up: mean 6 weeks					
Pain (VAS, 0-100, high is poor, change score) at ≤3 months	68 (1 RCT) follow up: 12 weeks	⨁⨁◯◯ LOW [a,b]	-	The mean pain was -5	MD **4 lower** (15.16 lower to 7.16 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, Katz and Akpom function ability [different scale ranges], high is poor, final values) at ≤3 months	132 (2 RCTs) follow up: mean 6 weeks	⨁◯◯◯ VERY LOW [a,b,c]	-	-	SMD **2.08 SD lower** (4.09 lower to 0.07 lower)	MID = 0.5 SD (SMD)
Osteoarthritis flares at ≤3 months	105 (2 RCTs) follow up: mean 10 weeks	⨁◯◯◯ VERY LOW [a,d]	RD 0.00 (-0.05 to 0.05)	0 per 1,000	**0 fewer per 1,000** (50 fewer to 50 more) [f]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.
Serious adverse events at ≤3 months	120 (2 RCTs) follow up: mean 10 weeks	⨁◯◯◯ VERY LOW [a,d,e]	RD 0.01 (-0.04 to 0.07)	0 per 1,000	**10 fewer per 1,000** (70 fewer to 40 more) [f]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)
f. Absolute effect calculated by risk difference due to zero events in at least one study arm

1.1.6.2 Knee osteoarthritis

Table 29: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Quality of life (SF-36, 0-100, high is good, final values) at ≤3 months	150 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 63.5	MD **8 higher** (3.39 higher to 12.61 higher)	MID = 0.5 SD (SMD)
Quality of life (SF-36, 0-100, high is good, final values) at >3 months	126 (1 RCT) follow up: 12 months	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 59.3	MD **2.7 higher** (1.57 lower to 6.97 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	1090 (10 RCTs) follow up: mean 11 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.24 SD lower** (0.86 lower to 0.37 higher)	MID = 0.5 SD (SMD)
Pain (KSS pain, VAS, 0-100, high is poor, final values) at >3 months	720 (7 RCTs) follow up: mean 33 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean pain was 30.4	MD **2.39 higher** (3.64 lower to 8.46 higher)	MID = 7.45 (0.5 x median baseline SD)
Pain (WOMAC, 0-20, high is poor, final values and change scores) at >3 months	586 (2 RCTs) follow up: mean 38 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean pain was 6.85	MD **2.21 lower** (6.67 lower to 2.25 higher)	MID = 1.45 (0.5 median baseline SD)
Physical function (WOMAC, KSS function [different scale	502 (5 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.05 SD lower** (0.79 lower to 0.68 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
ranges], high is poor, final values) at ≤3 months	follow up: mean 12 weeks					
Physical function (WOMAC, KSS function [different scale ranges], high is poor, final values) at >3 months	277 (2 RCTs) follow up: mean 38 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **1.77 SD lower** (4.1 lower to 0.56 higher)	MID = 0.5 SD (SMD)
Serious adverse events at ≤3 months	142 (3 RCTs) follow up: mean 12 weeks	⊕◯◯◯ VERY LOW [a,c,d]	RR 0.20 (-0.85 to 1.28)	70 per 1,000	**30 fewer per 1,000** (70 fewer to 140 more) [e]	MID (precision) = RR 0.8-1.25.
Serious adverse events at >3 months	1586 (8 RCTs) follow up: mean 32 weeks	⊕◯◯◯ VERY LOW [a,c,d]	RR 1.72 (1.32 to 2.12)	62 per 1,000	**20 more per 1,000** (70 fewer to 20 more) [e]	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

e. Absolute effect calculated from risk difference due to zero events in at least one study arm

Table 30: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Quality of life (KOOS, 0-100, high is poor, mean difference) at >3 months	197 (2 RCTs) follow up: mean 39 weeks	⊕⊕⊕◯ MODERATE [a]	-	-	MD **2.21 lower** (6.51 lower to 2.10 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	489 (6 RCTs) follow up: mean 7 weeks	⊕⊕◯◯ LOW [a]	-	-	SMD **0.3 SD lower** (0.47 lower to 0.12 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months	1670 (9 RCTs) follow up: mean 9 weeks	⊕⊕◯◯ LOW [a,b]	-	-	SMD **0.24 SD lower** (0.42 lower to 0.05 lower)	MID = 0.5 SD (SMD)
Pain (VAS [difference scale ranges], high is poor, final values) at ≤3 months	714 (2 RCTs) follow up: mean 12 weeks	⊕⊕⊕◯ MODERATE [b]	-	-	SMD **0.13 SD higher** (0.02 lower to 0.28 higher)	MID = 0.5 SD (SMD)
Pain (VAS, 0-100, high is poor, final values and change scores) at >3 months	2231 (10 RCTs) follow up: mean 36 weeks	⊕⊕⊕◯ MODERATE [a]	-	-	MD **2.25 lower** (4.44 lower to 0.06 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-20, high is poor, final values) at >3 months	464 (3 RCTs) follow up: mean 19 months	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was 6.57	MD **0.39 lower** (0.85 lower to 0.07 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months	1527 (7 RCTs) follow up: mean 27 weeks	⊕⊕◯◯ LOW [a,b]	-	-	SMD **0.15 SD lower** (0.32 lower to 0.03 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC-VAS disability and physical function subscale, 0-10, high is poor, final values) at ≤3 months	113 (2 RCTs) follow up: mean 4 weeks	⊕⊕◯◯ LOW [a,c]	-	The mean physical function was 2.13	MD **1.01 lower** (1.54 lower to 0.48 lower)	MID = 0.95 (0.5 x median baseline SD)
Physical function (WOMAC, 0-68, high is poor, change scores and final values) at ≤3 months	876 (6 RCTs) follow up: mean 10 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean physical function was 20.5	MD **0.21 lower** (1.85 lower to 1.43 higher)	MID = 5.5 (0.5 x median baseline SD)
Physical function (WOMAC, 0-100, high is poor, final values) at ≤3 months	365 (1 RCT) follow up: 12 weeks	⊕⊕⊕⊕ HIGH	-	The mean physical function was 31.7	MD **7 lower** (12.29 lower to 1.71 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months	1486 (7 RCTs) follow up: mean 29 weeks	⊕◯◯◯ VERY LOW [a,b]	-	-	SMD **0.22 SD lower** (0.45 lower to 0.00 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, final values) at >3 months	419 (2 RCTs) follow up: mean 22 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean physical function was 18.9	MD **1.77 lower** (4.29 lower to 0.75 higher)	MID = 6.37 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Physical function (KOOS activities subscale, WOMAC, 0-100, high is poor) at >3 months	912 (3 RCTs) follow up: mean 22 weeks	⊕⊕⊕⊕ HIGH	-	-	MD **3.06 lower** (6.09 lower to 0.03 lower)	MID = 0.5 SD (SMD)
Osteoarthritis flare-up at >3 months	262 (2 RCTs) follow up: mean 26 weeks	⊕◯◯◯ VERY LOW [b,d,e]	RR 1.00 (0.07 to 1.93)	54 per 1,000	**0 fewer per 1,000** (50 fewer to 50 more) [f]	MID (precision) = RR 0.8-1.25.
Serious adverse events at ≤3 months	271 (2 RCTs) follow up: mean 5 weeks	⊕◯◯◯ VERY LOW [b,d,e]	RD 0.01 (-0.02 to 0.03)	0 per 1,000	**10 fewer per 1,000** (30 fewer to 20 fewer) [f]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).
Serious adverse events at >3 months	6503 (28 RCTs) follow up: mean 34 weeks	⊕◯◯◯ VERY LOW [b,d,e]	RD 0.01 (0.00 to 0.02)	75 per 1,000	**10 more per 1,000** (0 fewer to 20 more) [f]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)
e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
f. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 31: Clinical evidence summary: intra-articular corticosteroids (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular corticosteroids (non-image guided)	
Quality of life (KOOS, 0-100, high is good, final value) at ≤3 months	414 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 12.2	MD **6.28 higher** (1.76 higher to 10.8 higher)	MID = 0.5 SD (SMD)
Quality of life (KOOS, 0-100, high is good, final value) at >3 months	414 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 10.25	MD **1.44 higher** (3.11 lower to 5.99 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	391 (4 RCTs) follow up: mean 11 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.53 SD lower** (1.07 lower to 0.02 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months	547 (3 RCTs) follow up: mean 11 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.55 SD lower** (1.07 lower to 0.03 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months	654 (3 RCTs) follow up: mean 1.5 years	⊕⊕◯◯ LOW [a,b]	-	-	SMD **0.02 SD higher** (0.3 lower to 0.34 higher)	MID = 0.5 SD (SMD)
Physical function (Health assessment questionnaire for lower limb function, WOMAC	269 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	-	SMD **0.28 SD lower** (0.69 lower to 0.13 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular corticosteroids (non-image guided)	
[different scale ranges], high is poor, final values) at ≤3 months	follow up: mean 10 weeks					
Physical function (WOMAC, 0-4, high is poor, change scores) at ≤3 months	468 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean physical function was -0.56	MD **0.26 lower** (0.42 lower to 0.1 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months	549 (3 RCTs) follow up: mean 1.5 years	⊕⊕⊕◯ MODERATE [a]	-	-	SMD **0.01 SD lower** (0.18 lower to 0.16 higher)	MID = 0.5 SD (SMD)
Serious adverse events at ≤3 months	190 (2 RCTs) follow up: mean 12 weeks	⊕⊕◯◯ LOW [a,e]	RD 0.00 (0.00 to 0.04)	0 per 1,000	**0 fewer per 1,000** (40 fewer to 40 more) [g]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).
Serious adverse events at >3 months	624 (2 RCTs) follow up: mean 16 months	⊕◯◯◯ VERY LOW [a,c,f]	RR 1.19 (-0.37 to 3.77)	17 per 1,000	**0 fewer per 1,000** (30 fewer to 20 more) [g]	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d. Downgraded by 1 or 2 increments because of outcome indirectness
e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
f. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)

Table 32: Clinical evidence summary: intra-articular stem cell therapy (image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular stem cell therapy (image guided)	
Pain (WOMAC, 0-20, high is poor, change score) at >3 months	20 (1 RCT) follow up: 52 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was -0.73	MD **1.63 lower** (4.23 lower to 0.97 higher)	MID = 0.5 SD (SMD)
Serious adverse events at >3 months	44 (2 RCTs) follow up: mean 39 weeks	⊕◯◯◯ VERY LOW [b,c]	RD 0.00 (-0.16 to 0.16)	0 per 1,000	**0 fewer per 1,000** (160 fewer to 160 more) [d]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[b] Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

[c] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[d] Absolute effect calculated from risk difference due to zero events in at least one study arm

Table 33: Clinical evidence summary: intra-articular stem cell therapy (non-image guided) compared to intra-articular hyaluronic acid (non-image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular hyaluronic acid (non-image guided)	Risk difference with intra-articular stem cell therapy (non-image guided)	
Quality of life (SF-12 physical component, 0-100, high is good, final value) at ≤3 months	30 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 39	MD **4 higher** (2.88 lower to 10.88 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular hyaluronic acid (non-image guided)	Risk difference with intra-articular stem cell therapy (non-image guided)	
Quality of life (SF-12 mental component, 0-100, high is good, final value) at ≤3 months	30 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 40	MD **3 lower** (10.16 lower to 4.16 higher)	MID = 0.5 SD (SMD)
Quality of life (SF-12 physical component, 0-100, high is good, final value) at >3 months	30 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 50	MD **5 higher** (1.88 lower to 11.88 higher)	MID = 0.5 SD (SMD)
Quality of life (SF-12 mental component, 0-100, high is good, final value) at >3 months	30 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 45	MD **5 lower** (11.88 lower to 1.88 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC [different scale ranges], high is poor, final values) at >3 months	57 (2 RCTs) follow up: mean 12 months	⊕⊕⊕◯ MODERATE [a]	-	-	SMD **0.65 SD lower** (1.2 lower to 0.1 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months	27 (1 RCT) follow up: 12 months	⊕⊕◯◯ LOW [a,b]	-	The mean physical function was 9.2	MD **3.1 lower** (9.94 lower to 3.74 higher)	MID = 0.5 SD (SMD)
Serious adverse events at >3 months	114 (3 RCTs) follow up: mean 10 months	⊕⊕◯◯ VERY LOW [b,c]	RD 0.09 (-0.12 to 0.31)	31 per 1,000	**90 more per 1,000** (120 fewer to 310 more) [d]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular hyaluronic acid (non-image guided)	Risk difference with intra-articular stem cell therapy (non-image guided)	

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Absolute effect calculated from risk difference due to zero events in at least one study arm

Table 34: Clinical evidence summary: intra-articular stem cell therapy (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with corticosteroids (non-image guided)	Risk difference with intra-articular stem cell therapy (non-image guided)	Comments
Quality of Life (KOOS quality of life, 0-100, high is good, change score) >3 months	31 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE[a]	-	The mean quality of life was 15.4	MD **7.6 higher** (11.66 lower to 26.86 higher)	MID = 0.5 SD (SMD)
Pain (KOOS pain, 0-100, high is good, change score) at >3 months	31 (1 RCT) follow up: 12 months	⊕⊕◯◯ LOW[a]	-	The mean pain was 19	MD **3.2 higher** (15.08 lower to 21.48 higher)	MID = 0.5 SD (SMD)
Physical function (KOOS function/daily living, 0-100, high is good, change score) >3 months	31 (1 RCT) follow up: 12 months	⊕⊕◯◯ LOW[a]	-	The mean physical function was 20.9	MD **5.8 higher** (14.76 lower to 26.36 higher)	MID = 0.5 SD (SMD)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 35: Clinical evidence summary: intra-articular stem cell therapy (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular stem cell therapy (non-image guided)	
Pain (WOMAC, VAS, 0-100, high is poor, change score) at ≤3 months	151 (2 RCTs) follow up: mean 12 weeks	⨁⨁◯◯ LOW [a,b]	-	The mean pain was 0	MD **15.19 lower** (23.44 lower to 6.94 lower)	MID = 7.6 (0.5 x median control group SD)
Pain (WOMAC, VAS, 0-100, high is poor, change score) at >3 months	151 (2 RCTs) follow up: mean 16 months	⨁⨁◯◯ LOW [a,b]	-	The mean pain was 0	MD **12.83 lower** (21.88 lower to 3.79 lower)	MID = 15.5 (0.5 x median control group SD)
Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months	41 (1 RCT) follow up: 12 weeks	⨁⨁◯◯ LOW [a,b]	-	The mean physical function was -6.8	MD **9.2 lower** (19.15 lower to 0.75 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-100, high is poor, change score) at >3 months	43 (1 RCT) follow up: 26 weeks	⨁⨁◯◯ LOW [a,b]	-	The mean physical function was -9.5	MD **13.4 lower** (39.4 lower to 12.6 higher)	MID = 0.5 SD (SMD)
Serious adverse events at >3 months	163 (3 RCTs) follow up: mean 51 weeks	⨁◯◯◯ VERY LOW [a,c]	RD 0.00 (-0.04 to 0.04)	0 per 1,000	**0 fewer per 1,000** (40 fewer to 40 more) [d]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

[a.] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b.] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[c.] Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

[d.] Absolute effect calculated from risk difference due to zero events in at least one study arm

1.1.6.3 Ankle osteoarthritis

Table 36: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Pain (ankle osteoarthritis scale pain subscale, VAS, 0-100, high is poor, final value and change score) at ≤3 months	84 (2 RCTs) follow up: mean 12 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean pain was -10.6	MD **4.29 higher** (7.18 lower to 15.76 higher)	MID = 9.68 (0.5 x median baseline SD)
Pain (ankle osteoarthritis scale pain subscale, 0-100, high is poor, change score) at >3 months	28 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean pain was -9.4	MD **19.2 lower** (41.65 lower to 3.25 higher)	MID = 0.5 SD (SMD)
Physical function (ankle osteoarthritis scale disability subscale, 0-100, high is poor, change score) at ≤3 months	28 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean physical function was -7.4	MD **26.9 lower** (52.81 lower to 0.99 lower)	MID = 0.5 SD (SMD)
Physical function (ankle osteoarthritis scale disability subscale, 0-100, high is poor, change score) at >3 months	28 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean physical function was -16	MD **14.7 lower** (40.09 lower to 10.69 higher)	MID = 0.5 SD (SMD)
Osteoarthritis flare at >3 months	28 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,c]	RD 0.00 (-0.13 to 0.13)	0 per 1,000	**0 fewer per 1,000** (130 fewer to 130 more) [d]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.
Serious adverse events at ≤3 months	64 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a,b]	Peto OR 5.16 (0.09 to 286.65)	0 per 1,000	**30 more per 1,000** (50 fewer to 100 more) [d]	MID (precision) = OR 0.8-1.25.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Serious adverse events at >3 months	17 (1 RCT) follow up: 26 weeks	⨁◯◯◯ VERY LOW [a,c]	RD 0.0 (-0.2 to 0.2)	0 per 1,000	**0 fewer per 1,000** (200 fewer to 200 more) [d]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
d. Absolute effect calculated from risk difference due to zero events in at least one study arm

1.1.6.4 Toe osteoarthritis

Table 37: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Pain (VAS, 0-100, high is poor, final value) at ≤3 months	36 (1 RCT) follow up: 12 weeks	⨁◯◯◯ VERY LOW [a,b]	-	The mean pain was 36.8	MD **12.6 higher** (27.08 lower to 1.88 higher)	MID = 0.5 SD (SMD)
Physical function (AOFAS-hallux function subscale, 0-45, high is good, final value) at ≤3 months	34 (1 RCT) follow up: 12 weeks	⨁◯◯◯ VERY LOW [a,b]	-	The mean physical function was 31.2	MD **4.5 higher** (0.51 lower to 9.51 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 38: Clinical evidence summary: intra-articular hyaluronic acid (image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 69.8	MD **2.6 higher** (4.03 lower to 9.23 higher)	MID = 3
Quality of life (SF-36 general health subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 75.9	MD **1.1 higher** (5.13 lower to 7.33 higher)	MID = 2
Quality of life (SF-36 mental health subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 79.9	MD **3 higher** (1.37 lower to 7.37 higher)	MID = 3
Quality of life (SF-36 physical function subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 81.1	MD **1.2 higher** (5.16 lower to 7.56 higher)	MID = 3
Quality of life (SF-36 role emotional subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 90.4	MD **0.6 higher** (4.23 lower to 5.43 higher)	MID = 4

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Quality of life (SF-36 role physical subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 82.3	MD **7 higher** (1.7 higher to 12.3 higher)	MID = 3
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 86.2	MD **4 higher** (1.93 lower to 9.93 higher)	MID = 3
Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 63.7	MD **4.6 higher** (1 lower to 10.2 higher)	MID = 2
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 70.7	MD **4.9 lower** (11.71 lower to 1.91 higher)	MID = 3
Quality of life (SF-36 general health subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 76.8	MD **0.6 lower** (6.68 lower to 5.48 higher)	MID = 2
Quality of life (SF-36 mental health subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 81.5	MD **1.2 higher** (3.14 lower to 5.54 higher)	MID = 3
Quality of life (SF-36 physical function subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 81.1	MD **1.4 higher** (4.46 lower to 7.26 higher)	MID = 3

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Quality of life (SF-36 role emotional subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 91.5	MD **0.9 higher** (3.26 lower to 5.06 higher)	MID = 4
Quality of life (SF-36 role physical subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 83.4	MD **2.6 higher** (3.27 lower to 8.47 higher)	MID = 3
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 89.1	MD **1.8 lower** (7.85 lower to 4.25 higher)	MID = 3
Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 61.1	MD **6 higher** (0.08 higher to 11.92 higher)	MID = 2
Pain (foot health status questionnaire pain dimension, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was 72.5	MD **4.3 lower** (10.67 lower to 2.07 higher)	MID = 0.5 SD (SMD)
Pain (foot health status questionnaire pain dimension, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕⊕⊕ HIGH	-	The mean pain was 71.4	MD **3.4 lower** (9.81 lower to 3.01 higher)	MID = 0.5 SD (SMD)
Physical function (foot health status questionnaire foot function, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 12 weeks	⊕⊕⊕⊕ HIGH	-	The mean physical function was 83.4	MD **1.6 higher** (4.61 lower to 7.81 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (image guided)	
Physical function (foot health status questionnaire foot function, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕⊕⊕ HIGH	-	The mean physical function was 84	MD **0.2 higher** (6.08 lower to 6.48 higher)	MID = 0.5 SD (SMD)
Serious adverse events at >3 months	151 (1 RCT) follow up: 26 weeks	⊕⊕⊕◯ MODERATE [a]	Peto OR 7.49 (0.15 to 377.42)	0 per 1,000	**10 more per 1,000** (20 fewer to 50 more) [b]	MID (precision) = OR 0.8-1.25.

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b. Absolute effect calculated by risk difference due to zero events in at least one study arm

1.1.6.5 Shoulder osteoarthritis

Table 39: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Pain (VAS, 0-100, high is poor, mean difference) at >3 months	562 (2 RCTs) follow up: mean 26 weeks	⊕◯◯◯ VERY LOW [a,b]	-	-	MD **5.01 lower** (9.83 lower to 0.19 lower)	MID = 0.5 SD (SMD)
Serious adverse events at >3 months	300 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,b]	RR 2.20 (0.78 to 6.18)	33 per 1,000	**40 more per 1,000** (7 fewer to 173 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.1.6.6 Thumb osteoarthritis

Table 40: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Intervention and comparator	Outcome	Intervention results	Intervention group (n)	Comparator results	Comparator group (n)	Risk of bias
Meenagh 2004[310]	Intra-articular corticosteroids (non-image guided) compared to placebo	Pain (visual analogue scale, 0-100, change score) at ≤3 months	Median (IQR): 3.5 (-8.5 to 4.9)	20	Median (IQR): 23.3 (6.0 to 29.3)	20	High
Meenagh 2004[310]	Intra-articular corticosteroids (non-image guided) compared to placebo	Pain (visual analogue scale, 0-100, change score) at >3 months	Median (IQR): 0.0 (-12.5 to 2.3)	20	Median (IQR): 14.0 (-12.5 to 16.9)	20	High
Monfort 2015[323]	Intra-articular hyaluronic acid (non-image guided) compared to Intra-articular corticosteroids (non-image guided)	Physical function (functional index for hand osteoarthritis, 0-30, high is poor, change score) at ≤3 months	Median (IQR): -4 (-8 to -1)	48	Median (IQR): -1 (-3 to -1)	40	Very high

Study	Intervention and comparator	Outcome	Intervention results	Intervention group (n)	Comparator results	Comparator group (n)	Risk of bias
Monfort 2015[323]	Intra-articular hyaluronic acid (non-image guided) compared to Intra-articular corticosteroids (non-image guided)	Physical function (functional index for hand osteoarthritis, 0-30, high is poor, change score) at >3 months	Median (IQR): -3 (-8.7 to -1)	48	Median (IQR): -1 (-3 to -3)	40	Very high

Table 41: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months	88 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 1.7	MD **1.19 lower** (4.7 lower to 2.32 higher)	MID = 2
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months	88 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 1.7	MD **2.19 lower** (6.03 lower to 1.65 higher)	MID = 3
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >3 months	88 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 1.31	MD **2.97 lower** (6.96 lower to 1.02 higher)	MID = 2

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >3 months	88 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 2.17	MD **0.62 higher** (3.86 lower to 5.1 higher)	MID = 3
Pain (visual analogue scale, 0-10, high is poor, final value and change scores) at ≤3 months	180 (3 RCTs) follow up: mean 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean pain was 2.4	MD **0.35 higher** (0.29 lower to 0.99 higher)	MID = 0.85 (0.5 x median baseline SD)
Pain (visual analogue scale, 0-10, high is poor, final value and change scores) at >3 months	180 (3 RCTs) follow up: mean 35 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean pain was 3.01	MD **0.3 higher** (0.64 lower to 1.25 higher)	MID = 0.85 (0.5 x median baseline SD)
Physical function (Duruöz hand index, 0-90, high is poor, final value) at ≤3 months	40 (1 RCT) follow up: 12 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean physical function was 11.2	MD **11 higher** (4.12 higher to 17.88 higher)	MID = 0.5 SD (SMD)
Physical function (Duruöz hand index, 0-90, high is poor, final value) at >3 months	40 (1 RCT) follow up: 12 months	⊕◯◯◯ VERY LOW [a,b]	-	The mean physical function was 21.1	MD **3.8 higher** (3.97 lower to 11.57 higher)	MID = 0.5 SD (SMD)
Serious adverse events at >3 months	190 (4 RCTs) follow up: mean 33 weeks	⊕◯◯◯ VERY LOW [a,d,e]	RD 0.01 (-0.05 to 0.07)	21 per 1,000	**10 more per 1,000** (50 fewer to 70 more) [f]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)
e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
f. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 42: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Serious adverse events at >3 months	38 (1 RCT) follow up: 26 weeks	⨁◯◯◯ VERY LOW [a,b]	RD 0.0 (-0.1 to 0.1)	0 per 1,000	**0 fewer per 1,000** (100 fewer to 100 more) [c]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
c. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 43: Clinical evidence summary: intra-articular corticosteroids (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular corticosteroids (non-image guided)	
Serious adverse events at >3 months	40 (1 RCT) follow up: 26 weeks	⊕◯◯◯ VERY LOW [a,b]	RD 0.00 (-0.09 to 0.09)	0 per 1,000	**0 fewer per 1,000** (90 fewer to 90 more) [c]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

[a.] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b.] Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

[c.] Absolute effect calculated from risk difference due to zero events in at least 1 study arm

1.1.6.7 Finger osteoarthritis

Table 44: Clinical evidence summary: intra-articular corticosteroids (non-image guided) compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with intra-articular corticosteroids (non-image guided)	
Pain (AUSCAN pain subscale, 0-20, high is poor, final value) at ≤3 months	60 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was 7	MD **1.7 lower** (4.1 lower to 0.7 higher)	MID = 0.5 SD (SMD)
Physical function (AUSCAN function subscale, 0-36, high is poor, final value) at ≤3 months	60 (1 RCT) follow up: 12 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean physical function was 16.7	MD **4.4 lower** (9.36 lower to 0.56 higher)	MID = 0.5 SD (SMD)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.1.6.8 Temporomandibular joint osteoarthritis

Table 45: Clinical evidence summary: intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (image guided)	Risk difference with intra-articular hyaluronic acid (image guided)	
Pain (VAS, 0-10, high is poor, final value) at ≤3 months	50 (1 RCT) follow up: 6 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean pain was 4.51	MD **1.1 lower** (1.69 lower to 0.51 lower)	MID = 0.5 SD (SMD)

[a.] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b.] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 46: Clinical evidence summary: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
Pain (VAS, 0-100, high is poor, final value) at ≤3 months	40 (1 RCT) follow up: 4 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean pain was 42	MD **10 lower** (26.56 lower to 6.56 higher)	MID = 0.5 SD (SMD)
Pain (VAS, 0-100, high is poor, final value) at >3 months	40 (1 RCT) follow up: 26 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean pain was 31	MD **17 lower** (32.6 lower to 1.4 lower)	MID = 0.5 SD (SMD)

[a.] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intra-articular corticosteroids (non-image guided)	Risk difference with intra-articular hyaluronic acid (non-image guided)	
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs						

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

Three health economic studies with the relevant comparison were included in this review.[189, 314, 333] These are summarised in the health economic evidence profiles below (Table 47, Table 48 & Table 49) and the health economic evidence table in Appendix H.

1.1.7.2 Excluded studies

One economic study relating to this review question was identified but excluded due to a combination of limited applicability and methodological limitations.[112] This is listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 47: Health economic evidence profile: Hyaluronic acid plus usual care vs usual care alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Hermans 2018 [189] [Netherlands]	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Within-RCT analysis (Hermans 2013[188]) • Cost-utility analysis (QALYs) • Population: People age 18-65 with symptomatic knee osteoarthritis • Comparators: 1. Usual care 2. Hyaluronic acid injection + usual care Time horizon: 1 year	£375[(c)]	0.052 QALYs	£7,212 per QALY gained	Probability hyaluronic acid injections are cost effective (€20K threshold): 86% No further sensitivity analyses undertaken.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Study does not include all comparators. Dutch resource use data (2009-2010) and unit costs (2010) may not reflect current NHS practice.

(b) Within-trial analysis and so may not reflect full body of available evidence for this comparison.

(c) 2010 Euros converted to UK pounds.[344]. Cost components incorporated: Knee-related physician and paramedical therapist visits, use of aids (e.g. braces, inlay soles, home care use, knee-related surgery, and medication use. Medication costs included prescription fees pharmacists receive per prescription.

Table 48: Health economic evidence profile: Hyaluronic acid (Hylan G-F 20) versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost [(c)]	Incremental effects (QALYs)	Cost effectiveness	Uncertainty
Migliore 2019[314] (Italy)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic Markov model based on data taken from various studies • Cost-utility analysis (QALYs) • Population: People with knee or hip OA • Comparators: 1. Usual care (NSAIDs) 2. Usual care (paracetamol) 3. 1 x 6ml hylan G-F 20 in knee OA 4. 3 x 2ml hylan G-F 20 in knee OA 5. 1 x 2ml hylan G-F 20 in hip OA • Time horizon: 5 years	Knee OA (3−1): £605 (3−2): £1,047 (4−1): £832 (4−2): £1,273 (95% CI: NR; p=NR) Hip OA (5−1): -£221 (5−2): £177 (95% CI: NR; p=NR)	Knee OA (3−1): 0.086 (3−2): 0.351 (4−1): 0.086 (4−2): 0.351 (95% CI: NR; p=NR) Hip OA (5−1): 0.066 (5−2): 0.268 (95% CI: NR; p=NR)	Knee OA (3 versus 1): £7,016 per QALY gained (3 versus 2): £2,980 per QALY gained (4 versus 1): £9,646 per QALY gained (4 versus 2): £3,628 per QALY gained (95% CI: NR) Hip OA (5 versus 1): Intervention 5 dominates intervention 1 (5 versus 2): £661 per QALY gained	Probability of cost effectiveness (£20/30K threshold): Knee OA 3 versus 1: 54%/56% 3 versus 2: 74%/76% 4 versus 1: 53%/55% 4 versus 2: 73%/77% Hip OA 5 versus 1: 59%/59% 5 versus 2: 82%/82% Analysis of uncertainty: In one-way sensitivity analyses, the cost per QALY gained for all Hylan G-F 20 formulations remained below £16K except for three scenarios which were deemed unlikely or unrealistic by authors. Further detail provided in evidence table.

Abbreviations: CI= confidence interval; GI= gastrointestinal; NR= not reported; NSAIDs=non-steroidal anti-inflammatory drugs; OA= osteoarthritis; PE= pulmonary embolism; pa= probabilistic analysis; QALYs= quality-adjusted life years; THR: total hip arthroplasty; TKR= total knee arthroplasty

(a) Unclear what utilities were used (e.g., EQ-5D), how they were sourced and how they were applied in the model

(b) Effectiveness of Hylan based on one systematic review from 2010 identified during the clinical review but does not take into account the other 25 studies since 2010 listed in the clinical review. Time horizon may not be sufficiently long to capture all important relevant costs and outcomes. Expert opinion regarding usual care treatment options and Italian unit costs (2013) may not reflect current NHS practice. Productivity loss resulting from treatment failure were included in the cost of interventions and could not be disaggregated.

(c) 2013 Italian Euro converted to UK pounds[344]. Cost components incorporated: Cost of administering hylan G-F 20. Drug costs included NSAID and paracetamol costs and subsequent serious AE costs (cardiovascular, GI or PE). TKR/THR surgery costs were also included.

Table 49: Health economic evidence profile: Hyaluronans vs placebo – analyses conducted for original NICE guideline CG59

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost effectiveness	Uncertainty
CG59 economic analysis [333]	**Directly applicable**	**Potentially serious limitations** [(a)]	The analysis used RCTs included in the CG59 clinical review, and converted the WOMAC scores of each intervention and comparator to EQ-5D utilities using the mapping method by Barton (2008). Costs included were the NHS cost of the interventions, plus one GP appointment per injection. Three RCTs were used for this economic analysis, all using different hyaluronan products vs saline. As a brief summary: **Hyalgan** (Qvitsgaard 2006) [30]**:** - Hip OA. - 12 week duration. - 3 injections at fourteen days interval. **Artz** (Day 2004) [48]: - Knee OA. - 18 week duration. - 5 injections one week apart.	**Hyalgan vs saline:** = £183 [(b)] **Artz vs saline:** = £305 [(c)] **Durolane vs saline:** **= £216**	**Hyalgan vs saline:** = 0.0045 **Artz vs saline:** = 0.0031 **Durolane vs saline:** **= – 0.013**	**Hyalgan vs saline:** £41,009 per QALY gained **Artz vs saline:** £97,997 **per QALY gained** **Durolane vs saline:** **Durolane dominated by placebo**	To allow a more robust assessment it was assumed the effects of hyaluronans were maintained for 26 weeks. The incremental QALYs extrapolated to 26 weeks are: **Hyalgan vs saline:** = 0.0020 [(d)] This gives an ICER of £90,152 **Artz vs saline:** = 0.0054 This gives an ICER of £56,098 Also undertook threshold analyses; what would the QALY have to be to make the ICER equal £20,000: **Hyalgan vs saline** = 0.0092 **Artz vs saline** = 0.0153 Durolane vs saline **= 0.0108**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost effectiveness	Uncertainty
			Durolane (Altman 2004)[47]: - Knee OA. - 26 week duration. - A single injection.				

(a) The cost analysis only considers the direct costs of the intervention i.e. the cost of the injections plus the GP consultation to administer the injection. It does not consider adverse event costs, or decreased use of other medical resources because of increased well-being. The QALYs are mapped from WOMAC onto EQ-5D using a mapping function by Barton et al. .

*(b) For Hyalgan, it costs £185 for 5 injections, so the cost was worked out for 3 injections (£111), plus the costs of three physician visits (£24*3 = £72), making a total of £183 (£111+£72).*
Costs would increase if the injections were given by someone other than a GP (for example rheumatologist), and if additional follow up were needed.

(c) No UK cost data was found for Artz, so the cost of another low molecular weight hyaluronan was used that also requires 5 injections (Hyalgan). The incremental cost also includes 5 GP consultations.

(d) CG59 assumed that the effects of the hyaluronan were maintained for up to 26 weeks. In other words, it is assumed the utility at the last time point (in this case 12 weeks) remains at that level until week 26.

In the Qvistgaard paper, the extrapolated QALY gain at 26 weeks is lower than at 12 weeks. This is because at the end of the follow up period of 12 weeks, the benefit of Hyalgan is beginning to fall, and has a higher (meaning worse) WOMAC score than saline at this time point. Therefore when this is extrapolated to 26 weeks, this incremental loss of utility from 12 to 26 weeks has reduced the overall quality of life gain of Hyalgan compared with saline.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 50: UK costs of intraarticular injections

Drug	Product description	Cost	No. of injections	Total cost
Corticosteroid injections				
Prednisolone (Deltastab®)	25mg/1ml suspension	£6.87	1	£6.87
Methylprednisolone with lidocaine	10mg/1ml suspension	£3.94	1	£3.94
	40mg/1ml suspension	£3.89	1	£3.89
	20mg/2ml suspension	£7.06	1	£7.06
	80mg/2ml suspension	£7.01	1	£7.01
Triamcinolone hexacetonide	20mg/1ml suspension	£12.00	1	£12.00
Methylprednisolone (Depo-Medrone®)	40mg/1ml	£3.40	1	£3.40
	80mg/2ml	£6.14	1	£6.14
Triamcinolone acetoride				
(Adcortyl®)	10mg/1ml	£0.89	1	£0.89
(Kenalog®)	40mg/1ml	£1.49	1	£1.49
Dexamethasone	3.3mg/1ml	£2.32	1	£2.32
Hydrocortisone (Hydrocortistab®)	100mg/1ml	£2.12	1	£2.12
Hyaluronans				
Durolane®	Box containing 1 pre-fillled 3ml syringe	£199.17	1	£199.17
Euflexxa®	Box containing 3 pre-filled 2ml syringes (1 treatment)	£195.00	3	£195.00
Fermathron®	Box containing 1 pre-filled 20mg/2ml syringe	£39.00	3	£117.00
Orthovisc®	Box containing 1 pre-filled 2ml syringe	£65.00	3	£195.00
Ostenil®	Box containing 1 pre-filled 20mg/2ml syringe	£34.23	3	£102.69
Ostenil Plus®	Box containing 1 pre-filled 40mg/2ml syringe	£80.65	3	£241.95
RenehaVis®	Box containing 1 pre-filled dual chambered 1.4ml syringe	£112.00	3	£336.00
Syplasyn®	Box containing 1 pre-filled 20mg/2ml syringe	£35.50	3	£106.50
Synocrom®	Box containing 1 pre-filled 20mg/2ml syringe	£30.00	3	£90.00
Synocrom Mini	Box containing 1 pre-filled 10mg/1ml syringe	£22.50	1	£22.50
Synolis	Box containing 3 pre-filled 2ml syringes (1 treatment)	£205.00	3	£205.00
Synvisc (Hylan G-F20)	Box containing 3 pre-filled 2ml syringes (1 treatment)	£205.00	3	£205.00
Synvisc ONE (Hylan G-F20)	Box containing 1 pre-filled 6ml syringe	£205.00	1	£205.00

Source: NHS Drug Tariff, Nov 2019 [340];

Table 51: UK costs of appointment time

Attendance type	Description	Total cost
GP appointment	9.22 minute GP appointment	£34.00
Rheumatologist outpatient	Non-consultant led outpatient appointment	£92.00

Source: NHS Reference Costs 2017-18[340]

Table 52: UK costs of imaging to guide injection

Type	Description	Total cost
Ultrasound	Ultrasound Scan, Mobile or Intraoperative Procedures, with duration of less than 20 minutes	£71.00
Fluoroscopy	Contrast Fluoroscopy, Mobile or Intraoperative Procedures, with duration of less than 20 minutes	£120.00

Source: NHS Reference Costs 2017-18[340]

1.1.11 Other calculations

To further assess the cost effectiveness of intraarticular injections with corticosteroid two threshold analyses were undertaken to determine the QALY gain required them be considered cost effective at the £20,000 per QALY gained threshold.

For the hip osteoarthritis population, current practice is to administer the injection in secondary care under image guidance, typically fluroscopy. For the knee osteoarthritis and other joints, intraarticular injections are typically administered in primary care without image guidance. Therefore, if the injection is delivered in primary care, it was assumed that an intraarticular injection would be delivered during one standard GP appointment. If the injection is delievered in secondary care, it was assumed that this would require an outpatient appointment with a rheumatologist.

The QALY gain required using the lowest cost corticosteroid is presented below for each each scenario.

Table 53. Corticosteroid intraarticular injections

Drug name and dose	Total cost	QALY gained needed
Scenario 1: Image guidance in secondary care		
Trimcinolone acetonide 40mg x 1	£213	0.011
Scenario 2: No image guidance in primary care		
Trimcinolone acetonide 40mg x 1	£35	0.0018

1.1.12 Economic evidence statements

Economic

- One cost utility analysis reported hyaluronic acid injection plus usual care was cost effective compared with usual care alone (ICER: £375). This analysis was graded as partially applicable with potentially serious limitations.
- One cost utility analysis reported that hyaluronic acid injection was cost effective at a threshold of £20,000 per QALY gained versus non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol in knee and hip osteoarthritis. This analysis was graded as partially applicable with potentially serious limitations.

- One original cost-utility analysis reported that Hyalgan and Artz were not cost effective versus saline (ICERs: £41,009 and £97,997, respectively). It also reported that Durolane was dominated by saline. This analysis was graded as directly applicable with potentially serious limitations.

1.1.13 The committee's discussion and interpretation of the evidence

1.1.13.1. The outcomes that matter most

The critical outcomes were quality of life, pain and physical function. These were considered critical due to their importance to people with osteoarthritis. The Osteoarthritis Research Society International (OARSI) consider that pain and physical function were the most important outcomes for evaluating interventions. Quality of life gives a broader perspective on the person's wellbeing, allowing for examination of the biopsychosocial impact of interventions. Psychological distress, osteoarthritis flares and serious adverse events (as defined by the specific study) were included as the important outcomes.

The committee considered osteoarthritis flares to be important in the lived experience and management of osteoarthritis. However, these were also considered difficult to measure with no clear consensus on their definition. The Flares in OA OMERACT working group have proposed an initial definition and domains of OA flares through a consensus exercise; "it is a transient state, different from the usual state of the condition, with a duration of a few days, characterized by onset, worsening of pain, swelling, stiffness, impact on sleep, activity, functioning, and psychological aspects that can resolve spontaneously or lead to a need to adjust therapy.". However, this has been considered to have limitations and has not been widely adopted. Therefore, the committee included osteoarthritis flares as an outcome accepting any reasonable definition provided by any study.

Mortality was considered a composite of serious adverse events rather than as a discreet outcome and was categorised as important rather than critical. Osteoarthritis as a disease process is not considered to cause mortality by itself and mortality is an uncommon outcome from osteoarthritis interventions, including intra-articular injections.

There was evidence available for all critical outcomes (quality of life, pain and physical function). However, there was limited evidence available for important outcomes apart from serious adverse events. Osteoarthritis flares and psychological distress were not frequently reported with no information being available for the majority of sites of osteoarthritis.

1.1.13.2 The quality of the evidence

Ninety-two randomised controlled trials were included in the review. These investigated hip, knee, ankle, toe, shoulder, thumb, finger and temporomandibular joint osteoarthritis. The majority of the evidence related to people with knee osteoarthritis. No relevant studies were identified for intra-articular injections in foot, wrist and hand osteoarthritis. The comparisons studies included were:

- Hip osteoarthritis
  - Intra-articular hyaluronic acid (image guided) compared to placebo
  - Intra-articular corticosteroids (image guided) compared to placebo
  - Intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)
- Knee osteoarthritis
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo
  - Intra-articular corticosteroids (non-image guided) compared to placebo
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

  - Intra-articular stem cell therapy (image guided) compared to placebo
  - Intra-articular stem cell therapy (non-image guided) compared to placebo
  - Intra-articular stem cell therapy (non-image guided) compared to intra-articular hyaluronic acid (non-image guided)
- Ankle osteoarthritis
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo
- Toe osteoarthritis
  - Intra-articular hyaluronic acid (image guided) compared to placebo
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)
- Shoulder osteoarthritis
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo
- Thumb osteoarthritis
  - Intra-articular hyaluronic acid (non-image guided) compared to placebo
  - Intra-articular corticosteroids (non-image guided) compared to placebo
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)
- Finger osteoarthritis
  - Intra-articular corticosteroids (non-image guided) compared to placebo
- Temporomandibular joint osteoarthritis
  - Intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)
  - Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

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. Where outcomes included inconsistent results, these could not be explained by subgroup analysis. In general, evidence quality was poorer for important outcomes (osteoarthritis 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 conducted in people with knee osteoarthritis, the analyses were based on data from a small number of participants.

Intra-articular hyaluronic acid compared to intra-articular corticosteroids

This comparison was reported in studies including people with hip, knee, toe, thumb and temporomandibular joint osteoarthritis. Both image guided and non-image guided studies were reported for people with temporomandibular joint osteoarthritis. Otherwise, image guided studies were reported for people with hip osteoarthritis, while non-image guided studies were reported for people with knee, toe and thumb osteoarthritis.

- For people with hip osteoarthritis, outcomes were reported in 3 studies. The number of participants in each outcome ranged from 65 to 312 people. Outcomes ranged from moderate to very low quality with the majority being of low quality. Outcomes were commonly downgraded due to risk of bias and imprecision.
- For people with knee osteoarthritis, outcomes were reported in 15 studies. The number of participants in each outcome ranged from 126 to 1586 people. Outcomes were of very low quality being downgraded for risk of bias, imprecision and inconsistency where heterogeneity was not resolved by subgroup analysis.

- For people with toe osteoarthritis, outcomes were reported in 1 study. 2 outcomes were reported which included data from 34 and 36 people respectively. Outcomes were of very low quality due to risk of bias and imprecision.
- For people with thumb osteoarthritis, outcomes were reported in 5 studies. Outcomes from 4 studies were able to be included in the GRADE analysis. The number of participants ranged from 40 to 190 people. Outcomes were of very low quality being downgraded for risk of bias, imprecision and inconsistency where heterogeneity was not resolved by subgroup analysis.
- For people with temporomandibular joint osteoarthritis, 1 study reported an image guided comparison while 1 study reported a non-image guided comparison. For the image guided comparison 1 outcome was reported which included 50 participants. This was of very low quality due to risk of bias and imprecision. For the non-image guided comparison, 2 outcomes were reported and included 50 participants. The outcomes were of low quality due to risk of bias and imprecision.

Intra-articular hyaluronic acid compared to placebo

This comparison was reported in studies including people with hip, knee, ankle, toe, shoulder, and thumb osteoarthritis. The procedures were image guided for studies including people with hip and toe osteoarthritis, and non-image guided for those including people with knee, ankle, shoulder and thumb osteoarthritis. The placebo injection used were either 0.9% saline or local anaesthetic, that the committee agreed were both appropriate placebos to use but noted that local anaesthetic may have an initial effect on reducing pain that may affect results.

- For people with hip osteoarthritis, outcomes were reported in 5 included studies. The number of participants in each outcome ranged from 65 to 312. Outcomes ranged between moderate and very low quality, with the majority being of low quality. Outcomes were commonly downgraded for risk of bias and imprecision.
- For people with knee osteoarthritis, outcomes were reported in 35 included studies. The number of participants in each outcome ranged from 113 to 6503. Outcomes ranged between high and very low quality, with the majority being of moderate quality. Outcomes were commonly downgraded for risk of bias. 7 outcomes were downgraded for inconsistency where heterogeneity could not be resolved by subgroup analysis or where there were a conflicting number of events in different studies (with zero events in at least one arm of one study).
- For people with ankle osteoarthritis, outcomes were reported in 3 included studies. The number of participants in each outcome ranged from 17 to 84. Outcomes ranged from low to very low quality, with the majority being of very low quality. Outcomes were commonly downgraded due to risk of bias and imprecision.
- For people with toe osteoarthritis, outcomes were reported in 1 included study. Each outcome included 151 participants. Outcomes ranged from high to low quality with outcomes being downgraded due to imprecision.
- For people with shoulder osteoarthritis, outcomes were reported in 2 included studies. 2 The outcomes were of very low quality being downgraded for risk of bias and imprecision.
- For people with thumb osteoarthritis, outcomes were reported in 1 included study. 1 outcome was reported which included 38 participants and was of very low quality due to risk of bias and imprecision.

Intra-articular corticosteroids compared to placebo

This comparison was reported in studies including people with hip, knee, thumb and finger osteoarthritis. The intra-articular injections were delivered with image guidance for people with hip osteoarthritis and without image guidance for people with knee and thumb

osteoarthritis. The placebo injection used were either 0.9% saline or local anaesthetic, that the committee agreed were both appropriate placebos to use but noted that local anaesthetic may have an initial effect on reducing pain that may affect results.

- For people with hip osteoarthritis, outcomes were reported in 4 included studies. The number of participants in each outcome ranged from 52 to 132 people. Outcomes ranged from low to very low quality. Outcomes were commonly downgraded due to risk of bias and imprecision. 3 outcomes were downgraded due to inconsistency, where heterogeneity was not resolved by subgroup analysis or where there were a conflicting number of events in different studies (with zero events in at least one arm of one study).
- For people with knee osteoarthritis, outcomes were reported in 9 included studies. The number of participants in each outcome ranged from 190 to 654 people. Outcomes ranged from moderate to very low quality, with the majority being of low quality. Outcomes were commonly downgraded due to risk of bias and inconsistency, with 6 outcomes having heterogeneity that was not resolved by subgroup analysis or where there were a conflicting number of events in different studies (with zero events in at least one arm of one study). Imprecision was seen in 4 outcomes. Indirectness was seen in one outcome where the outcome reported included a scale that was not directly related to the outcome.
- For people with thumb osteoarthritis, outcomes were reported in 2 included studies. 1 reported value could be included in a GRADE analysis. This study reported 1 outcome including 38 participants. The quality was very low being downgraded for risk of bias and imprecision.
- For people with finger osteoarthritis, outcomes were reported in 1 included study with 60 participants. 2 outcomes were included in the analysis which were both of moderate quality. The quality was downgraded due to imprecision.

Intra-articular stem cells compared to intra-articular hyaluronic acid

This comparison was reported for people with knee osteoarthritis only. This was investigated in 3 studies without image guidance with the number of participants in each outcome ranging from 27 to 114 people. The quality ranged from moderate to very low, with the majority of evidence being of moderate quality. Outcomes were commonly downgraded for imprecision.

Intra-articular stem cells compared to intra-articular corticosteroids

This comparison was reported for people with knee osteoarthritis only. This was investigated in 1 study without image guidance with 31 people being included. The quality ranged from moderate to low. Outcomes were downgraded for imprecision.

Intra-articular stem cells compared to placebo

This comparison was reported for people with knee osteoarthritis only. Image guided therapy was reported in 2 studies, while non-image guided therapy was reported in 4 studies. The number of participants ranged from 20 to 44 people and 41 to 163 people respectively.

- For image-guided therapy, studies reported 2 outcomes where the quality was moderate and very low respectively. Outcomes were downgraded for imprecision and risk of bias.
- For non-image guided therapy, the quality ranged from low to very low, with the majority of evidence being of low quality. Outcomes were commonly downgraded for risk of bias and imprecision.

1.1.13.3 Benefits and harms

Key uncertainties

The committee noted that there was sufficient evidence to show an effect of intra-articular corticosteroids injections for people with knee osteoarthritis, but insufficient evidence for other sites of osteoarthritis (although evidence for hip osteoarthritis was positive, more

evidence would be required to be certain). The committee made recommendations about the use of intra-articular hyaluronic acid and corticosteroids using the evidence and supported with their clinical knowledge when evidence was not present. Based on this, the committee recommended further research investigating the effects on other osteoarthritis joint sites (see research recommendation 1).

The committee agreed that there were limitations in using randomised controlled trials for understanding the harms and adverse events associated with intra-articular injections. The committee were aware of data which showed that intra-articular injections were associated with a 0.08% risk of septic arthritis, which was not seen in this review (ref: Peterson SK, Hansen IMJ, Andreasen RA. Low frequency of septic arthritis after arthrocentesis and intra-articular glucocorticoid injection. Scandinavian Journal of Rheumatology. 2019; 48:5:393-397. DOI: 10.1080/03009742.2019.1584329).

Separately, there is also evidence to show an increased risk of periprosthetic joint infection if joint replacement is performed in the months following intra-articular corticosteroid injection of a native joint. This contraindication should also be considered when referring for a surgical opinion at the same time as other therapeutic interventions. The committee considered these risks while making recommendations.

There is a current uncertainty regarding the long term use of intra-articular injections in people with osteoarthritis. Of particular note was the risk of repeat corticosteroid injections, which may lead to increased degeneration of the joint affecting whether joint replacement surgery could be performed. This review was not designed to investigate this in its entirety but the committee note the importance to consider this in the future.

There was no randomised controlled trial evidence comparing image-guided injections to non-image guided injections of any of the pharmacological agents. Image-guided injections may be essential for some deep joint sites and small joints with complex anatomy (for example: hip osteoarthritis and the tarsal joints) to ensure that the pharmacological agent will enter the joint space. The committee noted that there was observational trial evidence showing that there may be benefit for more superficial joint sites (for example: knee osteoarthritis). While no recommendation can be made from this information, the committee recommended that this is factored into future trials where this is standard practice thereby examining efficacy and cost effectiveness.

Intra-articular hyaluronic acid compared to corticosteroids

While examining the evidence, the committee once again noted the disparity in evidence for all joint sites of osteoarthritis, with the majority of evidence being for people with knee osteoarthritis. For people with knee osteoarthritis, the majority of evidence showed no difference between the two interventions at less than and more than 3 months. This was with the exception of quality of life at less than 3 months and pain and physical function at more than 3 months, where a clinically important benefit of hyaluronic acid was seen. These benefits were based on very low-quality evidence from a small number of studies.

The evidence for other joint sites of osteoarthritis showed different results. For hip osteoarthritis there was evidence of no clinically important difference in critical outcomes and serious adverse events, while there was a clinically important harm of hyaluronic acid in osteoarthritis flares. In comparison, the evidence for toe osteoarthritis showed clinically important benefits of hyaluronic acid for pain and physical function at less than 3 months. The evidence for thumb osteoarthritis showed a clinically important harm for the one quality of life outcome (specifically the SF-36 mental component) and physical function at less than 3 months but otherwise no clinically important difference for other quality of life outcomes, pain, physical function and serious adverse events. In temporomandibular joint osteoarthritis there was evidence of a clinically important benefit of hyaluronic acid at less than 3 months when given by image guidance while there was evidence of no clinically important difference when not given by image guidance.

The committee agreed that it was difficult to interpret these results due to the size of included studies and the inconsistency of results when compared to placebo controlled trials. The committee agreed that there was no consistent signal of benefit or harm that favoured either intra-articular hyaluronic acid or intra-articular corticosteroids based on this evidence.

Intra-articular hyaluronic acid compared to placebo

The majority of evidence for this comparison related to people with knee osteoarthritis and showed no clinically important difference in any of the critical or important outcomes at less than or more than three months, with the exception of physical function at less than three months, where the evidence was mixed.

These findings were similar for other strata, although the evidence for quality of life was mixed in people with toe osteoarthritis (where there was evidence of clinically important benefits and harms). The committee noted the evidence of clinically important harm of osteoarthritis flares in people with hip osteoarthritis at less than three months.

The use of image guidance varied between studies. The evidence for knee, shoulder and thumb osteoarthritis was conducted without image guidance, while only image guided evidence was available for hip osteoarthritis. The studies including people with toe osteoarthritis used both image guided and non-image guided injections.

Intra-articular corticosteroids compared to placebo

The committee discussed the evidence for intra-corticosteroids compared to placebo in people with osteoarthritis and noted that while intra-articular corticosteroid injections are widely used for the management of osteoarthritis related symptoms at many sites, the evidence identified for this review was limited to people with knee and hip osteoarthritis.

In people with knee osteoarthritis there was very low-quality evidence of short-term benefit for pain but no clinically important difference in physical function or quality of life at less than three months. In people with hip osteoarthritis, very low-quality evidence showed short-term benefit for physical function and quality of life, but the evidence for the effect on pain was mixed. There was no clinically important difference in any critical outcomes (pain, physical function or quality of life) in people with knee osteoarthritis at more than three months.

In relation to important outcomes, there was no clinically important difference between intra-articular corticosteroids and placebo for flare-ups or serious adverse events in people with hip, knee and thumb osteoarthritis.

Intra-articular stem cells compared to hyaluronic acid

Evidence for the use of intra-articular stem cells was identified for the knee osteoarthritis stratum only. There was evidence of a clinically important benefit of stem cells for the physical component summary of quality of life (as measured by the SF-12) at more than 3 months while there was evidence of no clinically important difference in both the physical and mental component summary at less than 3 months and evidence of a clinically important harm of stem cells in the mental component summary at more than 3 months (all based on 1 study with each outcome being of moderate quality). There was evidence of a clinically important benefit of stem cells for pain at more than 3 months (in 1 outcome based on 2 studies of moderate quality). There was evidence of no clinically important difference in physical function and serious adverse events at more than 3 months.

Intra-articular stem cells compared to corticosteroids

Evidence for the use of intra-articular stem cells was identified for the knee osteoarthritis stratum only. There was evidence of no clinically important difference in quality of life, pain and physical function at greater than 3 months, based on 1 study.

Intra-articular stem cells compared to placebo

Evidence for the use of intra-articular stem cells was identified for the knee osteoarthritis stratum only. There was evidence of a clinically important benefit for pain (in 1 outcome based on 2 studies of moderate quality) and physical function (in 1 outcome based on 1 study of low quality) at less than 3 months when given without image guidance. There was evidence of a clinically important benefit for pain at more than 3 months (in 1 outcome based on 1 study of moderate quality) when given by image guidance, with evidence of no clinically important difference when given without image guidance (in 1 outcome based on 2 studies of moderate quality). There was evidence of no clinically important difference in physical function at more than 3 months when given without image guidance (in 1 outcome based on 1 study of low quality). There was evidence of no clinically important difference in serious adverse events at more than 3 months (in 2 outcomes based on 5 studies of low quality) with no adverse events being reported in any study.

Weighing up the clinical benefits and harms

The committee agreed that there was insufficient evidence to determine the effectiveness of hyaluronic acid injections in people with ankle, foot, toe, shoulder, elbow, wrist, hand, thumb, finger and temporomandibular joint osteoarthritis due to relatively small and often singular studies for individual outcomes. The committee also agreed that evidence for hyaluronic acid injections in people with knee or hip osteoarthritis was limited due to there being no clear signal of benefit, small sample sizes in the majority of studies and imprecision. The committee concluded that the evidence for people with knee or hip osteoarthritis showed an absence of benefit, while there was an absence of evidence for people with ankle, foot, toe, shoulder, elbow, wrist, hand, thumb, finger and temporomandibular joint osteoarthritis. Based on both of these factors, the committee agreed to recommend against the use of hyaluronic acid injections.

The committee concluded that intra-articular corticosteroids may offer short-term benefit in relieving symptoms of knee and hip osteoarthritis in adults. Therefore, they recommended that intra-articular corticosteroids should be considered in people with osteoarthritis for short term relief of symptoms when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise. The length of time was discussed by the committee. The evidence from the included studies reported benefits in pain and physical function on average at 10 weeks. The committee discussed the findings in a Cochrane review investigating the use of corticosteroids[227] which had indicated that benefits may be seen between 2 and 6 weeks. Therefore, the committee agreed that the benefits may be seen between 2 and 10 weeks.

Despite the absence of high quality evidence for critical outcomes outside of people with hip, knee and finger osteoarthritis, the committee agreed that intra-articular corticosteroids could be considered for short-term management of symptoms in other joints with osteoarthritis. The committee agreed that there is widespread offer of corticosteroid injections for people with persistent osteoarthritis symptoms in the NHS and that there was no evidence of increased risk of adverse events associated with their use and the pathobiological mechanisms were anticipated to be the same. Due to the limited high quality evidence, the committee agreed that more research into the effectiveness of intra-articular corticosteroids for the management of osteoarthritis in joint sites other than the knee was required (see research recommendations).

The committee agreed that there was insufficient evidence to determine the effectiveness of intra-articular stem cells in people with osteoarthritis due to the limited number of studies and small number of participants. However, given the growing use of intra-articular stem cells in the management of people with osteoarthritis and some signal suggesting benefit in critical outcomes in people with knee osteoarthritis, the committee agreed that further research in this area is required (see research recommendations).

1.1.13.4 Cost effectiveness and resource use

Three published economic evaluations assessing the cost effectiveness of hyaluronic acid intraarticular injections were included in this review. One cost utility analysis assessed intraarticular injections with hyaluronic acid plus usual care compared to usual care alone in people with knee osteoarthritis. This analysis found intraarticular injections in addition to usual care to be cost effective compared to usual care alone (ICER: £7,212 per QALY gained). This was assessed as partially applicable with potentially serious limitations.

One cost utility analysis compared hyaluronic acid in knee and hip OA versus NSAIDs and paracetamol separately. Two dosage regimens were analyses in the knee osteoarthritis population: 1x6ml hyaluronic acid and 3x2ml hyaluronic acid. The study reported that hyaluronic acid was cost effective versus both comparators in people with knee osteoarthritis, with costs per QALY gained of £7,016 and £2,980 with 1x6ml hyaluronic acid versus NSAIDs and paracetamol, respectively, and £9,646 and £3,628 with 3x2ml hyaluronic acid versus NSAIDs and paracetamol, respectively. In people with hip osteoarthritis, 1x2ml hyaluronic acid dominated NSAIDs, being less costly and more effective overall, while the cost per QALY gained versus paracetamol was reported as £661. This study was assessed as partially applicable with potentially serious limitations.

An original economic analysis was undertaken in CG59 (first NICE osteoarthritis guideline) that was also presented to the committee. This analysis used data from three RCTs comparing hyaluronic acid to placebo in people with knee osteoarthritis and converted the WOMAC scores in each arm to EQ-5D utilities using the mapping method by Barton (2008). The analysis assumed that the effects of hyaluronic acid were maintained for up to 26 weeks. These analyses suggest that intraarticular injections with hyaluronic acid are not cost effective compared to placebo.

No published economic evidence was identified comparing intraarticular corticosteroid injections with placebo or usual care or comparing intraarticular injections with hyaluronic acid to corticosteroid.

Unit costs of corticosteroids and hyaluronans were also presented to the committee alongside the costs of an appointment to administer the injection(s) and imaging with either ultrasound or fluoroscopy if necessary.

The committee noted the differing results of the identified economic analyses. Upon comparison, it was observed that there was not much difference in the incremental cost estimates between the analyses and that these were in line with the range of unit costs presented, but that there were very different incremental QALY estimates. It was noted that one study reports EQ-5D directly, and the other uses indirect estimates of EQ-5D mapped from WOMAC. Although mapping isn't likely to be as precise as direct reporting, the difference in QALY estimates is so large that the committee did not consider that this was likely to be the reason.

The committee noted that the clinical review does not suggest that there is benefit of hyaluronic acid injections when compared to placebo for outcomes of quality of life, or for pain and physical function which are likely to affect people's quality of life, for any joint affected by osteoarthritis. Therefore, the committee considered the QALY estimates from the published cost-utility analysis were overestimated due to contextual effects and did not put much weight on this evidence.

Overall, given the high cost of hyaluronic acid intraarticular injections and the lack of evidence to suggest there is a clinical benefit to patients, the committee did not consider that intraarticular injections with hyaluronic acid would be a cost-effective use of NHS resources and therefore made a do not use recommendation.

The committee noted that the cost of corticosteroids is much lower than hyaluronic acid. The committee noted that the most commonly prescribed corticosteroids for intraarticular

injections are methylprednisolone and triamcinolone acetonide at a dose of 40mg/ml, the two lowest cost steroids currently available. The committee also noted that these are most commonly undertaken in primary care provided that image guidance is not routinely required (primarily needed in the hip), in which case a person would be referred to specialist centers or secondary care. Due to the lower cost of corticosteroids, a lower QALY gain would be required for these to be cost effective. It was noted that due to the need for image guidance in those with hip OA, there is a greater cost associated with corticosteroid intraarticular injections. Therefore, two threshold analyses were therefore undertaken to determine the QALY gain required for intra-articular corticosteroid injections to be cost effective: 1) corticosteroid injection in primary care with no image guidance, and 2) corticosteroid injection in secondary care with image guidance.

The results of the first of these analyses estimate that a QALY gain of 0.0018 would be required in those who receive a corticosteroid injection in primary care without image guidance. The committee noted that one study included in the clinical review suggests that for knee osteoarthritis non-image guided intraarticular injections with corticosteroid there is some benefit in quality of life according to the KOOS score at 3 months, although this wasn't found to have a clinically important benefit. The clinical evidence also suggests that there is a clinically important benefit in pain associated with corticosteroid injections compared to placebo at 3 months. Given that the QALY gain required is so small, the committee considered that this is likely to be met and that intraarticular corticosteroid injections are likely to be cost effective.

The results of the second of the analyses suggest that a QALY gain of 0.011 in those who receive a corticosteroid injection in secondary care with image guidance (primarily hip osteoarthritis). The committee noted that the clinical evidence suggests that there is a clinically important benefit in quality of life in both physical function and social function as measured by SF-36 at 3 months. The clinical evidence also suggests that there is a reduction in pain and improvement in physical function at 3 months. Given that the QALY gain required for corticosteroid injections to be cost effective is small, the committee considered that this is likely to be cost effective in the short term.

Given the lack of clinical evidence for the use of corticosteroid injections in other joints, the committee agreed that the evidence for knee and hip osteoarthritis is likely to be similar for the other joints. Furthermore, given that there was limited evidence of benefit in the longer term, the committee made a recommendation to consider intraarticular injections with corticosteroid for the short-term relief of osteoarthritis symptoms. The committee noted that intraarticular injections with corticosteroids is currently common practice, and therefore do not anticipate a change in practice or a substantial resource impact as a result of this recommendation.

1.1.13.5 Other factors the committee took into account

In the randomised controlled studies included, the majority of studies were in the short term (less than 3 months) despite the long-term duration of disease management required for people with osteoarthritis. This review did not included non-randomised evidence, including embedded cohort studies, which may include more evidence of the long term effects of intra-articular injections. The committee considered this while interpreting the evidence.

The committee noted that the research identified does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone. With this in mind the committee sub-grouped their research recommendation by these protected

characteristics where appropriate while suggesting that people from each group should be included in the research to ensure that it is applicable to the entire population

1.1.14 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.10 and 1.4.11 and the research recommendations for intra-articular corticosteroids and intra-articular stem cell injections. Other evidence supporting these recommendations can be found in evidence review J.

1.1.15 References

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Appendices

Appendix A – Review protocols

Review protocol for the clinical and cost-effectiveness of intra-articular injections with corticosteroids or hyaluronic acid for the management of osteoarthritis

Field	Content
PROSPERO registration number	N/A
Review title	Intra-articular injections with corticosteroids or hyaluronic acid for the management of osteoarthritis?
Review question	What is the clinical and cost-effectiveness of intra-articular injections for the management of osteoarthritis?
Objective	To evaluate the clinical and cost-effectiveness of intra-articular injections of corticosteroids or hyaluronic acid for the management of osteoarthritis.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded

	Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Osteoarthritis in adults (defined as a clinical diagnosis of osteoarthritis with or without imaging)
Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Stratify by site of osteoarthritis: • Hip • Knee • Ankle • Foot • Toe • Shoulder • Elbow • Wrist • Hand • Thumb • Finger • Temporomandibular joint (TMJ)

	To note that where evidence for other rare forms of osteoarthritis is identified the committee will stratify into the most appropriate group. Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies in people with meniscal injury without osteoarthritis • Studies with an unclear population (e,g, type of arthritis, proportion of participants with osteoarthritis) • Spinal osteoarthritis
Intervention/Exposure/Test	Stratify interventions by image guided versus non-image guided • Intra-articular hyaluronic acid (of any formulation) • Intra-articular corticosteroids (of any type) • Intra-articular stem cell therapy
Comparator/Reference standard/Confounding factors	• Compared to each other • Placebo
Types of study to be included	• Systematic reviews of RCTs • Parallel RCTs • Cross-over RCTs will be considered if insufficient evidence is available from parallel RCTs* Non-randomised studies will be excluded. *Insufficient evidence defined as evidence that is insufficient to inform recommendations (either quality or quantity).
Other exclusion criteria	• Non-English language studies • Non-randomised/observational studies

	• Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	N/A
Primary outcomes (critical outcomes)	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] *The COMET database was searched and several core outcome sets were identified for specific sites of osteoarthritis (including hand, knee and hip). The committee took these into account when defining outcomes:* https://onlinelibrary.wiley.com/doi/full/10.1002/acr.22868 https://www.ncbi.nlm.nih.gov/pubmed/26136489 https://www.ncbi.nlm.nih.gov/pubmed/30647185
Secondary outcomes (important outcomes)	• Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [validated patient-reported outcomes, continuous data prioritised] • Serious adverse events
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For intervention reviews the following checklists will be used according to the study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

	• Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified. Heterogeneity between studies in the effect measures will be assessed using the I^2 statistic and visual inspection. We will consider an I^2 value great than 50% as indicative of substantial heterogeneity. If significant heterogeneity is identified during meta-analysis then subgroup analysis, using subgroups predefined by the GC, will take place. If this does not explain the heterogeneity, the results will be presented using a random-effects model.
Analysis of sub-groups	Subgroup analysis to be conducted if heterogeneity in the meta-analysis is present: • Diagnosis with or without imaging (indicative of severity)

	• Multimorbidity (high versus low morbidity score; as defined by study, measured by validated instruments e.g. Charlson Comorbidity Index) • Age (≤/> 75 years)		
Type and method of review	☒	Intervention	
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	23/08/2019		
Anticipated completion date	25/08/2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☐
	Piloting of the study selection process	☐	☐
	Formal screening of search results	☐	☐

	against eligibility criteria		
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Rebecca Boffa [Senior systematic reviewer] George Wood [Systematic reviewer] Emma Cowles [Senior health economist] Joseph Runicles [Information specialist] Amber Hernaman [Project manager]		

Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10127	
Other registration details		
Reference/URL for published protocol		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Adults; Corticosteroids; Hyaluronic acid; Intra-articular; Injectable; Intervention; Osteoarthritis; Pharmacological	
Details of existing review of same topic by same authors		
Current review status	☒	Ongoing

	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

Table 54: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2005 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[335] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2005 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as ‘Not applicable’.
- Studies published before 2005 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- Intra-articular injections with corticosteroids or hyaluronic acid for the management of osteoarthritis?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[334]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using an Osteoarthritis population. All results were then sifted for each question. Search filters were applied to the search where appropriate.

Table 55: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 17 November 2021	Randomised controlled trials Systematic review studies Exclusions (animals studies, letters, comments)
Embase (OVID)	1974 – 17 November 2021	Randomised controlled trials Systematic review studies Exclusions (animals studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 11 of 12 CENTRAL to 2021 Issue 11 of 12	None

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	randomized controlled trial.pt.
28.	controlled clinical trial.pt.
29.	randomi#ed.ti,ab.
30.	placebo.ab.
31.	randomly.ti,ab.
32.	Clinical Trials as topic.sh.
33.	trial.ti.
34.	or/27-33
35.	Meta-Analysis/
36.	exp Meta-Analysis as Topic/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	26 and (34 or 45)

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.

12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 not English language
25.	random*.ti,ab.
26.	factorial*.ti,ab.
27.	(crossover* or cross over*).ti,ab.
28.	((doubl* or singl*) adj blind*).ti,ab.
29.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
30.	crossover procedure/
31.	single blind procedure/
32.	randomized controlled trial/
33.	double blind procedure/
34.	or/25-33
35.	systematic review/
36.	meta-analysis/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	24 and (34 or 45)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Osteoarthritis] explode all trees
#2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab
#3.	(degenerative near/2 arthritis):ti,ab
#4.	coxarthrosis:ti,ab
#5.	gonarthrosis:ti,ab

#6.	(or #1-#5)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updates after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies. Searches for quality of life studies were run for general information.

Table 56: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Embase	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16

18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.

57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.

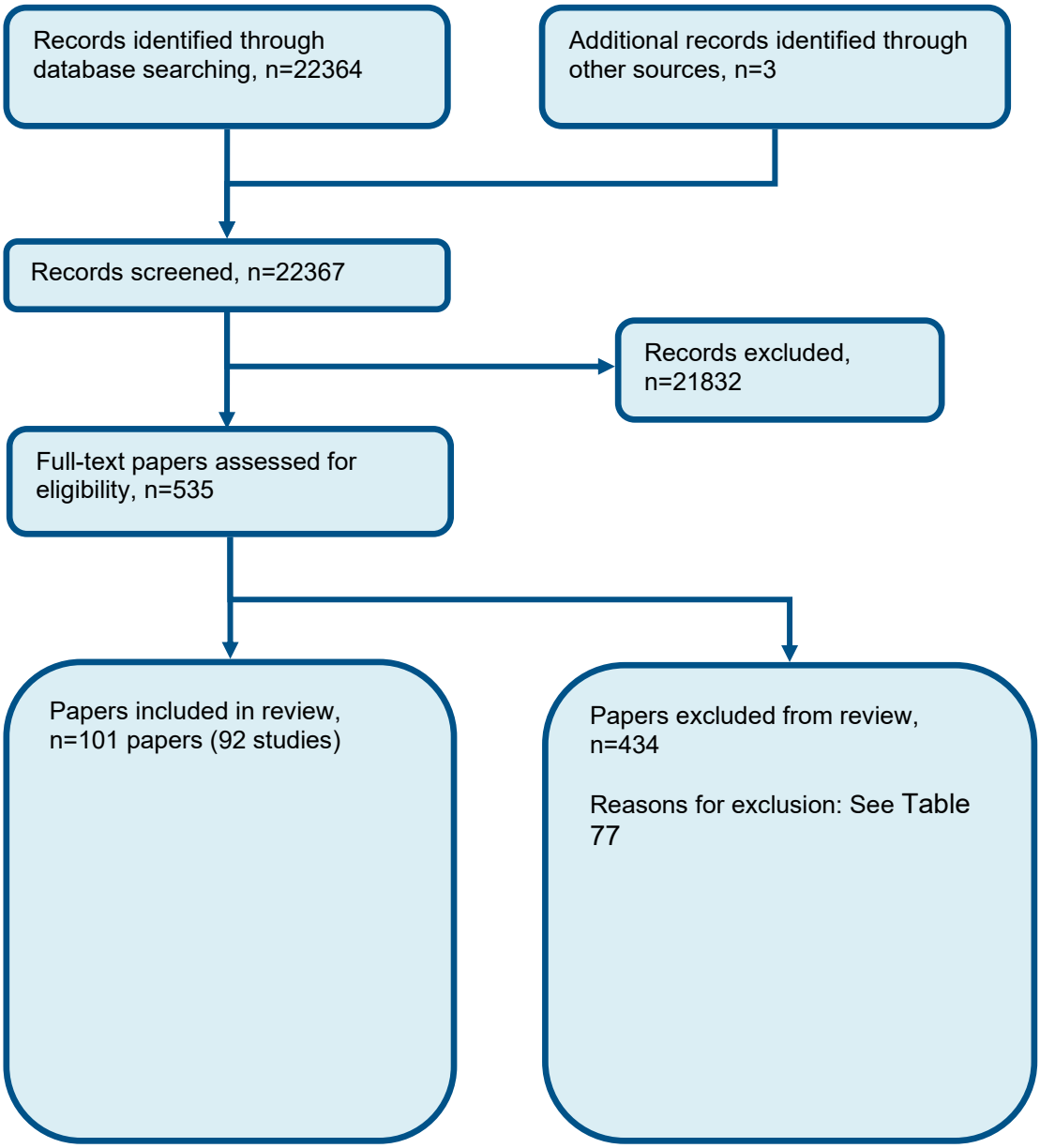
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	"quality of life index"/
41.	short form 12/ or short form 20/ or short form 36/ or short form 8/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/39-59
61.	24 and (38 or 60)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Osteoarthritis EXPLODE ALL TREES
#2.	((osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*))
#3.	((degenerative adj2 arthritis))
#4.	(coxarthrosis)
#5.	(gonarthrosis)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(#6) IN NHSEED
#8.	(#6) IN HTA

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of the clinical and cost-effectiveness of intra-articular injections for the management of osteoarthritis



Appendix D – Effectiveness evidence

Study (subsidiary papers)	Altman 1998[11] (Punzi 2001[381])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=495)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinically diagnosed osteoarthritis according to the American College of Rheumatology criteria with knee radiography showing at least 1 osteophyte and a KL grade 2 or 3.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men or women, ≥40 years old, with OA of knee (American College of Rheumatology criteria), with knee pain for at least 1 year, knee pain severity ≥20mm (100mm visual analogue scale) on a 50 foot walk, pain ≥20mm on ≥1 items of the WOMAC pain subscale, "moderate" or "marked" pain on a 6 point categorical scale, a knee radiography showing ≥1 osteophyte and a Kellgren-Lawrence grade 2 or 3, with no prior IA HA within one year and no other intraarticular injections including corticosteroids for the preceding 3 months. The more severely affected knee was selected for treatment in the presence of bilateral osteoarthritis.
Exclusion criteria	Not falling within the inclusion criteria
Recruitment/selection of patients	Consecutive patients from 15 participating academic and private practice centers
Age, gender and ethnicity	Age - Mean (SD): 63.6 (10.1). Gender (M:F): 114:189. Ethnicity: Majority Caucasian (~80%), minority black (~15%) and other (~5%).
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Moderate Symptom duration: Not explicitly stated
Indirectness of population	No indirectness
Interventions	(n=164) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Subcutaneous lidocaine local anaesthesia, aspiration of synovial

	fluid (if present), and then 2mL (20mg) hyaluronic acid in a saline vehicle in the study knee at baseline and then once weekly for a total of 5 injections. Synovial fluid was removed at each of the 5 visits. They also received and oral placebo twice daily for 26 weeks (a third intervention group was present for naproxen).. Duration 26 weeks. Concurrent medication/care: 500mg acetaminophen tablets were permitted up to 4000mg/day for escape analgesia as needed for knee pain. People were instructed not to take products containing aspirin, NSAIDs, other non-narcotic or narcotic analgesics, or corticosteroids.. Indirectness: No indirectness (n=168) Intervention 2: Placebo. Subcutaneous lidocaine local anaesthesia, aspiration of synovial fluid (if present), and then 2mL of saline vehicle (without HA) IA in the study knee at baseline and then once weekly for a total of 5 injections. Synovial fluid was removed (if present) at each of the 5 visits. The group also received an oral placebo twice daily for 26 weeks.. Duration 26 weeks. Concurrent medication/care: 500mg acetaminophen tablets were permitted up to 4000mg/day for escape analgesia as needed for knee pain. People were instructed not to take products containing aspirin, NSAIDs, other non-narcotic or narcotic analgesics, or corticosteroids.. Indirectness: No indirectness
Funding	Academic or government funding (Study sponsored by Fidia Pharmaceutical Corporation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual Analogue Scale 50 foot walk test at 26 weeks; Group 1: mean 18 (SD 21); n=105, Group 2: mean 24 (SD 27); n=113; Visual analogue scale 0-100 Top=High is poor outcome; Comments: Baseline hyaluronic acid: 54 (29). Baseline placebo: 55 (29).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, race, height, weight, NSAID use, use of assistive devices, physical therapy, and outcome baseline values; Blinding details: Required both a blinded and unblinded observer. The blinded observer recorded efficacy outcomes. The unblinded recorded safety outcomes and maintained blinding of others.; Group 1 Number missing: 59, Reason: 1 death, 4 gastrointestinal adverse events, 6 due to injection site pain, 7 lost to follow up, 17 lack of efficacy, 3 non-compliant/protocol violation, 12 other medical problem, 9 other musculoskeletal pain.; Group 2 Number missing: 53, Reason: 4 gastrointestinal adverse events, 1 injection site pain, 8 lost to follow up, 16 lack of efficacy, 5 noncompliant/protocol violation, 11 other medical problem, 8 other musculoskeletal pain

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Death and local joint pain and swelling at 26 weeks; Group 1: 22/164, Group 2: 22/168; Comments: Hyaluronic acid: 1 death, 21 local joint pain and swelling. Placebo: 22 local joint pain and swelling.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, race, height, weight, NSAID use, use of assistive devices, physical therapy, and outcome baseline values; Blinding details: Required both a blinded and unblinded observer. The blinded observer recorded efficacy outcomes. The unblinded recorded safety outcomes and maintained blinding of others.; Group 1 Number missing: 59, Reason: 1 death, 4 gastrointestinal adverse events, 6 due to injection site pain, 7 lost to follow up, 17 lack of efficacy, 3 non-compliant/protocol violation, 12 other medical problem, 9 other musculoskeletal pain.; Group 2 Number missing: 53, Reason: 4 gastrointestinal adverse events, 1 injection site pain, 8 lost to follow up, 16 lack of efficacy, 5 noncompliant/protocol violation, 11 other medical problem, 8 other musculoskeletal pain	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Altman 2004[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=346)
Countries and setting	Conducted in Canada, Sweden, USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: OA of the knee as defined by the American College of Rheumatology criteria - clinical diagnosis (with potential imaging)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Osteoarthritis of the knee as defined by the American College of Rheumatology criteria that was refractory to non-pharmacologic therapies; a Western Ontario McMasters Universities osteoarthritis index pain subscale score of at least 7 (range 0-20) in one knee and no greater than 15 in either knee; and significant knee pain in the signal knee for the majority of the preceding 3 months (patients had to be normally active and able to walk 50m, unaided).
Exclusion criteria	Isolated patelofemoral OA; use of systemic steroids, glucosamine or chondroitin within the past 3 months; intra-articular injection into the knee of corticosteroids in the past 3 months or intraarticular HA within the last 9 months; treatment with oral or topical NSAIDs during the previous week; use of topical non-NSAIDs within the previous 3 days; arthroscopy or other surgical procedure within the last 12 months and anticoagulant treatment (except acetylsalicylic acid, ≤325mg/day). Patients were also excluded if they presented with a systemic active inflammatory condition or infection, septic knee arthritis within the previous 3 months, significant venous or lymphatic stasis of the legs, active skin disease or infection at the injection site, or any other medical condition rendering the patient unsuitable for inclusion according to the investigator. Pregnant or breast feeding woman and those of childbearing potential not practicing adequate contraception were ineligible.
Recruitment/selection of patients	People were recruited from 18 centers (7 from USA, 6 from Canada, 5 from Sweden).
Age, gender and ethnicity	Age - Mean (range): 63.1 (18.4-61.1). Gender (M:F): 156:190. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Not stated / Unclear (Unclear - may include imaging (a part of the ARC criteria allow for this).). 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not explicitly stated, K-L grade II-IV Duration of symptoms (range): 5.75 (0-50.5) years
Indirectness of population	No indirectness
Interventions	(n=172) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). NASHA (Durolane, Q-Med AB, Uppsala, Sweden) - a single 3mL injection. The study product contained HA 60mg in a buffered sodium chloride (0.9%, pH 7) vehicle. Duration 26 weeks. Concurrent medication/care: Paracetamol (maximum daily dose, 4g) was permitted as rescue medication excepting during the 48-hour period prior to each study visit.. Indirectness: No indirectness (n=174) Intervention 2: Placebo. Buffered sodium chloride (0.9%, pH7) in a 3mL syringe.. Duration 26 weeks. Concurrent medication/care: Paracetamol (maximum daily dose, 4g) was permitted as rescue medication excepting during the 48-hour period prior to each study visit.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Q-Med AB, Uppsala, Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 3 months; Group 1: mean -2.87 (SD 3.97); n=172, Group 2: mean -3.42 (SD 4.1); n=174; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline IA HA: 9.90 (2.27). Baseline IA placebo: 10.42 (2.28).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: Adverse events (13), consent withdrawn (11), lost to follow-up (2), protocol violation (1), other reasons (mainly described as lack of efficacy, 10); Group 2 Number missing: 35, Reason: Adverse event (6), consent withdrawn (16), lost to follow-up (5), protocol violation (2), other reasons (6)
- Actual outcome for Knee: WOMAC pain at 6 months; Group 1: mean -2.5 (SD 4); n=172, Group 2: mean -2.89 (SD 4.17); n=174; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline IA HA: 9.90 (2.27). Baseline IA placebo: 10.42 (2.28).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: Adverse events (13), consent withdrawn (11), lost to follow-up (2), protocol violation (1), other reasons (mainly described as lack of efficacy, 10); Group 2 Number missing: 35, Reason: Adverse event (6), consent withdrawn (16), lost to follow-up (5), protocol violation (2), other reasons (6)

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function at 3 months; Group 1: mean -6.98 (SD 12.27); n=172, Group 2: mean -8.72 (SD 13.39); n=174; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline IA HA: 30.70 (11.00). Baseline IA placebo: 32.16 (11.06).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: Adverse events (13), consent withdrawn (11), lost to follow-up (2), protocol violation (1), other reasons (mainly described as lack of efficacy, 10); Group 2 Number missing: 35, Reason: Adverse event (6), consent withdrawn (16), lost to follow-up (5), protocol violation (2), other reasons (6) - Actual outcome for Knee: WOMAC physical function at 6 months; Group 1: mean -5.82 (SD 12.16); n=172, Group 2: mean -7.42 (SD 13.52); n=174; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline IA HA: 30.70 (11.00). Baseline IA placebo: 32.16 (11.06). Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: Adverse events (13), consent withdrawn (11), lost to follow-up (2), protocol violation (1), other reasons (mainly described as lack of efficacy, 10); Group 2 Number missing: 35, Reason: Adverse event (6), consent withdrawn (16), lost to follow-up (5), protocol violation (2), other reasons (6) Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 7/172, Group 2: 3/174 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 39, Reason: Adverse events (13 - unclear if the people with serious adverse events were the ones that withdrew), consent withdrawn (11), lost to follow-up (2), protocol violation (1), other reasons (mainly described as lack of efficacy, 10); Group 2 Number missing: 35, Reason: Adverse event (6 - unclear if the people with serious adverse events were the ones that withdrew), consent withdrawn (16), lost to follow-up (5), protocol violation (2), other reasons (6)	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	AMELIA trial: Navarro-sarabia 2011[336]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=306)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 40 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis in the medial tibialfemoral compartment according to the American College of Rheumatology with grade II to III radiographic stage osteoarthritis
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women of at least 45 years of age with knee osteoarthritis in the medial tibiofemoral compartment according to the American College of Rheumatology with grade II to III radiographic stage osteoarthritis and minimum medial femorotibial joint space width of the target knee of 2mm or greater. People were required to have pain of 55mm or greater on a visual analogue scale at any time during the week before inclusion.
Exclusion criteria	Body mass index greater than 32kg/m²; a history of trauma or surgery in the target knee; arthroscopy surgery during the year before inclusion; joint inflammatory diseases and/or microcrystalline arthropathies; coagulation/platelet disorders or any concomitant disease that could interfere with the evaluation; the administration of intraarticular steroids in the previous 3 months, HA injections during the past year or NSAID treatment during 2 weeks before inclusion.
Recruitment/selection of patients	19 participating centers screened a total of 446 people, in whom 140 were screening failures.
Age, gender and ethnicity	Age - Mean (SD): 63.5 (8.6). Gender (M:F): 50:256. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear (States that it allowed medication for vascular prevention and checked for medication being used for other chronic conditions. Therefore, may have included people with multimorbidity.).
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade II-III. Duration of symptoms: 7.5 (7.7) years.
Indirectness of population	No indirectness

Interventions	(n=153) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 2.5mL 1% sodium hyaluronate with a mean molecular weight of 900000 Daltons. The study consisted of four treatment cycles of five weekly injections each one. The follow up periods were 6 months long after the first and second cycles, and 1 year long after the third and fourth cycles, resulting in a total study duration of 40 months. In the case of bilateral OA, only the most severe knee was considered but both knees could be treated.. Duration 40 months. Concurrent medication/care: Acetylsalicylic acid (maximum 300mg/day) for vascular protection, partacetamol up to 4g/day as rescue medication as well as short cycles of NSAID were permitted (however for 1 day to 1 week prior to the study involvement respectively, the medication had to be stopped). During the whole study period intraarticular corticosteroid was not permitted in the target knee. Only two injections were allowed in the contralateral knee, and no more than two injections per year in any other joint than the knee.. Indirectness: No indirectness (n=153) Intervention 2: Placebo. Injections of 2.5mL of saline solution. The study consisted of four treatment cycles of five weekly injections each one. The follow up periods were 6 months long after the first and second cycles, and 1 year long after the third and fourth cycles, resulting in a total study duration of 40 months. In the case of bilateral OA, only the most severe knee was considered but both knees could be treated.. Duration 40 months. Concurrent medication/care: Acetylsalicylic acid (maximum 300mg/day) for vascular protection, partacetamol up to 4g/day as rescue medication as well as short cycles of NSAID were permitted (however for 1 day to 1 week prior to the study involvement respectively, the medication had to be stopped). During the whole study period intraarticular corticosteroid was not permitted in the target knee. Only two injections were allowed in the contralateral knee, and no more than two injections per year in any other joint than the knee.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Tedec Meiji Farma SA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Adverse events at 40 months; Group 1: 2/153, Group 2: 2/153; Comments: 2 arthralgia in each arm
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, duration of symptoms, pain (VAS), morning stiffness, joint crackles, Kellgren-Lawrence grade, joint space width, WOMAC baseline values for each subscale and total;

Group 1 Number missing: 44, Reason: 4 did not have efficacy data after randomisation. 6 lost to follow up. 38 discontinued (8 lack of efficacy, 12 patient's decision, 12 adverse events, 1 investigator's decision, 5 others).; Group 2 Number missing: 59, Reason: 1 did not have any efficacy data after randomisation, 5 lost to follow up, 59 discontinued (19 lack of efficacy, 13 patient's decision, 16 adverse events, 1 investigator's decision, 5 others)	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Arden 2014[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=218)
Countries and setting	Conducted in Germany, Sweden, United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee pain meeting the American College of Rheumatology criteria for the diagnosis of osteoarthritis provided that the osteoarthritis was confirmed in the study knee radiographically (Kellgren-Lawrence grades 2-3) and by a WOMAC pain score of 7-17 at their baseline visit
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Normally active men and women aged >5 years with the ability to walk 50 meters unaided and with knee pain meeting the American College of Rheumatology criteria for the diagnosis of osteoarthritis provided that the osteoarthritis was confirmed in the study knee radiographically (Kellgren-Lawrence grades 2-3) and by a WOMAC pain score of 7-17 at their baseline visit.
Exclusion criteria	Pain during the previous 3 months in the non-study knee; radiographically verified osteoarthritis of the non-study knee (Kellgren Lawrence grade >1), osteoarthritis or clinically significant pain from any part of the musculoskeletal system other than the study knee; previous intraarticular steroid injection into the study knee within the previous 3 months; and arthroscopy or other surgical procedures in the study knee within the last 12 months
Recruitment/selection of patients	The Durolane Study 2 group recruited people in Sweden for the study
Age, gender and ethnicity	Age - Median (range): HA: 64.5 (29-84). Saline: 60.9 (30-86).. Gender (M:F): 108:110. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on range). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-3. Duration of symptoms (median [range]): HA: 2.2 (0-21.2) years. Saline: 3.1 (0-44.1) years.
Indirectness of population	No indirectness

Interventions	(n=108) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). A single intraarticular injection in the study knee of NASHA (Durolane® 60mg in 3mL). This was administered into the synovial space with lateral mid-patellar, lateral upper-patellar or medial injection techniques being advised. Image guidance was not used.. Duration 1 injection. Concurrent medication/care: Rescue medication with paracetamol up to 4g per day was allowed throughout the study except during the 48 hour period preceding each study visit. NSAIDs, including topical agents for the knee, were not permitted. (n=110) Intervention 2: Placebo. A single intraarticular injection in the study knee of placebo (phosphate buffered saline, pH 7, 3mL). This was administered into the synovial space with lateral mid-patellar, lateral upper-patellar or medial injection techniques being advised. Image guidance was not used.. Duration 1 injection. Concurrent medication/care: Rescue medication with paracetamol up to 4g per day was allowed throughout the study except during the 48 hour period preceding each study visit. NSAIDs, including topical agents for the knee, were not permitted.. Indirectness: No indirectness
Funding	Study funded by industry (The study was supported by Q-Med AB, Uppsala, Sweden (study design, data collection, data analysis). Early versions of the manuscript were supported by Q-Med AB and Smith & Nephew UK Ltd through a Medical Writer (Ken Sutor whilst at Fishawack Communications, 100-102 King Street, Knutsford, UK, WA16 6HQ. N.K.A is a paid consultant for Q-Med AB and Smith & Nephew Inc, C.A. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article; R.D.A is a Ferring consultant, speaker, Abbott consultant, Novartis consultant, Astra Zeneca speaker, Rotta consultant, Covidien consultant and Lilly consultant; at the time of the study M.A. was a full time employee of Smith & Nephew UK Ltd. CMRO peer reviewers may have received honoraria for their review work. The peer reviews of this manuscript have disclosed that they have no relevant financial relationships.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain score at 6 weeks; Group 1: mean -2.56 (SD 3.46); n=108, Group 2: mean -2.45 (SD 3.06); n=110; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 9.98 (2.09). Baseline placebo: 9.83 (2.03).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, duration of osteoarthritis,

Kellgren Lawrence scores, baseline values for outcomes, presence of effusion, previous treatments with IA steroids or HA, previous knee surgery; Group 1 Number missing: 25, Reason: 5 premature discontinuations - 2 of which also had major protocol violations (2 due to consent withdrawn, 1 unrelated serious adverse event, 1 lost to follow-up, 1 lack of effect). 22 people had major protocol deviations (25 deviations) including: assessment of masking by treating investigator (10), randomisation envelope signed by both investigators (1), treatment with other study product (1), prohibited medication (3), rescue medication within 48 hours prior to visit 7 (8), WOMAC pain score missing on at least one visit (2); Group 2 Number missing: 19, Reason: 19 people had major protocol deviations. Assessment of masking by treating investigator (10. Treatment with the other study product (1). Prohibited medication (3). Rescue medication within 48 hours prior to visit 7 (5). Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function score at 6 weeks; Group 1: mean -6.26 (SD 10.81); n=108, Group 2: mean -5.59 (SD 10.58); n=110; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 30.42 (10.65). Baseline saline: 30.19 (10.24). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, duration of osteoarthritis, Kellgren Lawrence scores, baseline values for outcomes, presence of effusion, previous treatments with IA steroids or HA, previous knee surgery; Group 1 Number missing: 25, Reason: 5 premature discontinuations - 2 of which also had major protocol violations (2 due to consent withdrawn, 1 unrelated serious adverse event, 1 lost to follow-up, 1 lack of effect). 22 people had major protocol deviations (25 deviations) including: assessment of masking by treating investigator (10), randomisation envelope signed by both investigators (1), treatment with other study product (1), prohibited medication (3), rescue medication within 48 hours prior to visit 7 (8), WOMAC pain score missing on at least one visit (2); Group 2 Number missing: 19, Reason: 19 people had major protocol deviations. Assessment of masking by treating investigator (10. Treatment with the other study product (1). Prohibited medication (3). Rescue medication within 48 hours prior to visit 7 (5). Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Withdrawal due to non-treatment related serious adverse event at 6 weeks; Group 1: 1/108, Group 2: 0/110; Comments: Adverse events defined from the World Health Organisation definitions Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, duration of osteoarthritis, Kellgren Lawrence scores, baseline values for outcomes, presence of effusion, previous treatments with IA steroids or HA, previous knee surgery; Group 1 Number missing: 25, Reason: 5 premature discontinuations - 2 of which also had major protocol violations (2 due to consent withdrawn, 1 unrelated serious adverse event, 1 lost to follow-up, 1 lack of effect). 22 people had major protocol deviations (25 deviations) including: assessment of masking by treating investigator (10), randomisation envelope signed by both investigators (1), treatment with other study product (1), prohibited medication (3), rescue medication within 48 hours prior to visit 7 (8), WOMAC pain score missing on at least one visit (2); Group 2 Number missing: 19, Reason: 19 people had major protocol deviations. Assessment of masking by treating investigator (10. Treatment with the other study product (1). Prohibited medication (3). Rescue medication within 48 hours prior to visit 7 (5).	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Askari 2016[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=140)
Countries and setting	Conducted in Iran; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical and radiographic osteoarthritis - symptoms for at least 3 months, along with radiographic grade II-III (according to Kellgren and Lawrence grading scale).
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women from 45 to 80 years who were suffering from knee OA for at least 3 months, along with radiographic OA grade II-III (according to Kellgren and Lawrence grading scale), who signed the informed agreement form for participation.
Exclusion criteria	A history or presence of trauma or surgery or cancer or malignant tumours, infections and sores on the target knee, history of vasovagal shock, use of NSAIDs in 2 days prior to injection, any receiving corticosteroids injection in the knee in the last 6 months, pregnancy and lactation.
Recruitment/selection of patients	No additional information given
Age, gender and ethnicity	Age - Mean (SD): 57.8 (6.1). Gender (M:F): 21:119. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated (K-L grade II-III) Symptom duration: Not stated
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). One intraarticular injection of 2cc of high molecular weight (500,000-730,000) HA (Hylan, Fidia Farmaceuticic S.p.A, Italy). Duration 3 months. Concurrent medication/care: No additional information given. Indirectness: No indirectness (n=69) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). One intraarticular injection of 40mg corticosteroid (type not

	specified). Duration 3 months. Concurrent medication/care: No additional information given. Indirectness: No indirectness
Funding	Academic or government funding (Funded by Fasa University of Medical Sciences)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC pain at 3 months; Group 1: mean 13.11 (SD 4.24); n=71, Group 2: mean 12.6 (SD 3.69); n=69; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 13.90 (4.37). Baseline CS: 13.21 (3.56). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function at 3 months; Group 1: mean 33.54 (SD 12.38); n=71, Group 2: mean 33.29 (SD 11.03); n=69; WOMAC physical function 0-68 Top=High is poor outcome; Comments: Baseline HA: 35.90 (12.38). Baseline CS: 35.98 (11.36). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Atchia 2011[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=77)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with primary hip osteoarthritis fulfilling the American College of Rheumatology criteria for hip osteoarthritis
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary hip osteoarthritis. Age 50 years or greater, unilateral hip osteoarthritis, pain duration of more than a month, and either listed for elective total hip replacement or warranting consideration for total hip replacement
Exclusion criteria	Secondary hip osteoarthritis (different underlying pathology, eg. rheumatoid arthritis); total loss of joint space or collapse of femoral head on anteroposterior pelvic radiograph; co-morbid conditions resulting in gross lower limb asymmetry (e.g. stroke, amputees, severe leg shortening) or mobility impairement; hip injection within 6 months; listing for bilateral total hip replacement; combination of hip and back pain with the primary source of pain unclear.
Recruitment/selection of patients	Recruited from primary and secondary care
Age, gender and ethnicity	Age - Mean (SD): 69 (8). Gender (M:F): 34:43. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Mixed. Moderate to severe in the majority. Croft grade 1-2 in 14 people. Croft grade 3-4 in 63 people. Duration of symptoms: 36 (32) months
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Other. "Standard care" - defined as no injection. Duration 8 weeks. Concurrent medication/care: There were no restrictions regarding medication use, but participants were requested to notify changes in medication during follow up. Indirectness: No indirectness Comments: Included for completeness - is not an adequate comparator for this review

	(n=19) Intervention 2: Placebo. Intraarticular normal saline (3mL) given by ultrassound guided injection. The hip capsule was infiltrated with an aseptic technique under direct ultrasound visualisation. Injections were performed using a 20G spinal needle, under local anaesthetic, with 2mL 1% lidocaine followed by the active component. Distension of the capsule provided evidence of adequate localisation.. Duration 1 injection. Concurrent medication/care: There were no restrictions regarding medication use, but participants were requested to notify changes in medication during follow up. Indirectness: No indirectness (n=19) Intervention 3: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Intraarticular non-animal stabilised hyaluronic acid (durolane, 3mL/60mg) given by ultrassound guided injection. The hip capsule was infiltrated with an aseptic technique under direct ultrasound visualisation. Injections were performed using a 20G spinal needle, under local anaesthetic, with 2mL 1% lidocaine followed by the active component. Distension of the capsule provided evidence of adequate localisation.. Duration 1 injection. Concurrent medication/care: There were no restrictions regarding medication use, but participants were requested to notify changes in medication during follow up. Indirectness: No indirectness (n=19) Intervention 4: Intra-articular corticosteroids - Intra-articular corticosteroids (image guided). Intraarticular methylprednisolone acetate (depomedrone, 3mL/120mg) given by ultrassound guided injection. The hip capsule was infiltrated with an aseptic technique under direct ultrasound visualisation. Injections were performed using a 20G spinal needle, under local anaesthetic, with 2mL 1% lidocaine followed by the active component. Distension of the capsule provided evidence of adequate localisation.. Duration 1 injection. Concurrent medication/care: There were no restrictions regarding medication use, but participants were requested to notify changes in medication during follow up. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Durolane for injection was supplied by Q-Med. An authors fellowship was funded by Northumbria Healthcare NHS Foundation Trust. This work was supported by the UK NIHR Biomedical Research Centre for ageing and age-related disease award to the Newcastle upon Tyne Hospitals NHS foundation trust.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Osteoarthritis flares at ≤3- or >3- months

- Actual outcome for Hip: Post-injection flare at 8 weeks; Group 1: 4/18, Group 2: 0/18; Comments: Paper reports that 4 people had post-injection flares in the durolane group. No definition of what this meant. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, referral location, BMI, bone to capsule distance, synovitis, pain duration, disability duration, range of motion, number on medication, New Zealand Pain society baseline value, and radiographic grade; Group 1 Number missing: 1, Reason: 1 dropped out (reason not given); Group 2 Number missing: 1, Reason: 1 dropped out (reason not given) RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED) Protocol outcome 1: Osteoarthritis flares at ≤3- or >3- months - Actual outcome for Hip: Post-injection flare at 8 weeks; Group 1: 4/18, Group 2: 0/19; Comments: Paper reports that 4 people had post-injection flares in the durolane group. No definition of what this meant. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, referral location, BMI, bone to capsule distance, synovitis, pain duration, disability duration, range of motion, number on medication, New Zealand Pain society baseline value, and radiographic grade; Group 1 Number missing: 1, Reason: 1 dropped out (reason not given); Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Osteoarthritis flares at ≤3- or >3- months - Actual outcome for Hip: Post-injection flare at 8 weeks; Group 1: 0/19, Group 2: 0/18 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, referral location, BMI, bone to capsule distance, synovitis, pain duration, disability duration, range of motion, number on medication, New Zealand Pain society baseline value, and radiographic grade; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 dropped out (reason not given)	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Bastos 2020[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Brazil; Setting: Hospital/clinic
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: knee radiography (standing anterior–posterior and lateral views), knee magnetic resonance imaging (MRI)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged over 35 years with knee OA (based on American College of Rheumatology criteria) and confirmatory radiographs (Kellgren–Lawrence grade 1–4).
Exclusion criteria	history of untreated diabetes mellitus, glaucoma, immunodeficiency, chronic use of oral corticosteroid or immunosuppressive therapies, history or presence of malignant disorders and/or use of chemotherapy, infection or active wound in the knee area, history of severe trauma to the knee (post-traumatic OA), resence of systemic inflammation, body mass index (BMI) higher than 40 kg/m2, regnancy and any other comorbidity that prevented the bone marrow aspiration surgical procedure.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 57.3 ± 10.7 years old. Gender (M:F): 24 male, 23 female. Ethnicity: Not reported
Further population details	1. Age: <75 years (Age given as average, which are all below 75 years.). 2. Diagnostic method: Diagnosed with imaging (knee radiography (standing anterior–posterior and lateral views), knee magnetic resonance imaging (MRI)). 3. Multimorbidities: People with multimorbidities excluded (See exclusion criteria).
Extra comments	Mix of people with Kellgren–Lawrence grade 1–4 severity. . All participants were subjected to bone marrow extraction regardless of their allocated treatment group.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). Intra-articular injection of MSCs was performed between 2 and 3 weeks after the bone marrow aspiration procedure. After asepsis and adequate antisepsis procedures, intra-articular injection with a 20G needle was performed in the supero-lateral region of the patella, with the patient in the supine position and the knee in extension. Immediately after injection, patients were instructed to initiate daily prophylactic exercises for preventing deep venous thrombosis. . Duration 12 months follow up. Concurrent medication/care: The use of dipyrone 1 g every 6 h (analgesic non-anti-inflammatory) was allowed in case of severe pain.. Indirectness: No indirectness

Study
Study type
Number of stud
Countries and
Line of therapy
Duration of stu
Method of asse
Stratum
Subgroup anal
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Age, gender ar
Further popula
Extra comment
Indirectness of
Interventions

	Comments: KOOS baseline scores - mean (SD) Symptoms 41.5 (18.4) Pain 34.6 (11.4) Function, daily living 31.7 (19.1) Sports/recreation 13 (21) Quality of life 16.8 (12.4) Global KOOS score 30.3 (13.1) (n=17) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intra-articular corticosteroid injections. Duration 12 months follow up. Concurrent medication/care: The use of dipyrone 1 g every 6 h (analgesic non-anti-inflammatory) was allowed in case of severe pain.. Indirectness: No indirectness Comments: Baseline coricosteroid KOOS values - mean (SD): Symptoms 47.4 (17.9) Pain 40.5 (19.6) Function, daily living 40.7 (21) Sports/recreation 18 (28) Quality of life 16.5 (16.5) Global KOOS score 36.9 (17.8)	Funding RESULTS (NU INTRA-ARTICU Protocol outcor - Actual outcon analogue scale Risk of bias: Al Crossover - Lo outcome basel - Actual outcon analogue scale Risk of bias: Al Crossover - Lo outcome basel
Funding	No funding	
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Quality of life at ≤3- or >3- months - Actual outcome for Knee: KOOS quality of life at 12 months; Group 1: mean 23 (SD 24.5584); n=15, Group 2: mean 15.4 (SD 30.0265); n=16; WOMAC pain subscale 0-100 Top=High is good outcome; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 2: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: KOOS Pain at 12 months; Group 1: mean 22.2 (SD 25.4613); n=15, Group 2: mean 19 (SD 26.4609); n=16; WOMAC pain subscale 0-100 Top=High is good outcome; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	Protocol outcor - Actual outcon 0-90 Top=High Risk of bias: Al Crossover - Lo outcome basel - Actual outcon Index 0-90 Top Risk of bias: Al Crossover - Lo outcome basel Protocol outcor - Actual outcon Risk of bias: Al Crossover - Lo outcome basel

Protocol outcome 3: Physical function at ≤3- or >3- months - Actual outcome for Knee: KOOS function/daily living at 12 months; Group 1: mean 26.7 (SD 29.6146); n=15, Group 2: mean 20.9 (SD 28.7129); n=16; WOMAC pain subscale 0-100 Top=High is good outcome; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	Protocol outcor
Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Bisicchia 2016[45]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Italy; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 51 weeks (52 weeks after the first injection)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People presenting for unilateral primary knee osteoarthritis (based on American College of Rheumatology criteria) included if they had a Kellgren-Lawrence grade 2-3 knee osteoarthritis and a VAS for pain ≥3
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female walking people older than 45 years with a single symptomatic knee. People were included if they had a Kellgren-Lawrence grade 2-3 knee osteoarthritis and a VAS for pain ≥3
Exclusion criteria	People were excluded in the case of grade 1 or 4 osteoarthritis according to Kellgren Lawrence; symptoms in both knees; a varus or valgus deformity greater than 10 degrees; flexion contracture greater than 15 degrees; ligamentous instability or meniscal tears; NSAIDs used in the last 30 days; intra-articular injections in the last 12 months; septic, inflammatory or crystal arthritis; previous surgeries in the last 6 months; physical therapy in the last 30 days
Recruitment/selection of patients	Single centre. People recruited who presented to the investigator's clinic.
Age, gender and ethnicity	Age - Mean (SD): 70.1 (10.4). Gender (M:F): 47:103. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-3. Duration of symptoms: not stated
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 2 injections of hyaluronic acid (HYADD 4) - injected using an 18 gauge needle inserted through an anterolateral parapatellar approach, and knee effusions were aspirated (if necessary) into a separate syringe.. Duration 2 injections, 7 days apart. Concurrent medication/care: People were encouraged to refrain from strenuous activity for a day following the intra-articular injections. No formal physical

	therapy was prescribed. Furthermore, NSAIDs and paracetamol consumption were the only pain medications allowed. Indirectness: No indirectness (n=75) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 2 injections of corticosteroid (6-methylprednisolone acetate 40mg) - injected using an 18 gauge needle inserted through an anterolateral parapatellar approach, and knee effusions were aspirated (if necessary) into a separate syringe.. Duration 2 injections, 7 days apart. Concurrent medication/care: People were encouraged to refrain from strenuous activity for a day following the intra-articular injections. No formal physical therapy was prescribed. Furthermore, NSAIDs and paracetamol consumption were the only pain medications allowed. Indirectness: No indirectness
Funding	Principal author funded by industry (S. Bisicchia is a consultant for Fidia Farmaceutici S.p.A.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Knee: SF-36 at 12 weeks; Group 1: mean 71.5 (SD 16.4); n=75, Group 2: mean 63.5 (SD 12.1); n=75; SF-36 0-100 Top=High is good outcome; Comments: Baseline HA: 62.0 (12.7). Baseline CS: 58.5 (11.5).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age and baseline values of outcomes; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Knee: SF-36 at 52 weeks; Group 1: mean 62 (SD 13.7); n=72, Group 2: mean 59.3 (SD 11.7); n=64; SF-36 0-100 Top=High is good outcome; Comments: Baseline HA: 62.0 (12.7). Baseline CS: 58.5 (11.5).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age and baseline values of outcomes; Group 1 Number missing: 3, Reason: All people completed evaluation at 6 and 12 weeks. Between 12 and 26 weeks 2 people asked for a new injection cycle due to a significant reduction in effect. In the period between 26 and 52 weeks, 4 people (group unclear) returned to the clinic for a new injection cycle.; Group 2 Number missing: 9, Reason: All people completed evaluation at 6 and 12 weeks. Between 12 and 26 weeks 2 people were indicated for total knee arthroplasty, 9 people asked for a new injection cycle due to a significant reduction in effect. In the period between 26 and 52 weeks, 4 people (group unclear) returned to the clinic for a new injection cycle.

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 12 weeks; Group 1: mean 2 (SD 2); n=75, Group 2: mean 4 (SD 2); n=75; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Baseline HA: 6.3 (2.2). Baseline CS: 6.9 (1.8).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age and baseline values of outcomes; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Knee: Visual analogue scale (pain) at 52 weeks; Group 1: mean 5.8 (SD 2.3); n=72, Group 2: mean 6.4 (SD 2); n=64; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Baseline HA: 6.3 (2.2). Baseline CS: 6.9 (1.8). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age and baseline values of outcomes; Group 1 Number missing: 3, Reason: All people completed evaluation at 6 and 12 weeks. Between 12 and 26 weeks 2 people asked for a new injection cycle due to a significant reduction in effect. In the period between 26 and 52 weeks, 4 people (group unclear) returned to the clinic for a new injection cycle.; Group 2 Number missing: 9, Reason: All people completed evaluation at 6 and 12 weeks. Between 12 and 26 weeks 2 people were indicated for total knee arthroplasty, 9 people asked for a new injection cycle due to a significant reduction in effect. In the period between 26 and 52 weeks, 4 people (group unclear) returned to the clinic for a new injection cycle.	
Protocol outcomes not reported by the study	Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Bjornland 2007[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Norway; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who fulfilled the criteria for osteoarthritis of the TMJ and myofascial pain according to the Research Diagnostic Criteria for temporomandibular disorders by Dworkin and LeResche
Stratum	TMJ
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjective pain from the TMJ at function and rest for >1 year; restricted mandibular function; radiographic evidence of osteoarthritis of the TMJ such as: erosions, flattening, sclerosis and osteophytes of the condyle and/or the articulating fossa; should also have tried adequate conservative treatments (such as information and reassurance, NSAIDs, physiotherapy, and occlusal splints without alleviation of the symptoms); people of age >20 years.
Exclusion criteria	A history of general arthritis or other connective tissue disease; treatment with immunosuppressive drugs; any organ disease; general infection; pregnant or lactating women; any known allergy or hypersensitivity to eggs, feather, avian proteins or chicken; injections of any corticosteroids or any sodium hyaluronate preparation within the previous 12 months.
Recruitment/selection of patients	All people were seen in the Department of Oral Surgery and Oral Medicine, University of Oslo
Age, gender and ethnicity	Age - Mean (SD): 51.7 (13.2). Gender (M:F): 6:34. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated Duration of symptoms (mean [SD]): 5.9 (9.3) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 0.7-1mL of the sodium salt of hyaluronic acid (Hylan G-F 20). After disinfection of the pre-auricular area, approximately 1mL of 2% Xylocaine with

	12.5 micrograms/mL of Adrenaline was used as local anaesthesia from the skin to the TMJ capsule. The treatment consisted of two intraarticular injections 14 days apart.. Duration 2 injections, 14 days apart. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=20) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 0.7-1mL of betamethasone sodium phosphate betamethasone acetate. After disinfection of the pre-auricular area, approximately 1mL of 2% Xylocaine with 12.5 micrograms/mL of Adrenaline was used as local anaesthesia from the skin to the TMJ capsule. The treatment consisted of two intraarticular injections 14 days apart.. Duration 2 injections, 14 days apart. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Academic or government funding (The study was supported by grants from the Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Norway)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for TMJ: Visual analogue scale (pain) at 1 month; Group 1: mean 32 (SD 25.6); n=20, Group 2: mean 42 (SD 27.8); n=20; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 70 (16.2). Baseline CS: 73 (18.1). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, duration of symptoms and baseline outcome values; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for TMJ: Visual analogue scale (pain) at 6 months; Group 1: mean 14 (SD 16.2); n=20, Group 2: mean 31 (SD 31.7); n=20; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 70 (16.2). Baseline CS: 73 (18.1). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, duration of symptoms and baseline outcome values; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Blaine 2008[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=660)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: The study included people with persistent shoulder pain associated with limitation of motion due to glenohumeral joint osteoarthritis, rotator cuff tear (partial or complete), and/or primary or secondary adhesive capsulitis. They report the people with osteoarthritis separately.
Stratum	Shoulder
Subgroup analysis within study	Not applicable
Inclusion criteria	Thirty-five years of age or older with shoulder pain due to glenohumeral joint osteoarthritis, rotator cuff tear (partial or complete), and/or adhesive capsulitis for at least six months but less than five years. Pain with movement of the shoulder had been present for at least 50% of the days during the previous month. Pain was refractory to standard treatments as defined by a failure to obtain adequate or sustained relief following the use of physical therapy, at least one corticosteroid injection (more than three months prior to entry into the study), and the administration of oral pain medications. Required to have moderate to severe pain without analgesic use over the twenty four hours prior to entry into the study (as indicated by a rating of 40 to 90mm on a 100-mm visual analogue scale). People had limitations of active range of motion in at least one of several directions (i.e. abduction of ≤80 degrees with a scapula fixed, active internal rotation of ≤55 degrees, and/or external rotation ≤80 degrees). A range of motion of at least 20% in all directions was required.
Exclusion criteria	Minor injury (including sports injury) in the past year; chronic pain lasting for more than five years; cervical spine disease that could confound assessments; surgery involving the shoulder within the previous twelve months; inflammatory arthropathy; severe frozen shoulder involving either shoulder (with retention of <20% range of motion); gout or calcium pyrophosphate diseases involving the upper extremities within the previous 12 months; intraarticular corticosteroid injections of any other joint within the previous month; intraarticular hyaluronan therapy within the previous 12 months; radiographic findings indicative of acute fracture of the shoulder; severe loss of bone density; osteonecrosis or severe deformity; or osteoarthritis of the glenohumeral joint equivalent to Kellgren-Lawrence stage IV; general medical conditions (e.g. pregnancy,

	malignant disease, bleeding diathesis); any condition that might confound subsequent clinical evaluations; laboratory abnormalities that may confound the subsequent clinical evaluations
Recruitment/selection of patients	People were recruited from seventy nine outpatient study sites in the United States
Age, gender and ethnicity	Age - Mean (SD): 63.1 (12.5). Gender (M:F): 328:332. Ethnicity: Not stated
Further population details	1. Age: Mixed 2. Diagnostic method: Not stated / Unclear 3. Multimorbidities: Low comorbidity score (Paper reports that >98% had at least one medical history abnormality including other musculoskeletal disease (80-84%), previous operations other than uppr body or shoulder operations (67-72%) and cardiovascular disease (67-71%).).
Extra comments	Severity: Not stated. <stage 4 Kellgren and Lawrence changes Duration of symptoms: Not stated explicitly. At least six months but less than five years..
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Five weekly 2mL injections of hyaluronic acid at a dosage of 10mg/mL. Duration 5 injections over 5 weeks. Concurrent medication/care: All people were allowed to use paracetamol (4g/day) as rescue medication for shoulder pain, apart from in the 24 hours before any evaluation. Anti-inflammatory and analgesic drugs needed to be discontinued 2 weeks prior to the baseline evaluation.. Indirectness: No indirectness Comments: In the number of people randomised, we report the number with osteoarthritis rather than the total in the group (which may include people without osteoarthritis. This total = 221). The study does not report how many people with osteoarthritis withdrew from the study. Therefore, this will be downgraded for attrition bias as it is unclear how many withdrew. (n=136) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Three weekly injections of hyaluronic acid (2mL, 10mg/mL) followed by two weekly injections of placebo (phosphate buffered saline, 2mL). Duration 5 injections over 5 weeks (3 hyaluronic acid, 2 phosphate buffered saline). Concurrent medication/care: All people were allowed to use paracetamol (4g/day) as rescue medication for shoulder pain, apart from in the 24 hours before any evaluation. Anti-inflammatory and analgesic drugs needed to be discontinued 2 weeks prior to the baseline evaluation.. Indirectness: No indirectness Comments: This group will not be included in the outcome extraction due to the mixed

	intervention nature (both HA and placebo) - they are reported here for completeness. In the number of people randomised, we report the number with osteoarthritis rather than the total in the group (which may include people without osteoarthritis. This total = 218). The study does not report how many people with osteoarthritis withdrew from the study. Therefore, this will be downgraded for attrition bias as it is unclear how many withdrew. (n=133) Intervention 3: Placebo. Five weekly injections of placebo (phosphate buffered saline, 2mL). Duration 5 injections over 5 weeks. Concurrent medication/care: All people were allowed to use paracetamol (4g/day) as rescue medication for shoulder pain, apart from in the 24 hours before any evaluation. Anti-inflammatory and analgesic drugs needed to be discontinued 2 weeks prior to the baseline evaluation.. Indirectness: No indirectness Comments: In the number of people randomised, we report the number with osteoarthritis rather than the total in the group (which may include people without osteoarthritis. This total = 221). The study does not report how many people with osteoarthritis withdrew from the study. Therefore, this will be downgraded for attrition bias as it is unclear how many withdrew.
Funding	Study funded by industry (Sponsorship from Sanofi-Aventis)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Shoulder: Mean difference of reduction in pain from baseline between groups on visual analogue scale for shoulder pain at 6 months; MD; 7.8 (P value: 0.002) Visual analogue scale 0-100 Top=High is poor outcome, Comments: Reports MD and SE. Reports: 7.8 ± 2.5; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports for the group in general (not just people with osteoarthritis, so unclear if these people were different at baseline) age, gender, number of people with a body mass index >30.5 kg/m^2, and baseline VAS score; Group 1 Number missing: 0, Reason: Reports missing data for the overall population in the group (uses a modified intention to treat analysis, 221 people allocated to treatment, 20 people discontinued due to patient withdrawal) but unclear whether these are all people with osteoarthritis or whether they are people with other conditions; Group 2 Number missing: 0, Reason: Reports missing data for the overall population in the group (uses a modified intention to treat analysis, 221 people allocated to treatment, 17 people discontinued due to patient withdrawal (15) and protocol violation (2)) but unclear whether these are all people with osteoarthritis or whether they are people with other conditions	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Blanco 2008[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic osteoarthritis evidenced by pain according to the American College of Rheumatology criteria without joint inflammation but with grade 4 Kellgren-Lawrence radiographic changes
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People over 40 years of age without joint inflammation and symptomatic osteoarthritis evidence by pain according to the American College of Rheumatology criteria with grade 4 Kellgren and Lawrence changes.
Exclusion criteria	Have received intraarticular injections of corticosteroids in the target joints within 3 months of study entry; had HA injections within 1 year of study entry; people who had received glucosamine sulphate during the three months before beginning the study or had used an investigational drug within 30 days of study entry; people with previous knee surgery; people with a history of rheumatoid arthritis, ankylosing spondylitis, macrocrystalline arthropathies, chondrocalcinosis, fibromyalgia or any other pathology of the knee that could interfere with the study and assessments; people with severely impaired central nervous systems; impaired coagulation; known sensitivity to hyaluronic acid, paracetamol or diclofenac; immunocompromised people; people receiving systemic immunosuppresive therapy; people considered by the investigator to be unable to complete the treatment or follow up
Recruitment/selection of patients	People on the waiting list for knee replacement surgery at the Hospital Universitario A Coruña
Age, gender and ethnicity	Age - Mean (SD): 67.9 (8.6). Gender (M:F): 10:32. Ethnicity: All caucasian
Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 4. Duration of symptoms: 10.5 (9.1) years
Indirectness of population	No indirectness

Interventions	(n=26) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Two cycles of five weekly injections with a 24 week interval between each cycle of 2.5mL HA (25mg) in saline (after aspiration of the joint).. Duration 5 injections over 5 weeks in 2 cycles (separated by 24 weeks). Concurrent medication/care: Rescue analgesia with paracetamol 4000mg/day or diclofenac 150mg/day was permitted in all. Indirectness: No indirectness (n=26) Intervention 2: Placebo. Two cycles of five weekly injections with a 24 week interval between each cycle of 2.5mL saline vehicle (after aspiration of the joint).. Duration 5 injections over 5 weeks in 2 cycles (separated by 24 weeks). Concurrent medication/care: Rescue analgesia with paracetamol 4000mg/day or diclofenac 150mg/day was permitted in all. Indirectness: No indirectness
Funding	Study funded by industry (This study was supported by a grant from Tedec-Meiji Farma, S.A. Carlos Fernández-Lopez was supported by Fondo de Investigación Sanitaria, Programa Post-MIR)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain subscale at 6 months; Group 1: mean -21.7 (SD 25.9); n=22, Group 2: mean -11.2 (SD 21); n=20; WOMAC pain subscale 0-100 Top=High is poor outcome; Comments: Baseline HA: 62.6 (58.9-66.4). Baseline placebo: 67.6 (60.4-74.8).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, ethnicity, age, BMI, years since diagnosis, and baseline outcome values. Both the pain and physical function baseline values are worse in the placebo group than the HA group.; Group 1 Number missing: 4, Reason: They used carried forward data, but the people who completed the entirety of the study were 6 people. 1 withdrew informed consent, 5 withdrew after visit 5, 1 had a serious adverse event, 11 withdrew after visit 6, 4 after visit 7, 1 had a protocol violation, 1 had to use anticoagulation, 2 withdrew after visit 13, 2 withdrew after visit 14, 1 lost to follow up; Group 2 Number missing: 6, Reason: They used carried forward data. 3 withdrew informed consent at the start. 2 withdrew after visit 5. 1 withdrew for surgery. 7 withdrew at visit 6. 8 withdrew at visit 7. 1 protocol violation. 1 SAE. 3 withdrew after visit 12.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC functional capacity subscale at 6 months; Group 1: mean -24.7 (SD 18); n=22, Group 2: mean -4.4 (SD 18.8); n=20; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Baseline HA: 63.2 (55.6-70.7). Baseline placebo: 71.2 (63.5-78.9).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, ethnicity, age, BMI, years since diagnosis, and baseline outcome values. Both the pain and physical function baseline values are worse in the placebo group than the HA group.; Group 1 Number missing: 4, Reason: They used carried forward data, but the people who completed the entirety of the study were 6 people. 1 withdrew informed

consent, 5 withdrew after visit 5, 1 had a serious adverse event, 11 withdrew after visit 6, 4 after visit 7, 1 had a protocol violation, 1 had to use anticoagulation, 2 withdrew after visit 13, 2 withdrew after visit 14, 1 lost to follow up; Group 2 Number missing: 6, Reason: They used carried forward data. 3 withdrew informed consent at the start. 2 withdrew after visit 5. 1 withdrew for surgery. 7 withdrew at visit 6. 8 withdrew at visit 7. 1 protocol violation. 1 SAE. 3 withdrew after visit 12. Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 12 months; Group 1: 1/22, Group 2: 1/20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, ethnicity, age, BMI, years since diagnosis, and baseline outcome values. Both the pain and physical function baseline values are worse in the placebo group than the HA group.; Group 1 Number missing: 4, Reason: They used carried forward data, but the people who completed the entirety of the study were 6 people. 1 withdrew informed consent, 5 withdrew after visit 5, 1 had a serious adverse event, 11 withdrew after visit 6, 4 after visit 7, 1 had a protocol violation, 1 had to use anticoagulation, 2 withdrew after visit 13, 2 withdrew after visit 14, 1 lost to follow up; Group 2 Number missing: 6, Reason: They used carried forward data. 3 withdrew informed consent at the start. 2 withdrew after visit 5. 1 withdrew for surgery. 7 withdrew at visit 6. 8 withdrew at visit 7. 1 protocol violation. 1 SAE. 3 withdrew after visit 12.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Brander 2019[54]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=357)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hip OA (radiographically confirmed Kellgren Lawrence grade 2 or 3) per American College of Rheumatology criteria (hip pain at baseline plus at least 2 of the following 3 features - erythrocyte sedimentation rate <20mm/h, radiographic femoral and acetabular osteophytes, or radiographic joint space narrowing)
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of symptomatic hip osteoarthritis (radiographically confirmed Kellgren Lawrence grade 2 or 3 within 36 weeks of screening) per American College of Rheumatology criteria (hip pain at first baseline plus at least 2 of the following 3 features - erythrocyte sedimentation rate <20 mm/h, radiographic femoral and acetabular osteophytes, or radiographic joint space narrowing [superior, axial, and/or medial]); previous use of analgesics or nonsteroidal anti-inflammatory drugs for hip osteoarthritis pain with completion of pain and osteoarthritis medication washout period; hip pain as demonstrated by a WOMAC A1 score of 5-8 (on an 11 point numeric rating scale with 0=none and 10=extreme pain; age ≥35 years; and willingness to received image-guided injections (including any necessary imaging contrast agent).
Exclusion criteria	WOMAC A1 score of under 5 or 9-10 at screening; symptomatic contralateral hip osteoarthritis (WOMAC A1 greater than or equal to 4); decrease in WOMAC A1 >1 point from screening to baseline; presence of comorbidities that may affect target joint or impact measurement of efficacy; surgeries/procedures to the hip/lower extremities within 26 weeks of screening; IA corticosteroid injection within 12 weeks of screening
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 60.3 (9.4). Gender (M:F): 146:211. Ethnicity: Majority white (330). 24 people were black or African American. 2 people were unknown. 1 person was not reported.

Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Majority grade 2-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=182) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Hylan G-F 20 (48mg in one 6mL IA injection). Performed under fluoroscopy or ultrasound (dependent on study site) to ensure accurate needle placement. People entered a supine position. The region overlying the targeted hip was prepared and draped in a sterile manner. The skin and local soft tissues (but not into the capsule) were anaesthetised with 1% lidocaine. Intermittent fluoroscopy or musculoskeletal ultrasound (with sterile ultrasound gel) was used to place a 3.5 inch spinal needle into the hip joint, targeting the inferior femoral head, at the head-neck junction. A thorough arthrocentesis were performed prior to injection of the study material if synovial fluid present upon needle entry. If fluoroscopy was used, a small amount of nonionic contrast material was injected and limited arthrogram performed to confirm/document IA needle placement. Then one vial of study agent was injected. The spinal needle was removed and a band-aid applied.. Duration 1 injection. Concurrent medication/care: Paracetamol was the only allowable medication for target hip osteoarthritis pain. Short-acting NSAIDs and paracetamol for pain or for reasons other than pain in the target hip joint were allowed but needed to be recorded and weren't allowed to be used within 2 days of each study visit. Indirectness: No indirectness (n=175) Intervention 2: Placebo. Phosphate buffered saline (one 6mL IA injection). Performed under fluoroscopy or ultrasound (dependent on study site) to ensure accurate needle placement. People entered a supine position. The region overlying the targeted hip was prepared and draped in a sterile manner. The skin and local soft tissues (but not into the capsule) were anaesthetised with 1% lidocaine. Intermittent fluoroscopy or musculoskeletal ultrasound (with sterile ultrasound gel) was used to place a 3.5 inch spinal needle into the hip joint, targeting the inferior femoral head, at the head-neck junction. A thorough arthrocentesis were performed prior to injection of the study material if synovial fluid present upon needle entry. If fluoroscopy was used, a small amount of nonionic contrast material was injected and limited arthrogram performed to confirm/document IA needle placement. Then one vial of study agent was injected. The spinal needle was removed and a band-aid applied.. Duration 1 injection. Concurrent medication/care: Paracetamol was the only allowable medication

	for target hip osteoarthritis pain. Short-acting NSAIDs and paracetamol for pain or for reasons other than pain in the target hip joint were allowed but needed to be recorded and weren't allowed to be used within 2 days of each study visit. Indirectness: No indirectness
Funding	Study funded by industry (Sanofi Biosurgery, LLC funded the study. Sanofi authors were involved in the study design, collection, analysis and interpretation of data, and in the writing and decision to submit the manuscript for publication)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: WOMAC A (pain) at 12 weeks; Group 1: mean -2.27 (SD 2.56); n=182, Group 2: mean -2.36 (SD 2.51); n=175; WOMAC pain subscale NRS 0-11 Top=High is poor outcome; Comments: Reports mean (SEM). Reported HA: -2.27 (0.19). Reported placebo: -2.36 (0.19). Baseline (mean [SEM]) HA: 6.35 (0.07). Baseline placebo: 6.39 (0.08).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, ethnicity, BMI, prior medication usage, Kellgren-Lawrence grade, symptoms reported, need for arthrocentesis and type of imaging used for needle placement; Group 1 Number missing: 46, Reason: 10 had adverse events. 3 lost to follow up. 22 withdrawals by subject. 8 lack of efficacy. 1 other.; Group 2 Number missing: 44, Reason: 10 had adverse events. 3 lost to follow up. 17 withdrawals by subjects. 2 technical problems. 8 lack of efficacy. 1 other.
- Actual outcome for Hip: WOMAC A (pain) at 26 weeks; Group 1: mean -2.23 (SD 2.83); n=182, Group 2: mean -2.3 (SD 2.91); n=175; WOMAC pain subscale NRS 0-11 Top=High is poor outcome; Comments: Reports mean (SEM). Reported HA: -2.23 (0.21). Reported placebo: -2.30 (0.22). Baseline (mean [SEM]) HA: 6.35 (0.07). Baseline placebo: 6.39 (0.08).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, ethnicity, BMI, prior medication usage, Kellgren-Lawrence grade, symptoms reported, need for arthrocentesis and type of imaging used for needle placement; Group 1 Number missing: 46, Reason: 10 had adverse events. 3 lost to follow up. 22 withdrawals by subject. 8 lack of efficacy. 1 other.; Group 2 Number missing: 44, Reason: 10 had adverse events. 3 lost to follow up. 17 withdrawals by subjects. 2 technical problems. 8 lack of efficacy. 1 other.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Hip: WOMAC C (physical function) at 12 weeks; Group 1: mean -1.94 (SD 2.56); n=182, Group 2: mean -2.28 (SD 2.51); n=175; WOMAC physical function subscale NRS 0-11 Top=High is poor outcome; Comments: Reports mean (SEM). Reported HA: -1.94 (0.19). Reported placebo: -2.28 (0.19). Baseline (mean [SEM]) HA: 6.33 (0.09). Baseline placebo: 6.44 (0.08).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, ethnicity, BMI, prior medication usage, Kellgren-Lawrence grade, symptoms reported, need for arthrocentesis and type of imaging used for needle placement; Group 1 Number missing: 46, Reason: 10 had adverse events. 3 lost to follow up. 22 withdrawals by subject. 8 lack of efficacy. 1 other.; Group 2 Number missing: 44, Reason: 10 had adverse events. 3 lost to follow up. 17 withdrawals by subjects. 2 technical problems. 8 lack of efficacy. 1 other.

- Actual outcome for Hip: WOMAC C (physical function) at 26 weeks; Group 1: mean -2.09 (SD 2.83); n=182, Group 2: mean -2.13 (SD 2.78); n=175; WOMAC physical function subscale NRS 0-11 Top=High is poor outcome; Comments: Reports mean (SEM). Reported HA: -2.09 (0.21). Reported placebo: -2.13 (0.21). Baseline (mean [SEM]) HA: 6.33 (0.09). Baseline placebo: 6.44 (0.08). Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, ethnicity, BMI, prior medication usage, Kellgren-Lawrence grade, symptoms reported, need for arthrocentesis and type of imaging used for needle placement; Group 1 Number missing: 46, Reason: 10 had adverse events. 3 lost to follow up. 22 withdrawals by subject. 8 lack of efficacy. 1 other.; Group 2 Number missing: 44, Reason: 10 had adverse events. 3 lost to follow up. 17 withdrawals by subjects. 2 technical problems. 8 lack of efficacy. 1 other. Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Hip: Serious adverse events at 26 weeks; Group 1: 10/182, Group 2: 15/172; Comments: Not defined. Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, ethnicity, BMI, prior medication usage, Kellgren-Lawrence grade, symptoms reported, need for arthrocentesis and type of imaging used for needle placement; Group 1 Number missing: 46, Reason: 10 had adverse events. 3 lost to follow up. 22 withdrawals by subject. 8 lack of efficacy. 1 other.; Group 2 Number missing: 44, Reason: 10 had adverse events. 3 lost to follow up. 17 withdrawals by subjects. 2 technical problems. 8 lack of efficacy. 1 other.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Brandt 2001[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=226)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Idiopathic osteoarthritis according to the American College of Rheumatology cirteria, with Kellgren-Lawrence Grade II or III radiographic evidence of knee osteoarthritis
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People older than 50 years, willing to discontinue all analgesics and non-steroidal antiinflammatory drugs in a washout period equivalent to five half-lives of the relevant drug preceding entry into the study, able to walk 50 feet unassisted, and not pregnant or planning a pregnancy. All people had idiopathic osteoarthritis according to American College of Rheumatology criteria, Kellgren-Lawrence Grade II or III radiographic evidence of knee osteoarthritis, and a summed Western Ontario and McMaster University Osteoarthritis Index pain score of 13 or greater (possible range, 5-25) in the index knee and less than 13 in the contralateral (untreated) knee.
Exclusion criteria	Initiation of a quadriceps exercise program within 4 months of screening; oral or intramuscular steroid use within 2 months of screening; intraarticular injection of hyaluronic acid within the past 12 months; Kellgren-Lawrence Grade IV radiographic changes in either knee; treatment with anticoagulants, immunosuppressives, or muscle relaxants; inability to tolerate acetaminophen; clinically significant co-morbidity (renal or hepatic disease) or abnormality in routine laboratory tests; or allergy to lidocaine.
Recruitment/selection of patients	Multicenter trial
Age, gender and ethnicity	Age - Mean (SD): 65.99 (8.459). Gender (M:F): 83:143. Ethnicity: Majority white (73%), minority black (19.5%), remainder other.
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity not stated explicitly - K-L grade II-III Duration of symptoms not stated

Indirectness of population	No indirectness
Interventions	(n=114) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Three intraarticular injections of sodium hyaluronate 2mL (15mg/mL) of ORTHOVISC (high molecular weight HA, 1-2.9 MDa).. Duration 6 months. Concurrent medication/care: Paracetamol (to a maximum of 4g daily) was allowed for rescue analgesia. No other pain medication was allowed. Both groups were anaesthetised with 3-5mL of 1% lidocaine HCl.. Indirectness: No indirectness (n=112) Intervention 2: Placebo. Three intraarticular injections of 2mL saline administered during a 2 week period.. Duration 6 months. Concurrent medication/care: Paracetamol (to a maximum of 4g daily) was allowed for rescue analgesia. No other pain medication was allowed. Both groups were anaesthetised with 3-5mL of 1% lidocaine HCl.. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by a grant from Anika Therapeutics, Inc, Woburn, MA.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 6/114, Group 2: 4/112; Comments: These included diverticulitis, oesophagitis, cholecystitis (recorded in two patients), hyperglycaemia, atrial fibrillation, congestive heart failure, deep vein thrombosis, pneumonia, asthma, congenital hernia, prostatic disorder, and carcinoma. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Caborn 2004[59]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=218)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Following criteria of the American College of Rheumatology
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Ambulatory men and women, 40 years of age or older, in generally good health, who had been diagnosed with OA of the knee (criteria of the American College of Rheumatology) at least 3 months prior to entering the study, and had given informed consent to participate. People were required to have been taking analgesics/NSAIDs to control OA knee pain at least 3 days per week for a minimum of 2 months before enrollment, and have a score ≥2 on Question A1 of the WOMAC scale at screening, 14 days prior to starting therapy. They also needed to have a score of 50 to 90mm on a 100 mm VAS for both patient and investigator overall assessments of the target knee at baseline. Women of child-bearing potential were required to be using adequate means of contraception.
Exclusion criteria	Any unstable medical condition, or any of the following diagnoses: acute synovitis, allergy to avian productions/hyaluronan-based injection components/corticosteroid injections/acetaminophen, inflammatory arthropathy or infection in the area of the injection site, a clinical diagnosis of primarily patellofemoral knee pain, effusion of >10mL at screening or baseline, venous or lymphatic stasis in the leg, claudication or peripheral vascular disease, malignancy within 5 years, diabetic neuropathy or related infections, and laboratory abnormalities. The use of glucosamine and/or chondroitin sulfate was prohibited. People were not to have been exposed to prior viscosupplementation in the target knee, oral corticosteroids, or IA corticosteroid injection of a target knee within 3 months of screening or a nontarget joint within 4 weeks. Longer acting analgesics and NSAIDs were to be discontinued at least 7 days before baseline and could not be used during the study. People with a history of target joint arthroplasty were not permitted to participate in the study.
Recruitment/selection of patients	No additional information given

Age, gender and ethnicity	Age - Mean (SD): 63.07 (11.88). Gender (M:F): 93:123. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Not stated / Unclear 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity not stated. Symptom duration not stated.
Indirectness of population	No indirectness
Interventions	(n=113) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hylan G-F 20 (Synvisc) - given as three 2mL intraarticular injections, at one week intervals.. Duration 3 weeks (one injection per week) followed up for 26 weeks. Concurrent medication/care: Preadministration of anaesthetic skin spray or subcutaneous local anaesthetics were permitted. If effusions were present, they were aspirated and assessed for infection and cystals. Mixing of other agents into the intraarticular agent was not permitted (including local anaesthetic). The following oral pain medications were allowed except for within 24 hours of a study visit: paracetamol (up to 4g per day), analgesics or short-acting NSAIDs with a washout period of at least 24 hours for pain other than in the target knee, but not for more than 3 consecutive days or 1- days per month, and low dose aspirin (≤325mg/day) for antithrombotic prophylaxis. NSAIDs with once-daily dose regimens were prohibited.. Indirectness: No indirectness (n=105) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular triamcinolone hexacetonide (Aristospan) given as a single injection of 40mg (2mL of a 20mg/mL suspension).. Duration 1 session followed up for 26 weeks. Concurrent medication/care: Preadministration of anaesthetic skin spray or subcutaneous local anaesthetics were permitted. If effusions were present, they were aspirated and assessed for infection and cystals. Mixing of other agents into the intraarticular agent was not permitted (including local anaesthetic). The following oral pain medications were allowed except for within 24 hours of a study visit: paracetamol (up to 4g per day), analgesics or short-acting NSAIDs with a washout period of at least 24 hours for pain other than in the target knee, but not for more than 3 consecutive days or 1- days per month, and low dose aspirin (≤325mg/day) for antithrombotic prophylaxis. NSAIDs with once-daily dose regimens were prohibited.. Indirectness: No indirectness
Funding	Study funded by industry (Sponsored by Wyeth Pharmaceuticals. Hylan G-F 20 used in this study was generously provided by Genzyme Biosurgery, Ridgefield, NJ, USA.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Patient assessed visual analogue scale score at 6 months; Group 1: mean 28 (SD 26.6); n=113, Group 2: mean 12.4 (SD 26.3); n=102; Visual analogue scale 0-100 Top=High is poor outcome; Comments: Reports least-square means and standard error measurements. Standard error converted to standard deviation. 6 months HA: 28.0 (2.5). 6 month TH: 12.4 (2.6). Baseline HA: 68.4 (1.39). Baseline TH: 67.3 (1.29).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: 1 person switched from the TH to the HA group. 2 not included in the efficacy analysis.
- Actual outcome for Knee: Patient assessed visual analogue scale score at 3 months; Group 1: mean 31.3 (SD 24.5); n=113, Group 2: mean 17.4 (SD 24.3); n=102; Visual analogue scale 0-100 Top=High is poor outcome; Comments: Reports least-square means and standard error measurements. Standard error converted to standard deviation. 3 months HA: 31.3 (2.3). 3 month TH: 17.4 (2.41). Baseline HA: 68.4 (1.39). Baseline TH: 67.3 (1.29).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: 1 person switched from the TH to the HA group. 2 not included in the efficacy analysis.

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Arthralgia at 6 months; Group 1: 36/113, Group 2: 32/103
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: 1 person switched from the TH to the HA group. 2 not included in the efficacy analysis.

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Chao 2010[72]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=79)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiographically proven osteoarthritis of the knee with knee pain who met the American College of Rheumatology criteria
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Radiograph of the affected knee within 1 year of enrollment. People with knee pain who met the American College of Rheumatology criteria for knee osteoarthritis.
Exclusion criteria	People taking oral corticosteroids, who had a primary inflammatory connective tissue disease, or who had received IA corticosteroids in the affected knee within 3 months of study entry.
Recruitment/selection of patients	People were recruited from the musculoskeletal and arthritis clinics at the San Diego Veterans Affairs Hospital and the UUniversity of California San Diego Medical Center.
Age, gender and ethnicity	Age - Mean (SD): 64.3 (11.9). Gender (M:F): 65:2. Ethnicity: Not stated
Further population details	1. Age: Mixed (Upper range of confidence intervals fall above the 75 years range). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated Symptom duration (range): 14 years (0.3-51 years)
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 1cc of 40mg/mL triamcinolone acetonide via syringe covered in opaque tape prior to the patient encounter. Given using a 22-guage, 1.5 inch needle via an anterior lateral approach with the person in an upright 90 degrees position.. Duration 1 injection, followed up over 12 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=39) Intervention 2: Placebo. 1cc of 0.9% sodium chloride via syringe covered in opaque tape prior to the patient encounter. Given using a 22-guage, 1.5 inch needle via an anterior lateral approach with the person in an upright 90 degrees position..

	Duration 1 injection, follow up over 12 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC pain score at 3 months; Group 1: mean -1 (SD 2.8); n=30, Group 2: mean -0.2 (SD 2.2); n=29; WOMAC pain score 0-20 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Opaque syringe. Injection given by a separate person to the one assessing the person.; Group 1 Number missing: 9, Reason: 3 people were randomised twice (two where baseline outcomes were not able to assessed sufficiently at the two so were re-enrolled, one had done the study 3 years prior and their results from the baseline examination were included), no other reasons for attrition given; Group 2 Number missing: 9, Reason: 3 people were randomised twice (two where baseline outcomes were not able to assessed sufficiently at the two so were re-enrolled, one had done the study 3 years prior and their results from the baseline examination were included), no other reasons for attrition given	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Chen 2021[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=57)
Countries and setting	Conducted in Taiwan; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 96 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis as determined by the American College of Rheumatology (with radiographic evidence)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 40-80 years; Kellgren-Lawrence grading I-II, as determined by American College of Rheumatology criteria for knee osteoarthritis; WOMAC pain score 7-17.
Exclusion criteria	Surgery history on the target knee joint; previous intra-articular intervention on the target knee joint within past 3 months; hypersensitivity to any component used in the study; inadequate hematologic and hepatic function; human immunodeficiency virus infection or body mass index greater than 35 kg/m2; people participating in any other interventional study within 4 weeks of entering the study; people applying treatments to the target knee area or using analgesics other than paracetamol or NSAIDs.
Recruitment/selection of patients	There were two study sites in this trial, including Linkou Chang Gung Memorial Hospital and Taipei Veterans General Hospital in Taiwan.
Age, gender and ethnicity	Age - Mean (SD): 67.6 (6.60). Gender (M:F): 11:46. Ethnicity: Not stated/unclear
Further population details	1. Age: Mixed 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Kellgren Lawrence grading II-III (median grade II). Duration of symptoms (mean [SD]): 2.96 (4.164) years. NCT02784964
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). ELIXCYTE stem cells injected into the knee. The study included three stem cell groups: one receiving 16 million cells (n=17), the second 32 million cells (n=17), the third 64 million cells (n=15). Each person would have one target knee for the efficacy assessment.. Duration One injection, followed up for 96 weeks in total. Concurrent medication/care: People were allowed to use paracetamol and NSAIDs during the study.. Indirectness: No indirectness

	Comments: The three groups were combined in the analysis as they reported the same intervention class as agreed in the protocol. (n=8) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Active control group who received Hya Joint Plus Synovial fluid supplement 3mL, SciVision Biotech Inc.. Duration One injection, followed up for 96 weeks in total. Concurrent medication/care: People were allowed to use paracetamol and NSAIDs during the study.. Indirectness: No indirectness
Funding	Study funded by industry (This study was funded by UnicoCell BioMed Co. Ltd. and the A+Industrial Innovative R&D Program, Ministry of Economic Affairs, R.O.C (Grant No. 105-EC-17-A-22-I5-0007).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED)

Protocol outcome 1: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: At least one treatment-relative adverse events at 24 weeks; Group 1: 24/49, Group 2: 1/8; Comments: Types of adverse events included: injection site erythema, joint effusion, inflammation, pain and swelling, pharyngitis, procedural vomiting, alpha tumor necrosis factor increased, arthralgia, joint stiffness, joint swelling, benign pharyngeal neoplasm, dizziness and cold sweat - people could have had more than one event. 16 million cells: 1 injection site inflammation, 1 injection site pain, 2 injection site joint swelling, 1 pharyngitis, 2 arthralgia, 1 joint swelling, 1 pharyngeal neoplasm benign, 1 dizziness, 1 cold sweat. 32 million cells: 1 injection site erythema, 3 injection site joint pain, 3 injection site joint swelling, 1 procedural vomiting, 1 alpha tumour necrosis factor increased, 2 arthralgia, 1 joint stiffness, 3 joint swelling, 1 dizziness. 64 million cells: 1 injection site joint effusion, 4 injection site joint pain, 2 injection site joint swelling, 4 arthralgia, 1 joint stiffness, 2 joint swelling. Hyaluronic acid: 1 injection site joint pain. The 0-24 week data was used rather than the supplementary data that reported later time periods as the 0-24 weeks data included any adverse events up to 24 weeks while the later time point data reported any adverse events from after 24 weeks.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 16 million: 2 early termination, 32 million: 1 early termination, 64 million: 1 early termination.; Group 2 Number missing: 0, Reason: 0 early termination

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Chevalier 2010[75]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=253)
Countries and setting	Conducted in Belgium, Czech Republic, France, Germany, Netherlands, United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People meeting the American College of Rheumatology criteria for osteoarthritis (knee pain for most days of the previous month and osteophyte(s) at the joint margin visible on x-ray)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 40 years or greater; diagnosis of primary osteoarthritis of the target knee; radiographic evidence of osteoarthritis in the medial and/or lateral tibiofemoral compartment (one or more osteophytes and a measurable joint space on a standard radiograph taken within 3 months before screening); continued osteoarthritis pain in the target knee despite conservative treatments. People were required to have a score of 2 or 3 (0 to 4 scale) on question 1 of the WOMAC (Likert version 3.1) pain (A) subscale (pain while walking on a flat surface) as this is the most commonly reported symptom in clinical practice and the protocol was designed to weight this symptom more heavilly. Included people required a mean score of 1.5-3.5 on the WOMAC A subscore.
Exclusion criteria	Secondary osteoarthritis in the target knee; grade IV radiographic stage osteoarthritis (Kellgren-Lawrence grading system); clinically apparent tense effusion of the target knee; significant valgus/varus deformities; viscosupplementation in any joint in the past 9 months; surgery in the knee within the past 6 months; symptomatic osteoarthritis in the contralateral knee or either hip unresponsive to paracetamol; systemic or intraarticular injection of corticosteroids in any joint within 3 months before screening
Recruitment/selection of patients	Enrolled at 21 sites in the UK, France, the Czech Republic, Germany, Belgium and The Netherlands
Age, gender and ethnicity	Age - Mean (SD): 63.0 (9.4). Gender (M:F): 73:180. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not explicitly stated. Majority Kellgren Lawrence grade 2-3. Duration of symptoms (mean [SD]): 73.6 (70.7) months.
Indirectness of population	No indirectness
Interventions	(n=124) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 6mL intraarticular hyaluronic acid (Hylan G-F 20) with arthrocentesis. Duration 1 injection. Concurrent medication/care: Paracetamol (≤4000mg/day) was permitted as rescue medication for the target knee. Other permitted medications were analgesics/non-steroidal anti-inflammatory drugs with a half-life of 5 hours or less for indications other than osteoarthritis pain (not to be taken for more than five consecutive days or >10 days/month) and aspirin (≤325mg/day). However, for 48 hours before a study visit, people were required to abstain from any paracetamol, pain or osteoarthritis medications.. Indirectness: No indirectness (n=129) Intervention 2: Placebo. 6mL intraarticular phosphate buffered saline with arthrocentesis. Duration 1 injection. Concurrent medication/care: Paracetamol (≤4000mg/day) was permitted as rescue medication for the target knee. Other permitted medications were analgesics/non-steroidal anti-inflammatory drugs with a half-life of 5 hours or less for indications other than osteoarthritis pain (not to be taken for more than five consecutive days or >10 days/month) and aspirin (≤325mg/day). However, for 48 hours before a study visit, people were required to abstain from any paracetamol, pain or osteoarthritis medications.. Indirectness: No indirectness
Funding	Study funded by industry (The manuscript is based upon clinical trial results from a study sponsored by Genzyme Biosurgery)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC A (pain) at 26 weeks; Group 1: mean -0.76 (SD 1.06); n=125, Group 2: mean -0.58 (SD 1.59); n=129; WOMAC pain subscale 0-4 Top=High is poor outcome; Comments: Reports mean (SE). Reported HA: -0.76 (0.07). Reported placebo: -0.58 (0.07). Baseline HA: 2.30 (0.04). Baseline placebo: 2.25 (0.04).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, involvement of the tibiofemoral compartment, Kellgren-Lawrence grade, previous treatment, baseline outcome values, response to pharmacological treatment, and time since diagnosis; Group 1 Number missing: 10, Reason: 1 switched to the control arm. 9 discontinued: 1 due to adverse effects, 1 non compliant, 1 wished to withdraw, 6 lack of efficacy; Group 2 Number missing: 12, Reason: 1 gained from the HA arm. 12 discontinued: 3 due to adverse effects, 2 noncompliant, 1 wished to withdraw, 4 lack of efficacy, 2 other.

Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC C (function) at 26 weeks; Group 1: mean -0.59 (SD 1.1); n=124, Group 2: mean -0.48 (SD 1.6); n=129; WOMAC physical function subscale 0-4 Top=High is poor outcome; Comments: Reports mean (SE). Reported HA: -0.59 (0.076). Reported placebo: -0.48 (0.074). Baseline HA: 2.29 (0.04). Baseline placebo: 2.28 (0.04). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, involvement of the tibiofemoral compartment, Kellgren-Lawrence grade, previous treatment, baseline outcome values, response to pharmacological treatment, and time since diagnosis; Group 1 Number missing: 10, Reason: 1 switched to the control arm. 9 discontinued: 1 due to adverse effects, 1 non compliant, 1 wished to withdraw, 6 lack of efficacy; Group 2 Number missing: 12, Reason: 1 gained from the HA arm. 12 discontinued: 3 due to adverse effects, 2 noncompliant, 1 wished to withdraw, 4 lack of efficacy, 2 other. Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 26 weeks; Group 1: 0/123, Group 2: 0/130; Comments: No definition Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, involvement of the tibiofemoral compartment, Kellgren-Lawrence grade, previous treatment, baseline outcome values, response to pharmacological treatment, and time since diagnosis; Group 1 Number missing: 10, Reason: 1 switched to the control arm. 9 discontinued: 1 due to adverse effects, 1 non compliant, 1 wished to withdraw, 6 lack of efficacy; Group 2 Number missing: 12, Reason: 1 gained from the HA arm. 12 discontinued: 3 due to adverse effects, 2 noncompliant, 1 wished to withdraw, 4 lack of efficacy, 2 other.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Cohen 2008[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ankle osteoarthritis with pain associated with X-ray changes
Stratum	Ankle
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible men or women over 50 years of age with a diagnosis of ankle OA established by pain associated with X-ray changes of OA, and AOS values greater than or equal to 3 months but for less than 5 years present at least 50% of the time and without improvement in the previous month, and must have discontinued all nonsteroidal antiinflammatory drugs (NSAIDs) or other analgesic medication with the exception of acetaminophen (500mg x 1-2 tables 4 times daily as needed, maximum 4g per day) and aspirin up to 325mg/day used as an antiplatelet. All people had X-rays and/or CT scans confirming ankle arthritis with a Kellgren-Lawrence grade of 2-4. People must have been active and able to ambulate 50 feet without the aid of a walker, crutches or cane.
Exclusion criteria	Bilateral ankle OA requiring treatment for both ankles other than simple analgesics such as acetaminophen; change in physical therapy/occupational therapy within the last 3 months; treatment with NSAIDs during the last week (or 5 half-lives of the drug, whichever was longer) prior to the baseline visit; use of systemic corticosteroids (excluding inhalational or topical corticosteroids) or intraarticular injections of cocrticosteroids in the treated ankle within the last 3 months; HA injections within the last 9 months in the treated ankle; arthroscopy or other surgical procedure within the last 12 months in the treated ankle; significant changes in activity relevant to baseline; concomitant periankle tendonitis; Achilles tendonitis; chronic or acute enthesopathy; arthritis in the adjacent hindfoot joints
Recruitment/selection of patients	Consecutive patients presenting with pain
Age, gender and ethnicity	Age - Mean (SD): 50.3 (16.3) years. Gender (M:F): 25:3. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not explicitly stated. Kelgren-Lawrence grade 2-4. Duration of symptoms: Not stated.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Five weekly intraarticular injections of 2mL Hyalgan (MW 500-730kDa) into the tibiotalar joint. Duration 5 injections over 5 weeks. Concurrent medication/care: Paracetamol (up to 4g/day) as rescue medication. Otherwise no anti-inflammatory drugs.. Indirectness: No indirectness (n=14) Intervention 2: Placebo. Five weekly injections of phosphate buffered saline (2mL) into the tibiotalar joint. Duration 5 injections over 5 weeks. Concurrent medication/care: Paracetamol (up to 4g/day) as rescue medication. Otherwise no anti-inflammatory drugs.. Indirectness: No indirectness
Funding	Study funded by industry (Funded by Sanofi-Aventis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Ankle: Ankle Osteoarthritis Scale - pain at 3 months; Group 1: mean -17.3 (SD 35.2); n=15, Group 2: mean -10 (SD 35.7); n=13; Ankle Osteoarthritis Scale - Pain subscale 0-100 Top=High is poor outcome; Comments: Reports percent improvement (on a 0-100 scale, therefore change scores) (SEs). SDs calculated from this. Reported HA: 17.3 (9.1). Reported placebo: 10 (9.9). Baseline HA: 58.8 (16.3). Baseline placebo: 51.9 (14.6).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, body mass index, right ankle involvement, Kellgren-Lawrence grade, signal ankle range of motion, and baseline values for outcomes. There is difference between the baseline values for AOS pain and disability (active group = more severe at baseline).; Group 1 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention; Group 2 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention
- Actual outcome for Ankle: Ankle Osteoarthritis Scale - pain at 6 months; Group 1: mean -28.6 (SD 30.6); n=15, Group 2: mean -9.4 (SD 29.9); n=13; Ankle Osteoarthritis Scale - Pain subscale 0-100 Top=High is poor outcome; Comments: Reports percent improvement (on a 0-100 scale, therefore change scores) (SEs). SDs calculated from this. Reported HA: 28.6 (7.9). Reported placebo: 9.4 (8.3). Baseline HA: 58.8 (16.3). Baseline placebo: 51.9 (14.6).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, body mass index, right ankle involvement, Kellgren-Lawrence grade, signal ankle range of motion, and baseline values for outcomes. There is difference between the baseline values for AOS pain and disability (active group = more severe at baseline).; Group 1 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention; Group 2 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention

Protocol outcome 2: Physical function at ≤3- or >3- months

- Actual outcome for Ankle: Ankle Osteoarthritis Scale - disability at 3 months; Group 1: mean -34.3 (SD 35.2); n=15, Group 2: mean -7.4 (SD 34.6); n=13; Ankle Osteoarthritis Scale - Disability subscale 0-100 Top=High is poor outcome; Comments: Reports percent improvement (on a 0-100 scale, therefore change scores) (SEs). SDs calculated from this. Reported HA: 34.3 (9.1). Reported placebo: 7.4 (9.6). Baseline HA: 69.4 (12.1). Baseline placebo: 52.9 (18.7). Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, body mass index, right ankle involvement, Kellgren-Lawrence grade, signal ankle range of motion, and baseline values for outcomes. There is difference between the baseline values for AOS pain and disability (active group = more severe at baseline).; Group 1 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention; Group 2 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention - Actual outcome for Ankle: Ankle Osteoarthritis Scale - disability at 6 months; Group 1: mean -30.7 (SD 34.5); n=15, Group 2: mean -16 (SD 33.9); n=13; Ankle Osteoarthritis Scale - Disability subscale 0-100 Top=High is poor outcome; Comments: Reports percent improvement (on a 0-100 scale, therefore change scores) (SEs). SDs calculated from this. Reported HA: 30.7 (8.9). Reported placebo: 16 (9.4). Baseline HA: 69.4 (12.1). Baseline placebo: 52.9 (18.7). Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, body mass index, right ankle involvement, Kellgren-Lawrence grade, signal ankle range of motion, and baseline values for outcomes. There is difference between the baseline values for AOS pain and disability (active group = more severe at baseline).; Group 1 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention; Group 2 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention Protocol outcome 3: Osteoarthritis flares at ≤3- or >3- months - Actual outcome for Ankle: Post-injection flare ups at 6 months; Group 1: 0/15, Group 2: 0/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, body mass index, right ankle involvement, Kellgren-Lawrence grade, signal ankle range of motion, and baseline values for outcomes. There is difference between the baseline values for AOS pain and disability (active group = more severe at baseline).; Group 1 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention; Group 2 Number missing: 1, Reason: 1 person screened by decline therapy prior to receiving the intervention	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study (subsidiary papers)	Conaghan 2018[85] (Langworthy 2019[265])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=486)
Countries and setting	Conducted in Australia, Canada, France, Hong Kong (China), New Zealand, United Kingdom, USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiographic knee osteoarthritis and presence of knee pain
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions, male or female ≥40 years of age, has symptoms associated with osteoarthritis of the index knee for at least 6 months prior to screening, currently meets American College of Rheumatology criteria for OA, Kellgren-Lawrence grade 2 or 3 in the index knee prior to screening, index knee pain for >15 days over the last month, qualifying mean score on the 24-h average pain score (0-10 numeric rating scale), body mass index ≤40kg/m², willingness to abstain from use of restricted medications.
Exclusion criteria	Any condition that could possibly confound the patient's assessment of index knee pain in judgment of the investigator (i.e. ipsilateral hip OA, gout, radicular low back pain and hip pain that is referred to the knee that could cause misclassification, pain in any other area of the lower extremities or back that is equal or greater than the index knee pain); fibromyalgia, Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis; arthritis associated with inflammatory bowel disease; history of infection in the index knee; clinical signs and symptoms of active knee infection or crystal disease of the index knee within 1 month of screening; unstable joint within 12 months of screening; IA corticosteroid (investigational or marketed) in any joint within 3 months of screening; Ia hyaluronic acid (investigational or marketed) in the index knee within 6 months of screening; any other IA investigational drug/biologic within 6 months of screening; prior use of FX006; women of child-bearing potential not using effective contraception or who are pregnant or nursing.
Recruitment/selection of patients	Multinational study including 38 centers in North America, Australia, New Zealand, Asia (Hong Kong), and the European Union.
Age, gender and ethnicity	Age - Mean (SD): 62.07 (9.516). Gender (M:F): 188:296. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. K-L grade II-III. Symptom duration: 7.2 (6.37) years.
Indirectness of population	No indirectness

Interventions	(n=161) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). FX006 (a microsphere formulation of triamcinolone acetonide) 32mg given in 5mL. Duration 1 injection, followed up over 24 weeks. Concurrent medication/care: People were allowed to use paracetamol (≤3g/day by 500mg tablets provided) for rescue treatment. Otherwise analgesic medications were withdrawn. Comments: Results for individual groups reported on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1) (n=163) Intervention 2: Placebo. Intraarticular saline-solution placebo (5mL). Duration 1 injection, follow up over 24 weeks. Concurrent medication/care: People were allowed to use paracetamol (≤3g/day by 500mg tablets provided) for rescue treatment. Otherwise analgesic medications were withdrawn.. Indirectness: No indirectness Comments: Results for individual groups reported on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1) (n=162) Intervention 3: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Triamcinolone acetonide immediate release 40mg (1mL).. Duration 1 injection, followed up over 24 weeks. Concurrent medication/care: People were allowed to use paracetamol (≤3g/day by 500mg tablets provided) for rescue treatment. Otherwise analgesic medications were withdrawn.. Indirectness: No indirectness Comments: Results for individual groups reported on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1)
Funding	Equipment / drugs provided by industry (Flexion Therapeutics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) - MICROSPHERE PREPARATION versus PLACEBO

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Knee: Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale at 3 months (12 weeks); Group 1: mean 21.19 (SD 22.2); n=136, Group 2: mean 12.22 (SD 22.4); n=144; Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale 0-100 Top=High is good outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 12 weeks corticosteroid: 21.19 (1.907). Reported 12 weeks placebo: 12.22 (1.869). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 12 weeks steroid (mean [SD]): 18.5 (22.2) in 270 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).; Group 2 Number missing: 19, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).

- Actual outcome for Knee: Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale at 6 months (24 weeks); Group 1: mean 11.95 (SD 22.4); n=136, Group 2: mean 10.25 (SD 22.5); n=144; Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale 0-100 Top=High is good outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 24 weeks corticosteroid: 11.95 (1.923). Reported 24 weeks placebo: 10.25 (1.878). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 24 weeks steroid (mean [SD]): 11.7 (22.3) in 270 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).; Group 2 Number missing: 19, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC A (pain subscale) at 3 months (12 weeks); Group 1: mean -0.88 (SD 0.89); n=156, Group 2: mean -0.5 (SD 0.88); n=158; WOMAC pain subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 12 weeks corticosteroid: -0.88 (0.071). Reported 12 weeks placebo: -0.50 (0.071). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 12 weeks steroid (mean [SD]): -0.79 (0.89) in 314 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 withdrew consent, 2 lack of efficacy, 1 other; Group 2 Number missing: 8, Reason: 1 withdrew consent, 2 withdrawn by investigator/sponsor, 1 lost to follow up, 4 lack of efficacy
- Actual outcome for Knee: WOMAC A (pain subscale) at 6 months (24 weeks); Group 1: mean -0.63 (SD 0.84); n=144, Group 2: mean -0.49 (SD 0.85); n=149; WOMAC pain subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 24 weeks corticosteroid: -0.63 (0.070). Reported 24 weeks placebo: -0.49 (0.070). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 24 weeks steroid (mean [SD]): -0.59 (0.85) in 294 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: 7 withdrew consent, 1 protocol non-compliance (after injection), 1 lost to follow up, 7 lack of efficacy,31 other; Group 2 Number missing: 14, Reason: 1 adverse event, 3 withdrew consent, 2 withdrawn by investigator/sponsor, 1 protocol non-compliance (after injection), 3 lost to follow up, 4 lack of efficacy

Protocol outcome 3: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC C (function subscale) at 3 months (12 weeks); Group 1: mean -0.93 (SD 0.86); n=156, Group 2: mean -0.56 (SD 0.84); n=154; WOMAC function subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 12 weeks corticosteroid: -0.93 (0.069). Reported 12 weeks placebo: -0.56 (0.068). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 12 weeks steroid (mean [SD]): -0.824 (0.87) in 314 people.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 withdrew consent, 2 lack of efficacy, 1 other; Group 2 Number missing: 8, Reason: 1 withdrew consent, 2 withdrawn by investigator/sponsor, 1 lost to follow up, 4 lack of efficacy
- Actual outcome for Knee: WOMAC C (function subscale) at 6 months (24 weeks); Group 1: mean -0.59 (SD 0.83); n=144, Group 2: mean 0.51 (SD 0.84); n=149; WOMAC function subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 24 weeks corticosteroid: -0.59 (0.069). Reported 24 weeks placebo: -0.51 (0.069). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 24 weeks steroid (mean [SD]): -0.564 (0.83) in 294 people.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: 7 withdrew consent, 1 protocol non-compliance (after injection), 1 lost to follow up, 7 lack of efficacy,31 other; Group 2 Number missing: 14, Reason: 1 adverse event, 3 withdrew consent, 2 withdrawn by investigator/sponsor, 1 protocol non-compliance (after injection), 3 lost to follow up, 4 lack of efficacy

Protocol outcome 4: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: ≥1 serious adverse events at 6 months (24 weeks); Group 1: 5/161, Group 2: 3/162; Comments: Individual events reported on https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=2&rank=1&view=results. Steroid group: 6 adverse events in 5 people - 1 atrial fibrillation, 1 large intestine polyp, 1 pneumonia, 1 arthralgia, 1 rectal cancer, 1 dizziness. Control group: 3 events in 3 people - 1 abdominal hernia, 1 sepsis, 1 cholangitis.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 did not receive treatment

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) - IMMEDIATE RELEASE versus PLACEBO

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Knee: Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale at 3 months (12 weeks); Group 1: mean 15.77 (SD 21.9); n=134, Group 2: mean 12.22 (SD 22.4); n=144; Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale 0-100 Top=High is good outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 12 weeks corticosteroid: 15.77 (1.895). Reported 12 weeks placebo: 12.22 (1.869). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 12 weeks steroid (mean [SD]): 18.5 (22.2) in 270 people.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).; Group 2 Number missing: 19, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).

- Actual outcome for Knee: Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale at 6 months (24 weeks); Group 1: mean 11.44 (SD 22.1); n=134, Group 2: mean 10.25 (SD 22.5); n=144; Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life Subscale 0-100 Top=High is good outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 24 weeks corticosteroid: 11.44 (1.906). Reported 24 weeks placebo: 10.25 (1.878). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 24 weeks steroid (mean [SD]): 11.7 (22.3) in 270 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).; Group 2 Number missing: 19, Reason: Included patient values given for the last possible time period for quality of life (as this was different compared to the other outcomes). Therefore, this was used for both time periods in the absence of further information. Reason for missing data unclear (outside of those for other people in the study).

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC A (pain subscale) at 3 months (12 weeks); Group 1: mean -0.7 (SD 0.88); n=158, Group 2: mean -0.5 (SD 0.88); n=154; WOMAC pain subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 12 weeks corticosteroid: -0.70 (0.070). Reported 12 weeks placebo: -0.50 (0.071). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 12 weeks steroid (mean [SD]): -0.79 (0.89) in 314 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 withdrew consent, 1 lack of efficacy; Group 2 Number missing: 8, Reason: 1 withdrew consent, 2 withdrawn by investigator/sponsor, 1 lost to follow up, 4 lack of efficacy
- Actual outcome for Knee: WOMAC A (pain subscale) at 6 months (24 weeks); Group 1: mean -0.56 (SD 0.069); n=150, Group 2: mean -0.49 (SD 0.07); n=149; WOMAC pain subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 24 weeks corticosteroid: -0.56 (0.069). Reported 24 weeks placebo: -0.49 (0.070). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 24 weeks steroid (mean [SD]): -0.59 (0.85) in 294 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 1 adverse event, 3 withdrew consent, 4 lack of efficacy, 4 other; Group 2 Number missing: 14, Reason: 1 adverse event, 3 withdrew consent, 2 withdrawn by the investigator/sponsor, 1 protocol non-compliance (after injection), 3 lost to follow up, 4 lack of efficacy

Protocol outcome 3: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC C (function subscale) at 3 months (12 weeks); Group 1: mean -0.72 (SD 0.86); n=158, Group 2: mean -0.56 (SD 0.84); n=154; WOMAC function subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 12 weeks corticosteroid: -0.72 (0.068). Reported 12 weeks placebo: -0.56 (0.068). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 12 weeks steroid (mean [SD]): -0.824 (0.87) in 314 people.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 withdrew consent, 1 lack of efficacy; Group 2 Number missing: 8, Reason: 1 withdrew consent, 2 withdrawn by investigator/sponsor, 1 lost to follow up, 4 lack of efficacy - Actual outcome for Knee: WOMAC C (function subscale) at 6 months (24 weeks); Group 1: mean -0.54 (SD 0.83); n=150, Group 2: mean -0.51 (SD 0.84); n=149; WOMAC function subscale 0-4 Top=High is poor outcome; Comments: Uses least squares means and standard errors (reported on clinicaltrials.gov [https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=1&rank=1]). Reported 24 weeks corticosteroid: -0.54 (0.068). Reported 24 weeks placebo: -0.51 (0.069). Above is the reported least square means and calculated standard deviations. In the final report we use the combined microsphere preparation and immediate release corticosteroid results versus placebo. Combined 24 weeks steroid (mean [SD]): -0.564 (0.83) in 294 people. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 1 adverse event, 3 withdrew consent, 4 lack of efficacy, 4 other; Group 2 Number missing: 14, Reason: 1 adverse event, 3 withdrew consent, 2 withdrawn by the investigator/sponsor, 1 protocol non-compliance (after injection), 3 lost to follow up, 4 lack of efficacy Protocol outcome 4: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: ≥1 serious adverse events at 6 months (24 weeks); Group 1: 4/161, Group 2: 3/162; Comments: Individual events reported on https://clinicaltrials.gov/ct2/show/results/NCT02357459?term=NCT02357459&draw=2&rank=1&view=results. Steroid group: 4 adverse events in 4 people - 1 unstable angina, 1 tonic clonic seizure, 1 cerebrovascular accident, 1 depression. Control group: 3 events in 3 people - 1 abdominal hernia, 1 sepsis, 1 cholangitis. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive treatment; Group 2 Number missing: 1, Reason: 1 did not receive treatment	
Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Corrado 1995[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinically and radiologically ascertained mono- or bilateral osteoarthritis of the knee (Altman criteria) of at least 6 months duration
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinically and radiologically ascertained osteoarthritis of the knee (Altman criteria) of at least 6 months duration who presented with at least 3mL joint effusion and pain on movement > 40mm as measured on a Visual Analogue Scale (VAS).
Exclusion criteria	People not falling within the inclusion criteria.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 61.30 (11.14) years. Gender (M:F): 9:31. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms: At least 6 months
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Five injections of sodium hyaluronate (20mg Hyalgan in 2mL phosphate buffer) by intraarticular injection after arthrocentesis (on days 0, 7, 14, 21 and 28).. Duration 5 injections over 5 weeks. Concurrent medication/care: No additional information available. Indirectness: No indirectness (n=19) Intervention 2: Placebo. Five injections of placebo (2mL water for injection containing 17mg sodium chloride, 0.1mg of monobasic sodium phosphate, 1.2mg of bibasic sodium phosphate) by intraarticular injection after arthrocentesis (on days 0, 7, 14, 21 and 28).. Duration 5 injections over 5 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: Pain on movement (visual analogue scale) at 8 weeks; Group 1: mean 29.7 (SD 22.9); n=19, Group 2: mean 43.2 (SD 22.3); n=16; Visual analogue scale (pain on movement) 0-100 Top=High is poor outcome; Comments: Baseline HA: 68.7 (18.9). Baseline placebo: 62.3 (18.8). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age and duration of disease. States that severity was the same between groups.; Group 1 Number missing: 2, Reason: Reports that overall 5 people were excluded from the efficacy analysis: 2 due to accidental trauma to the knee during treatment, 1 for personal reasons, 1 for unknown causes, 1 because the treatment was judged to be unsatisfactory; Group 2 Number missing: 3, Reason: Reports that overall 5 people were excluded from the efficacy analysis: 2 due to accidental trauma to the knee during treatment, 1 for personal reasons, 1 for unknown causes, 1 because the treatment was judged to be unsatisfactory	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Day 2004[102]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=240)
Countries and setting	Conducted in Australia; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 18 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with a diagnosis of mild to moderate, idiopathic, painful femorotibial OA of the knee as defined by: knee pain while standing, walking, and/or in motion, of at least 3 month duration; and evidence of femorotibial osteophytes and/or joint space narrowing based on standing (extended knee) anteroposterior and lateral knee radiographs taken during the previous 6 months.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged between 40 and 75 years inclusive with a body mass index <40. People with a diagnosis of mild to moderate, idiopathic, painful femorotibial osteoarthritis of the knee as defined by: knee pain while standing, walking and/or in motion, of at least 3 months duration, and evidence of femorotibial osteophytes and/or joint space narrowing based on standing anterior posterior and lateral knee radiographs taken during the previous 6 months. People with unilateral or predominantly unilateral symptomatology. People who gave their informed written consent to participate. People willing to discontinue their current osteoarthritis treatment for the study duration (18 weeks), starting one week prior to their first injection. This included treatment with any IA injections, oral corticosteroids, NSAID, nutriceuticals, complementary and herbal therapies, occlusive dressings, physiotherapy (other than that sanctioned for the study), or orthopaedic devices.
Exclusion criteria	Pregnant and lactating. Fertile women not using sufficient contraception. Complete loss of joint space. Predominant patellofemoral osteoarthritis as the primary diagnosis on clinical and radiographic grounds. People with severe malalignment of the knee or a large, tight effusion. People with clinical manifestations of osteoarthritis of the hip and/or history of a joint replacement in the lower extremities, a history of surgery on the knee within the previous 12 months, or arthroscopy within the previous 6 months were excluded. People with other arthritides such as inflammatory arthritis or gout. People with a history of any IA injection of corticosteroid or HA in the previous 3 months.

Recruitment/selection of patients	Carried out over 17 investigational centers throughout Australia.
Age, gender and ethnicity	Age - Mean (range): 62 (33-79). Gender (M:F): 99:141. Ethnicity: Not stated
Further population details	1. Age: Mixed 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Mild to moderate Symptom duration: Median 2-5 years..
Indirectness of population	No indirectness
Interventions	(n=116) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 25mg of sodium hyaluronic acid in 2.5mL of phosphate buffered saline (ARTZ). The sodium HA was extracted from rooster combs and the purified material has a molecular weight of 6.2-11.7x10^5 Da.. Duration 1 injection, followed up over 18 weeks. Concurrent medication/care: People were provided with instruction on a set of physiotherapy exercises to be performed throughout the study and with paracetamol for breakthrough pain.. Indirectness: No indirectness (n=124) Intervention 2: Placebo. 2.5mL of phosphate buffered saline vehicle. Duration 1 injection, followed up over 18 weeks. Concurrent medication/care: People were provided with instruction on a set of physiotherapy exercises to be performed throughout the study and with paracetamol for breakthrough pain.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by the Seikagaku Corporation, Tokyo, Japan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 18 weeks; Group 1: mean 3.84 (SD 3.27); n=108, Group 2: mean 4.61 (SD 3.14); n=115; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 7.96 (3.10). Baseline placebo: 8.68 (3.72).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values of WOMAC pain and physical function are higher for the controls than the intervention group.; Group 1 Number missing: 8, Reason: Modified ITT. 8 people excluded as they did not receive any treatment. 3 additional people did not finish the follow up period - last values used.; Group 2 Number missing: 9, Reason: Modified ITT. 9 excluded as 7 did not receive any treatment and 2 did not return for visit 3. An additional 1 did not finish follow up - last values used.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC disability at 18 weeks; Group 1: mean 15.37 (SD 11.41); n=108, Group 2: mean 17.81 (SD 10.53); n=115; WOMAC

physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 28.07 (11.81). Baseline placebo: 31.25 (13.68). Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values of WOMAC pain and physical function are higher for the controls than the intervention group.; Group 1 Number missing: 8, Reason: Modified ITT. 8 people excluded as they did not receive any treatment. 3 additional people did not finish the follow up period - last values used.; Group 2 Number missing: 9, Reason: Modified ITT. 9 excluded as 7 did not receive any treatment and 2 did not return for visit 3. An additional 1 did not finish follow up - last values used.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study (subsidiary papers)	Decaria 2012[109] (Decaria 2011[108])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Canada; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiographically diagnosed mild-moderate knee OA
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People between 60 and 80 years old, all providing informed consent at the pre-treatment visit 1 week before the first injection. All had diagnosed knee osteoarthritis based on the criteria set forth by the American College of Rheumatology. Specifically, participants had radiographically diagnosed knee osteoarthritis, grade 2-3 based on the Kellgren-Lawrence scale, and presented clinically with knee pain. Radiographic evidence of knee osteoarthritis was based on a routine lateral view and a standing anterior-posterior weight bearing radiograph, taken at the pre-treatment visit. If participants had bilateral knee osteoarthritis, the knee regarded as the worst symptomatically by the participant was considered as the study knee. At the time of consent, participants agreed to discontinue any pharmacological knee osteoarthritis medication they were taking for the duration of the study.
Exclusion criteria	Had any non-osteoarthritis arthritis (such as microcystalline arthritis); osteoarthritis in any other of the lower limb joints besides the knee; end stage knee osteoarthritis; lower back pathology that limited their walking capacity; a leg length differential >2cm; diagnosed with a neurological or cardiovascular condition that could impair gait function; were cognitively impaired; underwent knee surgery on the study knee (barring arthroscopy 18 months prior to study commencement), received an intraarticular injection within 6 months prior to study commencement; or for the chronic use of oral steroids.
Recruitment/selection of patients	Community dwelling older adults who have lived with knee OA for multiple years were recruited from the Joint Pain Relief Center at Parkwood hospital in London, Ontario, Canada
Age, gender and ethnicity	Age - Mean (SD): 72.4 (6.2). Gender (M:F): 16:14. Ethnicity: Not stated

Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: High comorbidity score (Number of co-morbidities HA: 2.07 (1.98). Number of co-morbidities placebo: 1.94 (1.03).).
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 2-3 changes. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hyaluronic acid injections - 2.0mL of 20mg/mL hyaluronic acid (730kDa). Three weekly injections given by the blinded study physician using a 23 gage 1.5 inch needle with an anteromedial approach. Duration 3 injections over 3 weeks. Concurrent medication/care: All participants were given rescue medication (500mg paracetamol, 4g/day maximum) that could be used up to 8 hours before their next study visit and information on a home exercise program specifically designed for people with knee osteoarthritis (consisted of joint unloading, as well as knee range of motion and isotonic strength training activities).. Indirectness: No indirectness (n=15) Intervention 2: Placebo. Placebo injections of inert hyaluronic acid - 1.2mL of 0.001mg/mL hyaluronic acid. Three weekly injections given by the blinded study physician using a 23 gage 1.5 inch needle with an anteromedial approach. Duration 3 injections over 3 weeks. Concurrent medication/care: All participants were given rescue medication (500mg paracetamol, 4g/day maximum) that could be used up to 8 hours before their next study visit and information on a home exercise program specifically designed for people with knee osteoarthritis (consisted of joint unloading, as well as knee range of motion and isotonic strength training activities).. Indirectness: No indirectness
Funding	Academic or government funding (The study was supported, in part, by grants from the Physicians' Services Incorporated Research Foundation, and by the Canadian Institutes of Health Research. Dr Montero Odasso is the first recipient of the Schulich Clinician Scientist Award and recipient of the CIHR New Investigator Award)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 3 months; Group 1: mean -2.2 (SD 2.84); n=15, Group 2: mean -1.73 (SD 3.2); n=15; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 5.20 (3.43). Baseline placebo: 7.27 (3.75).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, number of comor-bidities, knee OA, and baseline values of outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Knee: WOMAC pain at 6 months; Group 1: mean -1.87 (SD 2.12); n=15, Group 2: mean -0.6 (SD 3.23); n=15; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 5.20 (3.43). Baseline placebo: 7.27 (3.75). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, number of comor-bidities, knee OA, and baseline values of outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function at 3 months; Group 1: mean -9.07 (SD 10.28); n=15, Group 2: mean -7.47 (SD 10.05); n=15; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 23.40 (11.54). Baseline placebo: 28.74 (7.28). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, number of comor-bidities, knee OA, and baseline values of outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Knee: WOMAC physical function at 6 months; Group 1: mean -9.07 (SD 8.14); n=15, Group 2: mean -3.53 (SD 10.15); n=15; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 23.40 (11.54). Baseline placebo: 28.74 (7.28). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, number of comor-bidities, knee OA, and baseline values of outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 0/15, Group 2: 0/15 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, number of comor-bidities, knee OA, and baseline values of outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Degroot 2012[110]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ankle arthritis classified on radiographs as Kellgren and Lawrence grade 2 or higher
Stratum	Ankle
Subgroup analysis within study	Not applicable
Inclusion criteria	Age of ≥18 years with ankle pain and ankle arthritis classified on radiographs as Kellgren and Lawrence grade 2 or highers. American orthopaedic foot and ankle society score of ≤90 points. Willingness to discontinue all pain medications and nonsteroidal anti-inflammatory drugs other than the rescue pain medications provided in the study
Exclusion criteria	Pregnancy; systemic inflammatory condition; infection to the ankle or nearby soft tissues; injection of steroid or surgery on the involved joint within 6 months; local cellulitis, rash or skin condition; diabetic or neuropathic Charcot arthropathy; substantial vascular insufficiency; current treatment with anticoagulants; lower-extremity pain syndromes; recent history of sciatica, ankle sprains or plantar fasciitis; severe ankle instability or malalignment; known allergy to any of the components of either injection; disabling degenerative joint disease of the ipsilateral hip, knee or foot.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 57.2 (14.8). Gender (M:F): 36:28. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Supartz - sodium hyaluronate injected into the ankle. Non-cross linked sodium hyaluronate derived from rooster combs with a molecular weight of 620000 to 1170000 Da. 2.5mL (25mg). Injections were given by means of an anteromedial or

	anterolateral approach with use of fluoroscopic guidance.. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=25) Intervention 2: Placebo. One injection of 2.5mL of normal saline following the same methodology. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Other author(s) funded by industry (One or more of the authors received payments of services, either directly or indirectly, from a third party in support of an aspect of this work. None of the authors or their institutions, have had any financial relationship in the third six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have potential to influence what is written in this work)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Ankle: Visual analogue scale (pain) at 12 weeks; Group 1: mean -4.1 (SD 26.5); n=35, Group 2: mean -11.1 (SD 21.6); n=21; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 33.4 (22.4). Baseline placebo: 35.0 (23.1). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, Kellgren and Lawrence score, and baseline values of outcomes; Group 1 Number missing: 4, Reason: Unclear form of imputation, reports ITT with all people. 4 people withdrew (but not for AEs).; Group 2 Number missing: 4, Reason: Unclear form of imputation, reports ITT with all people. 4 people withdrew (but not for AEs). Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Ankle: Adverse events at 12 weeks; Group 1: 1/39, Group 2: 0/25; Comments: 1 enlarged lymph note in the ipsilateral groin, which resolved without treatment in the HA group Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, Kellgren and Lawrence score, and baseline values of outcomes; Group 1 Number missing: 0, Reason: Unclear form of imputation, reports ITT with all people. 4 people withdrew (but not for AEs).; Group 2 Number missing: 0, Reason: Unclear form of imputation, reports ITT with all people. 4 people withdrew (but not for AEs).	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Diracoglu 2009[122]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Bilateral knee osteoarthritis according to the criteria of the American College of Rheumatology and at stage 2 and 3 according to the Kellgren Lawrence scale
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People diagnosed with bilateral knee osteoarthritis according to the criteria of the American College of Rheumatology, and were at stage 2 and 3 according to the Kellgren Lawrence scale. They also had a minimum of 50 points from the VAS-pain scale of 100mm during motion on both knees
Exclusion criteria	People with septic arthritis, Paget's disease, gout and pseudogout, major dysplasia or congenital abnormalities, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary osteochondromatosis, Ehlers-Danlos syndrome, neuropathic arthropathy (Charcot joints), hyperparathyroidism, hypothyroidism, or active synovitis; people who have had serious knee trauma or surgical operation; people who had undergone arthroscopy of the knee joint in the last one year; people who have received intra-articular steroids or hyaluronic acid injection in the knee joint in the last 6 months; people with concomitant rheumatoid disease; pregnant people
Recruitment/selection of patients	Enrolled to a single study site
Age, gender and ethnicity	Age - Mean (SD): 58.3 (9.2). Gender (M:F): 4:56. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 2-3. Duration of symptoms: not stated
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronic acid (Hylan G-F 20, Synvisc) injected into both knees (no information on dose). Duration 3 injections over 3 weeks. Concurrent

	medication/care: No additional information. Indirectness: No indirectness (n=21) Intervention 2: Placebo. Intraarticular sterile physiological saline (0.9% sodium chloride) injected into both knees (no information on dose). Duration 3 injections over 3 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC pain subscale at 4 weeks; Group 1: mean -1.66 (SD 1.1); n=40, Group 2: mean -0.41 (SD 0.9); n=20; WOMAC pain subscale 0-10 Top=High is poor outcome; Comments: Baseline HA: 5.84 (1.32). Baseline placebo: 5.6 (1.13). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI and baseline outcomes. States there was no difference in Kellgren-Lawrence scores at baseline.; Group 1 Number missing: 2, Reason: 2 people had difficulty in coming to the clinic for treatment; Group 2 Number missing: 1, Reason: 1 person did not benefit from the treatment Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function subscale at 4 weeks; Group 1: mean -1.5 (SD 1); n=40, Group 2: mean -0.53 (SD 1.1); n=20; WOMAC physical function subscale 0-10 Top=High is poor outcome; Comments: Baseline HA: 5.87 (1.3). Baseline placebo: 5.7 (0.95). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI and baseline outcomes. States there was no difference in Kellgren-Lawrence scores at baseline.; Group 1 Number missing: 2, Reason: 2 people had difficulty in coming to the clinic for treatment; Group 2 Number missing: 1, Reason: 1 person did not benefit from the treatment	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Dixon 1988[123]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 25 weeks (48 weeks after the first injection)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic osteoarthritis in one or both knees
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People of either sex or age were considered for the trial if they were suffering from symptomatic osteoarthritis of one or both knees
Exclusion criteria	If they had accompanying osteoarthritis of the hip; if there were primary inflammatory conditions of the knee, e.g. rheumatoid arthritis, psoriatic arthropathy, pseudogout, or joint infection; poor general health; if they had skin conditions overlying the joint through which it was considered unwise to make injections; if thy were receiving regular analgesic therapy for reasons other than painful osteoarthritis of the knee
Recruitment/selection of patients	Involved three hospital centres
Age, gender and ethnicity	Age - Mean (range): 68.5 (43-85). Gender (M:F): 29:34. Ethnicity: Not stated
Further population details	1. Age: Mixed 2. Diagnostic method: Diagnosed without imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms: Not stated.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Sodium hyaluronate injection (20mg). Duration 11 injections over 23 weeks. Concurrent medication/care: Treatment with corticosteroids, non-steroidal anti-inflammatory agents and strong analgesics were not permitted during the trial period but there were no other restrictions regarding concomitant therapy. People were permitted to take paracetamol tablets, up to a total dose of 1g 3 times daily, for the treatment of their knee pain. Indirectness: No indirectness (n=33) Intervention 2: Placebo. Sodium hyaluronate injection (0.2mg) - 1/100th of the

	dose of the intervention drug. Duration 11 injections over 23 weeks. Concurrent medication/care: Treatment with corticosteroids, non-steroidal anti-inflammatory agents and strong analgesics were not permitted during the trial period but there were no other restrictions regarding concomitant therapy. People were permitted to take paracetamol tablets, up to a total dose of 1g 3 times daily, for the treatment of their knee pain. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Development of a haemarthrosis and severe pain at 48 weeks; Group 1: 1/30, Group 2: 1/33; Comments: HA: 1 person developed a haemarthrosis. Placebo: 1 person developed severe pain. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports overall values and states that there was no significant difference between groups; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Dougados 1993[126]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in France; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year (intervention once a week for 3 weeks, then followed up for 1 year in total)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American college of Rheumatology criteria for osteoarthritis of the knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients fulfilling the criteria of the American College of Rheumatology (ACR) for the diagnosis of osteoarthritis of the knee with femorotibial localisation of the disease, the presence of a knee effusion, a painful knee defined as a pain evaluated by the patient at 40mm or more on a 100mm visual analogue scale.
Exclusion criteria	People with a serious concomitant medical illness; a secondary osteoarthritis of the knee as defined by the ACR; knee with prosthesis; any intra-articular surgery of the evaluated knee (for example, meniscectomy in the 10 years prior to the study); any extra-articular surgery of the evaluated knee (e.g. osteotomy) during the last 2 years prior to the study; any arthrocentesis of the evaluated knee during the previous 3 months; any physiotherapy and the dose of any nonsteroidal antiinflammatory drugs (NSAIDs) and/or analgesics had to be stable during the previous month before entry into the trial.
Recruitment/selection of patients	Outpatients at one hospital - no additional information
Age, gender and ethnicity	Age - Mean (SD): 68.0 (10.2). Gender (M:F): 32:78. Ethnicity: Not stated
Further population details	1. Age: Mixed (Confidence intervals fall over the 75 years region.). 2. Diagnostic method: Not stated / Unclear (Could have been diagnosed without imaging, but the ACR criteria also allow for imaging based diagnosis). 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms (mean [SD]): 68.5 (61.8) months
Indirectness of population	No indirectness

Interventions	(n=55) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hyalectin (20mg) in a saline vehicle (2mL). Supplied in coded indistinguishable ampuoles. However, the viscosity of the vehicle was lower than that of the hyalectin. One intraarticular injection once a week for 3 weeks (four injections total).. Duration 4 weeks (1 weekly injection) with follow up for 12 months in total. Concurrent medication/care: They were allowed to use 'basic' therapy for osteoarthritis as long as the dose had been stable during the previous 3 months - including physiotherapy, NSAIDs and/or other analgesics. Indirectness: No indirectness (n=55) Intervention 2: Placebo. Intraarticular saline vehicle (2mL) alone. Given as four injections over four weeks.. Duration 4 weeks (1 weekly injection) with follow up for 12 months in total. Concurrent medication/care: They were allowed to use 'basic' therapy for osteoarthritis as long as the dose had been stable during the previous 3 months - including physiotherapy, NSAIDs and/or other analgesics. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Pain (VAS) after exercise at 4 weeks; Group 1: mean -35.5 mm (SD 26.4); n=49, Group 2: mean -25.8 mm (SD 21.4); n=46; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline pain (VAS) after exercise HA: 67.6 (16.3). Baseline pain (VAS) after exercise placebo: 61.9 (12.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Two had a total knee replacement. Two discontinued due to adverse event (painful injection). One discontinued due to lack of efficacy). One refused to continue treatment after the third injection due to marked improvement. 2 received an IA corticosteroid injection between week 4 and 7. 3 were lost to follow up between week 7 and 52. Used values reported in text.; Group 2 Number missing: 9, Reason: Five had a total knee replacement. Other information not provided. One discontinued the treatment due to adverse events (painful injection), one due to lack of efficacy, three due to reasons unrelated to the treatment (traumatic haemarthrosis after the first injection, refusal to continue in one person after the first injection and one after the second injection). Four received corticosteroid injection between week 4 and 7. 4 were lost to follow up between week 7 and 52.
- Actual outcome for Knee: Pain (VAS) after exercise at 52 weeks; Group 1: mean -38.9 mm (SD 30.9); n=47, Group 2: mean -32.7 mm (SD 28.8); n=48; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline pain (VAS) after exercise HA: 67.6 (16.3). Baseline pain (VAS) after exercise placebo: 61.9 (12.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: Two had a total knee replacement. Two discontinued due to adverse event (painful injection). One discontinued due to lack of efficacy). One refused to continue treatment after the third injection due

to marked improvement. 2 received an IA corticosteroid injection between week 4 and 7. 3 were lost to follow up between week 7 and 52. Used values reported in text.; Group 2 Number missing: 7, Reason: Five had a total knee replacement. Other information not provided. One discontinued the treatment due to adverse events (painful injection), one due to lack of efficacy, three due to reasons unrelated to the treatment (traumatic haemarthrosis after the first injection, refusal to continue in one person after the first injection and one after the second injection). Four received corticosteroid injection between week 4 and 7. 4 were lost to follow up between week 7 and 52. Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Severe adverse events at 52 weeks; Group 1: 0/55, Group 2: 0/55 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Two had a total knee replacement. Two discontinued due to adverse event (painful injection). One discontinued due to lack of efficacy). One refused to continue treatment after the third injection due to marked improvement. 2 received an IA corticosteroid injection between week 4 and 7. 3 were lost to follow up between week 7 and 52. Used values reported in text.; Group 2 Number missing: 0, Reason: Five had a total knee replacement. Other information not provided. One discontinued the treatment due to adverse events (painful injection), one due to lack of efficacy, three due to reasons unrelated to the treatment (traumatic haemarthrosis after the first injection, refusal to continue in one person after the first injection and one after the second injection). Four received corticosteroid injection between week 4 and 7. 4 were lost to follow up between week 7 and 52.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Emadedin 2018[130]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in Iran; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People fulfilling the clinical and radiological criteria for knee osteoarthritis according to the American College of Rheumatology
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-65 years; Kellgren and Lawrence grade 2-4; osteoarthritis diagnosed using X-rays; no severe joint involvement for grade 4 osteoarthritis; angle of parenthesis feet not >20 degrees; WOMAC pain score >25
Exclusion criteria	Malignancy; organ failure; uncontrolled chronic disease other than OA; allergic reaction to anaesthesia; positive viral markers (HIV, hepatitis B and C, human T-cell leukemia virus type 1/2); allergic reaction to components of study treatment and/or study implantation procedure; pregnancy or lactation
Recruitment/selection of patients	People who frequented the Orthopedic Clinic at Royan Cell Therapy Center
Age, gender and ethnicity	Age - Mean (SD): 53.4 (7.4). Gender (M:F): 27:16. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-4. Duration of symptoms: 13.1 (7.9) months.
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). One intraarticular implantation of 40x10^6 mesenchymal stem cells in 5mL saline supplemented with 2% human serum albumin. Performed according to each person's anatomy, which was shown in the knee radiograph (no real time imaging, so placed in the non-image guided group?).. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=25) Intervention 2: Placebo. One intraarticular injection of 5mL normal saline

	supplemented with 2% human serum albumin. Performed according to each person's anatomy, which was shown in the knee radiograph.. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant from the Royan Institute)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain subscale at 6 months; Group 1: mean -35 (SD 77.7); n=19, Group 2: mean -12.2 (SD 30.5); n=24; WOMAC pain subscale 0-100 Top=High is poor outcome; Comments: Reports change score and 95% CIs. Reported stem cells: -35 (-44.9-25). Reports placebo -12.2 (-18.5-5.9). Does not report baseline values.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of symptoms, BMI, Kellgren Lawrence grade. Does not report outcome baseline values.; Group 1 Number missing: 5, Reason: 2 did not receive treatment. 3 were lost to follow up (withdrew consent).; Group 2 Number missing: 1, Reason: 1 was lost to follow up (withdrew consent).
- Actual outcome for Knee: WOMAC pain subscale at 3 months; Group 1: mean -27.9 (SD 23.4); n=18, Group 2: mean -11.7 (SD 15.1); n=23; WOMAC pain subscale 0-100 Top=High is poor outcome; Comments: Reports change score and 95% CIs. Reported stem cells: -27.9 (-38.7,-17.1). Reports placebo -11.7 (-17.9,-5.5). Does not report baseline values.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of symptoms, BMI, Kellgren Lawrence grade. Does not report outcome baseline values.; Group 1 Number missing: 5, Reason: 2 did not receive treatment. 3 were lost to follow up (withdrew consent).; Group 2 Number missing: 1, Reason: 1 was lost to follow up (withdrew consent).

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function subscale at 6 months; Group 1: mean -22.9 (SD 51); n=19, Group 2: mean -9.5 (SD 30.6); n=24; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Reports change score and 95% CIs. Reported stem cells: -22.9 (-32.9-12.9). Reports placebo -9.5 (-21.8-2.7). Does not report baseline values.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of symptoms, BMI, Kellgren Lawrence grade. Does not report outcome baseline values.; Group 1 Number missing: 5, Reason: 2 did not receive treatment. 3 were lost to follow up (withdrew consent).; Group 2 Number missing: 1, Reason: 1 was lost to follow up (withdrew consent).
- Actual outcome for Knee: WOMAC physical function subscale at 3 months; Group 1: mean -16 (SD 19.3); n=18, Group 2: mean -6.8 (SD 10.8); n=23; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Reports change score and 95% CIs. Reported stem cells: -16 (-24.9,-7.1). Reports placebo -6.8 (-11.2,-2.4). Does not report baseline values.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of symptoms, BMI, Kellgren Lawrence grade. Does not report outcome baseline values.; Group 1 Number missing: 5, Reason: 2 did not receive treatment. 3 were lost to follow up

(withdrew consent).; Group 2 Number missing: 1, Reason: 1 was lost to follow up (withdrew consent). Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 0/18, Group 2: 0/23; Comments: No definition Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, duration of symptoms, BMI, Kellgren Lawrence grade. Does not report outcome baseline values.; Group 1 Number missing: 5, Reason: 2 did not receive treatment. 3 were lost to follow up (withdrew consent).; Group 2 Number missing: 1, Reason: 1 was lost to follow up (withdrew consent).	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	FLEXX trial: Altman 2009[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=588)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Osteoarthritis of the knee by the American College of Rheumatology criteria
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	OA of the knee by American College of Rheumatology criteria; moderate to severe pain score of 41 to 90 mm recorded on 100-mm visual analog scale (VAS) immediately following a 50-foot walk; bilateral standing anterior-posterior radiograph demonstrating Kellgren and Lawrence grade 2 or 3 OA of the target knee; ability and willingness to use only acetaminophen as the analgesic (rescue) study medication; unassisted walking 50 feet on a flat surface and going up and down stairs; and willingness and ability to complete efficacy and safety questionnaires. Subjects having radiographic confirmation of OA in the nontarget (contralateral) knee were eligible as long as the target knee was the more symptomatic knee and met the criteria listed above. Pain in the nontarget knee must have been limited to <40mm following the 50-foot walk test at screening.
Exclusion criteria	Any major injury to the target knee within the prior 12 months; any surgery to the target knee within the prior 12 months or surgery to the contralateral knee or other weight-bearing inflammatory arthropathies; gout or pseudogout within the previous 6 months; radiographic acute fracture, severe loss of bone density, avascular necrosis, and/or severe bone or joint deformity in the target knee; osteonecrosis of either knee; fibromyalgia, pes anserine bursitis, lumbar radiculopathy, and/or neurogenic or vascular claudication; significant anterior knee pain due to diagnosed isolated patella-femoral syndrome or chondromalacia in the target knee; target knee joint infection or skin disorder/infection within the previous 6 months; symptomatic osteoarthritis of the hips, spine or ankle; known hypersensitivity to acetaminophen, IA-BioHA, or phosphate-buffered saline solution; women of childbearing potential who are pregnant, nursing, or planning to become pregnant, and those who do not agree to remain on an acceptable method of birth control throughout the study; history of immune disorders; vascular insufficiency of lower limbs or peripheral neuropathy; current treatment or

	treatment of cancer within the previous 2 years (excluding basal cells or squamous cell carcinoma of the skin); active liver or renal disease; any clinically significant abnormal laboratory value; any intercurrent chronic disease or condition that might interfere with the completion of the study; and participation in any experimental device study within the prior 6 months or any experimental drug study within the prior month.
Recruitment/selection of patients	Subjects were enrolled at 36 sites.
Age, gender and ethnicity	Age - Mean (SD): 61.64 (10.54). Gender (M:F): 216:370. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Not stated / Unclear (Unclear - American College of Rheumatology criteria allow for imaging and clinical diagnosed). 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated (K-L grade 2-3) Duration of symptoms: Not explicitly stated.
Indirectness of population	No indirectness
Interventions	(n=293) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 3 weekly injections of IA-BioHA (20mg/2mL of 1% sodium hyaluronate). Duration 26 weeks. Concurrent medication/care: Aspirin to a maximum of 325mg a day was allowed for cardiovascular protection. Nonprescription neutraceuticals (e.g. glucosamine, chondroitin), topical analgesics, and nasal or inhaled corticosteroids were allowed if the dosage had been stable for at least 1 month and the identical regimen was to be continued throughout the study period. Nonpharmacologic treatments (physical therapy, acupuncture, osteopathic, and chiropractic manipulations) were allowed if treatment had been stable for a tleast 1 month and there was no plan to change frequency throughout the course of the study. The following had to be discontinued: NSAIDs, opioid narcotics, local corticosteroid knee injections, systemic corticosteroids, IA-HA in the past 6 months.. Indirectness: No indirectness (n=295) Intervention 2: Placebo. Three weekly injections of intraarticular phosphate buffered saline (2mL). Duration 26 weeks. Concurrent medication/care: Aspirin to a maximum of 325mg a day was allowed for cardiovascular protection. Nonprescription neutraceuticals (e.g. glucosamine, chondroitin), topical analgesics, and nasal or inhaled corticosteroids were allowed if the dosage had been stable for at least 1 month and the identical regimen was to be continued throughout the study period. Nonpharmacologic treatments (physical therapy, acupuncture, osteopathic, and chiropractic manipulations) were allowed if treatment had been stable for a tleast 1 month and there was no plan to change frequency throughout the course of the study.

	The following had to be discontinued: NSAIDs, opioid narcotics, local corticosteroid knee injections, systemic corticosteroids, IA-HA in the past 6 months.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Ferring Pharmaceuticals Inc. Parsippany, New Jersey)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain (mm VAS) at 6 months; Group 1: mean -19.2 mm (SD 26.8); n=291, Group 2: mean -16.3 mm (SD 26.8); n=295; WOMAC pain subscale (mm VAS) 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34, Reason: 34 discontinued: 11 adverse events, 1 exclusion meds, 3 protocol violations, 12 withdrew consent, 4 lost to follow up, 3 other; Group 2 Number missing: 34, Reason: 34 discontinued: 6 adverse events, 2 exclusion meds, 3 protocol violations, 13 withdrew consent, 3 lost to follow up, 7 other

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function (mm VAS) at 6 months; Group 1: mean -19.5 mm (SD 24.7); n=291, Group 2: mean -14.6 mm (SD 25.8); n=295; WOMAC physical function subscale (mm VAS) 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34, Reason: 34 discontinued: 11 adverse events, 1 exclusion meds, 3 protocol violations, 12 withdrew consent, 4 lost to follow up, 3 other; Group 2 Number missing: 34, Reason: 34 discontinued: 6 adverse events, 2 exclusion meds, 3 protocol violations, 13 withdrew consent, 3 lost to follow up, 7 other

Protocol outcome 3: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Serious treatment-emergent adverse events at 6 months; Group 1: 11/293, Group 2: 11/295; Comments: Individual events not reported clearly. Includes at least 2 TIAs, 2 pneumonia and 1 death due to a car accident.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Initially blinded for 6 months, then followed up an open additional follow up period.; Group 1 Number missing: 34, Reason: 34 discontinued: 11 adverse events (unclear if included in outcome), 1 exclusion meds, 3 protocol violations, 12 withdrew consent, 4 lost to follow up, 3 other; Group 2 Number missing: 34, Reason: 34 discontinued: 6 adverse events (unclear if included in outcome), 2 exclusion meds, 3 protocol violations, 13 withdrew consent, 3 lost to follow up, 7 other

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Frizziero 2002[151]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Italy; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with primary OA (n=50) or secondary OA due to trauma (n=49) with Kellgren-Lawrence grades I-III and fulfilling the clinical and radiological criteria of the American College of Rheumatology. Diagnosis confirmed by arthroscopy.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary or secondary osteoarthritis of the knee with Kellgren-Lawrence grades I-III changes and fulfilling the clinical and radiological criteria of the American College of Rheumatology. When bilateral OA was present the most severely affected knee was selected for treatment.
Exclusion criteria	People judged not controllable or unreliable, those with presence of severe concomitant diseases, suspected joint infection, concomitant treatment with NSAIDs, intra-articular steroid treatment in the previous 3 months, pregnancy and breast feeding.
Recruitment/selection of patients	People referred to the Rheumatology Unit (Department of Internal Medicine, Maggiore Hospital, Bologna, Italy), usually by their family doctor.
Age, gender and ethnicity	Age - Mean (SD): 49.5 (14.5). Gender (M:F): 46:53. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Majority moderate Symptom duration: 25.1 (24.1) months
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Five injections once a week for five weeks of 20mg (in 2mL) hyaluronic acid (Hyalgan, 500-730 kDa).. Duration 5 injections over 5 weeks. Concurrent medication/care: Not clearly stated. Not allowed other intraarticular injections or concomitant treatment with NSAIDs.. Indirectness: No indirectness

	(n=47) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Methylprednisolone acetate (dose unclear due to typo in the paper) once a week for 3 weeks.. Duration 3 injections over 3 weeks. Concurrent medication/care: Not clearly stated. Not allowed other intraarticular injections or concomitant treatment with NSAIDs.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 0/52, Group 2: 0/47 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Fuchs 2006[152]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in Germany; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic osteoarthritis of the carpometacarpal joint of the thumb associated with radiographic evidence according to the Kellgren score
Stratum	Thumb
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged between 44 and 80 years showing symptomatic osteoarthritis of the carpometacarpal joint of the thumb associated with radiographic evidence according to the Kellgren scale with pain (according to the visual analogue scale) ≥40mm for at least 6 months who were in good general condition and had good compliance. Willing to stop other treatments (including physical therapy, splints, nutritional supplements, NSAIDs, other oral analgesics).
Exclusion criteria	History or presence of alcohol or drug abuse; psychotic disorders; epilepsy; high risk of suicide; subjects unable to understand informed consent or having a high probability or non-compliance; intra-articular treatment of any joint with corticosteroids or glycosaminoglycans within 3 months or with a sodium hyaluronate based product within 6 months prior to the first injection; people with a known allergy or other contraindications to administered reagents; critical skin conditions at injection side; hemarthrosis or joint effusion; non-osteoarthritic joint disease (rheumatoid arthritis, inflammatory joint diseases, chondrocalcinosis); immune deficiencies; malignant diseases; uncontrolled diabetes; use of anticoagulants or joint infection
Recruitment/selection of patients	Seen in two centres
Age, gender and ethnicity	Age - Range: 44-80. Gender (M:F): 11:45. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on range). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms: Not stated. Pain for at least 6 months..
Indirectness of population	No indirectness

Interventions	(n=28) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Three injections of Ostenil mini - 1mL prefilled syringe containing 1% sodium hyaluronate. Duration 3 injections over 3 weeks. Concurrent medication/care: Paracetamol was allowed as rescue analgesia, otherwise other treatments were stopped. Indirectness: No indirectness (n=28) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Three injections of triamcinoline acetonide - 1mL prefilled syringe containing 10mg triamicinolone acetonide in a crystal suspension. Duration 3 injections over 3 weeks. Concurrent medication/care: Paracetamol was allowed as rescue analgesia, otherwise other treatments were stopped. Indirectness: No indirectness
Funding	Study funded by industry (Study funded by TRB Chemedica AG, Richard-Reitzner-Allee 1, 85540 Haar/Mucnich, Germany. This company was not involved in the treatment and assessment of patients.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Thumb: Adverse events that led to withdrawal from the study at 6 months; Group 1: 2/28, Group 2: 3/28; Comments: Five adverse events (three in the SH-group and two in the TA group: e.g. collapse, pain in index, lumbal ischialgia and lung carcinoma) caused the early withdrawal of subjects from the study Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports homogeneity analysis for a lot of outcomes, but doesn't report the outcomes themselves; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Gaffney 1995[153]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical and radiographic evidence of knee OA with knee pain and functional impairment during a 6 month period.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with clinical and radiographic evidence of knee OA who presented to a general rheumatology clinic with knee pain and functional impairment (modified Health Assessment Questionnaire >0) during a six month period. Those with bilateral knee OA had the most painful knee studied.
Exclusion criteria	No additional exclusion criteria stated
Recruitment/selection of patients	People presenting to a general rheumatology clinic
Age, gender and ethnicity	Age - Mean (SD): 67.0 (9.2). Gender (M:F): 24:60. Ethnicity: Not stated
Further population details	1. Age: Mixed (Due to standard deviation, could overlap). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated explicitly Symptom duration: 6.9 (6.5) years.
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular triamcinolone hexacetonide (20mg in 1mL). Duration 1 injection followed up for 6 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=42) Intervention 2: Placebo. Intraarticular placebo (1mL of 0.9% normal saline). Duration 1 injection followed up for 6 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 6 weeks; Group 1: mean 35.8 mm (SD 26.8); n=42, Group 2: mean 42.9 mm (SD 26); n=40; Visual analogue scale 0-100 Top=High is poor outcome; Comments: Baseline CS: 52.0 (21.1). Baseline placebo: 57.0 (22.0).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in the VAS and HAQ scores at baseline - has an effect of the result interpretation; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 2 withdrew due to lack of efficacy

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: Health assessment questionnaire modified for lower limb function at 6 weeks; Group 1: mean 4.5 (SD 2.3); n=42, Group 2: mean 4.2 (SD 2); n=40; Health assessment questionnaire modified for lower limb function 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Not one of our preferred methods of measuring physical function; Baseline details: Difference in the VAS and HAQ scores at baseline - has an effect of the result interpretation; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 2 withdrew due to lack of efficacy

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Gencer 2014[159]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TMJ derangement present on CT. People were evaluated according to the Wilkes classification. Late intermediate or late stage people were included in the study group (stage 4-5). These had radiological evidence of significant degenerative changes. The control group (placebo) selected from people in stage 1 (no significant symptoms, slight forward displacement but overall acceptable radiography).
Stratum	TMJ:
Subgroup analysis within study	Not applicable
Inclusion criteria	People with clinical evidence of TMJ disease. CT examination was performed on people who presented with symptoms of jaw pain, limited or painful jaw movement, clicking or grating within the joint. TMJ disorder diagnosis was confirmed with demonstration of temporomandibular joint degeneration on CT. Late intermediate and late Wilkes stage changes in people led to the people being included in the study groups. Control groups selected from people with early stage changes.
Exclusion criteria	Recent operations, systemic disorders, fibromyalgia syndromes, known hypersensitivities to NSAIDs, positive history for peptic ulcer, and presence of headache or earache due to other reasons were excluded
Recruitment/selection of patients	All people were prescribed an NSAID (Etodolac 400mg twice a day, PO) and a muscle relaxant drug (Thiocolchicoside 8mg twice a day, PO) for a week as the non-invasive treatment. If they did not benefit then they were advised to have an intraarticular injection.
Age, gender and ethnicity	Age - Mean (SD): 42.5 (10.2). Gender (M:F): 45:55. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Late intermediate to late changes. Wilkes grade 4-5. Duration of symptoms: Not stated.
Indirectness of population	No indirectness

Interventions	(n=25) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Intra articular hyaluronic acid (Hyalgan, 10mg/mL, 2mL syringe) 0.5mL. Injected by a 2mL syringe with a 27 gauge needle. The injection took place under ultrasound guidance. The needle was inserted into the superior joint space, behind the condyle and beneath the zygoma and passed until three fourths of the needle was in the joint space under ultrasonographic guidance. It was ensured that the needle was not in a blood vessel by aspirating before injection.. Duration 1 injection. Concurrent medication/care: An ice pack was applied immediately after injection. Five minutes after the injection, the person was examined for signs of facial palsy, and manual mobilisation of the jaw was performed to improve mouth opening.. Indirectness: No indirectness (n=25) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (image guided). Intra articular corticosteroid (betamethasone, 7mg/mL) 0.5mL. Injected by a 2mL syringe with a 27 gauge needle. The injection took place under ultrasound guidance. The needle was inserted into the superior joint space, behind the condyle and beneath the zygoma and passed until three fourths of the needle was in the joint space under ultrasonographic guidance. It was ensured that the needle was not in a blood vessel by aspirating before injection.. Duration 1 injection. Concurrent medication/care: An ice pack was applied immediately after injection. Five minutes after the injection, the person was examined for signs of facial palsy, and manual mobilisation of the jaw was performed to improve mouth opening.. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for TMJ: Pain score (visual analogue scale) at 6 weeks; Group 1: mean 3.41 (SD 0.9); n=25, Group 2: mean 4.51 (SD 1.2); n=25; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Does not report baseline values

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Does not report baseline values for the outcome - this seems important for this one given that there is a difference between the HA and CS groups. Reports age and gender.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	**Gomoll 2021[162]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in USA; Setting:
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiiographs to confirm Kellgren-Lawrence (KL) grade of 2 or 3
Stratum	Knee
Subgroup analysis within study	Not applicable:
Inclusion criteria	Eligible patients included adults aged18years and older with a body mass index(BMI) less than 40 kg/m2, a diagnosis of moderate kneeOA defined by a Kellgren-Lawrence (KL) grade of 2 or 3, and a 7-day average pain score of 4 or greater on a scale of 1 to 10. All eligible female patients were abstinent, surgically sterilized, actively practicing an accepted contraceptive method, or most menopausal.
Exclusion criteria	regular use of anticoagulants, use of pain medication other than acetaminophen for conditions unrelated to OA of the index knee, use of pain medications less than 15 days prior to the injection, patients with a history of substance abuse, or patients who failed to agree not to take additional knee symptom-modifying drugs during the course of the study without reporting the medication use to the study team. Physical or knee-related treatment exclusion criteria included intra-articular injections with either corticosteroid or viscosupplementation in the index knee within 3 months, knee surgery on the index knee within 12 months or on the contralateral knee within 6 months, acute injury to the index knee within 3months, or confirmed mechanical symptoms such as locking, intermittent block to range of motion, or loose body sensations(meniscal displacement or intra-articular loose body). History of solid organ or hematologic transplantation, rheumatoid arthritis and other autoimmune

	disorders, current immunosuppressive treatment, infection requiring antibiotic treatment within 3 months, diagnosis of malignancy apart from treated basal cell cancer of the skin within the last 5 years, or workers' compensation patients. Female patients were excluded if they were pregnant or had a desire to become pregnant during the course of the study.
Age, gender and ethnicity	Age - Mean (SD): ASA group 55.9 (12.3), HA 55.4 (11), saline 54.9 (9.8). Gender (M:F): ASA 33 females and 35 males, HA 31 females and 33 males, saline 31 female and 37 males. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging (KL stage 2 or 3). 3. Multimorbidities: People with multimorbidities excluded
Extra comments	Kellgren-Lawrence (KL) grade of 2 or 3. Not reported
Indirectness of population	No indirectness
Interventions	(n=64) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 4 ml HA intra articular injection (Monovisc High Molecular Weight Hyaluronan; Anika Therapeutics, Boston, MA). Duration 12 months post-intervention follow up. Concurrent medication/care: None reported. Indirectness: No indirectness (n=68) Intervention 2: Placebo. 4 ml saline intra articular injection. Duration 12 months follow-up post intervention. Concurrent medication/care: none stated. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Organogenics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Knee: KOOS quality of life at 12 months; Group 1: mean 9.3 mean (SD) (SD 16.2); n=14, Group 2: mean 10.9 mean (SD) (SD 18.1); n=15; KOOS score 0-100 Top=High is good outcome; Comments: 4 items with 5 possible scores per item
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: mentions baseline checks but results not given; Blinding details: patients were blinded and outcomes was self-reported; Group 1 Number missing: 50; Group 2 Number missing: 53

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: KOOS pain at 12 months; Group 1: mean 5.7 change score: average (SD) (SD 16.5); n=15, Group 2: mean 7.1 change score: average (SD) (SD 17.7); n=14; KOOS score 0-100 Top=High is good outcome; Comments: scoring: 5 possible answers for 9 questions within the pain

subscale of the KOOS score Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: mentions baseline checks but results not given; Blinding details: patients were blinded and outcomes was self-reported; Group 1 Number missing: 50; Group 2 Number missing: 53 Protocol outcome 3: Physical function at ≤3- or >3- months - Actual outcome for Knee: KOOS activities of daily living at 12 months; Group 1: mean 5 mean (SD) (SD 15.5); n=14, Group 2: mean 7.3 mean (SD) (SD 17.9); n=15; KOOS score 0-85 Top=High is good outcome; Comments: 17 items with 5 possible scores for each item. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: mentions baseline checks but results not given; Blinding details: patients were blinded and outcomes was self-reported; Group 1 Number missing: 50; Group 2 Number missing: 53 Protocol outcome 4: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: treatment-emergent adverse event (TEAE) that met serious criteria at 12 months; Group 1: 2/64, Group 2: 0/68; Comments: HA: 3.1%, Saline: 0% Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: mentions baseline checks but results not given; Blinding details: patients were blinded and outcomes was self-reported; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Hangody 2018[179]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=368)
Countries and setting	Conducted in Bulgaria, Canada, Czech Republic, Hungary, Poland; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiologically confirmed osteoarthritis of the knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Radiologically confirmed osteoarthrits of the knee. Age 40-75 years of age with a BMI ≤40kg/m², and Kellgren-Lawrence OA grade I, II, or II in the index knee as determined by X-ray. At baseline, subjects had to have a WOMAC pain score ≥40mm and ≤90mm in the affected knee and ≤30mm in the contralateral knee on a 100-mm visual analog scale.
Exclusion criteria	Certain joint disorders, some medical conditions, or prior knee treatments (including HA or steroid injections in the index knee in the past 6 months); taking medications that could interfere with the procedure, healing and/or assessments; synovial fluid aspirate volume >20mL or if there was visual evidence of cloudiness, crystals or blood; pregnant women.
Recruitment/selection of patients	Recruited from 30 sites in Europe and Canada.
Age, gender and ethnicity	Age - Mean (SD): 58.3 (8.6). Gender (M:F): 121:247. Ethnicity: Essentially all people were Caucasian (1 person was of an other ethnicity)
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Majority K-L grade II. Duration of symptoms: Not stated .
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronic acid - Monovisc (4mL, 88mg HA). One injection.. Duration 1 injection, followed up for 26 weeks. Concurrent medication/care:

	People were not allowed to use medication that would interfere with the trial (what constituted this was not stated).. Indirectness: No indirectness (n=69) Intervention 2: Placebo. Intraarticular placebo - 4mL of 0.9% sodium chloride.. Duration 1 injection, followed up for 26 weeks. Concurrent medication/care: People were not allowed to use medication that would interfere with the trial (what constituted this was not stated).. Indirectness: No indirectness
Funding	Study funded by industry (Sponsored by Anika Therapeutics Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain score at 12 weeks (3 months); Group 1: mean -39 mm (SD 21.9); n=150, Group 2: mean -30.8 mm (SD 23.7); n=69; WOMAC pain subscale visual analogue scale 0-100 Top=High is poor outcome; Comments: Baseline HA: 61.0 (11.7). Baseline saline: 58.8 (10.6).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 discontinued study (1 lost to follow up, 4 withdrew consent). Computed as ITT with a mixed methods analysis to predict results.; Group 2 Number missing: 3, Reason: 3 discontinued study (3 withdrew consent). Computed as ITT with a mixed methods analysis to predict results.
- Actual outcome for Knee: WOMAC pain score at 24 weeks (6 months); Group 1: mean -39.5 mm (SD 22.8); n=150, Group 2: mean -32.9 mm (SD 23.6); n=69; WOMAC pain subscale visual analogue scale 0-100 Top=High is poor outcome; Comments: Baseline HA: 61.0 (11.7). Baseline saline: 58.8 (10.6).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 discontinued study (1 lost to follow up, 4 withdrew consent). Computed as ITT with a mixed methods analysis to predict results.; Group 2 Number missing: 3, Reason: 3 discontinued study (3 withdrew consent). Computed as ITT with a mixed methods analysis to predict results.

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Serious adverse events at 24 weeks (6 months); Group 1: 9/150, Group 2: 2/69
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 discontinued study (1 lost to follow up, 4 withdrew consent). Computed as ITT with a mixed methods analysis to predict results.; Group 2 Number missing: 3, Reason: 3 discontinued study (3 withdrew consent). Computed as ITT with a mixed methods analysis to predict results.

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Henderson 1994[183]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=91)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: Weekly injections for 5 weeks, followed by 5 months of follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical history and radiological evidence of osteoarthritis of the knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with clinical and radiological evidence of osteoarthritis of the knee with pain at the time of recruitment in at least one knee of moderate or greater severity as defined by a minimum score of 30mm or more on a 100mm visual analogue scale for pain evoked by at least one of five specified activities during the two week pre-study assessment period.
Exclusion criteria	People with inflammatory joint disease, metabolic bone disease, anserine bursitis, or pain referred from other structures (for example, the ipsilateral hip or the lumbar spine)
Recruitment/selection of patients	Recruited from the rheumatology outpatient clinics of the Royal London Hospital
Age, gender and ethnicity	Age - Mean (SD): 66.5 (4.9) - Unclear whether bracketed number is SD or SE. Gender (M:F): 28:63. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated - median radiological grade III Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronic acid (Hyalgan, 750 kDa) in phosphate buffered saline extracted from rooster combs.. Duration 5 injections over 5 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=46) Intervention 2: Placebo. Phosphate buffered saline vehicle alone. Duration 5 injections over 5 weeks. Concurrent medication/care: Not stated. Indirectness: No

	indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: Pain on climbing stairs (Visual analogue scale) at 5 weeks; Group 1: mean 60.8 mm (SD 7.7); n=40, Group 2: mean 65.3 mm (SD 10.3); n=44; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Paper reports subgroups for the two intervention groups (based on severity). These were merged in this analysis. Baseline HA combined: 70.3 (6.0). Baseline placebo combined: 76.4 (5.6). Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: More severe people in the placebo group, worse VAS score on climbing stairs in the placebo group; Group 1 Number missing: 5, Reason: Unable to tolerate the injections; Group 2 Number missing: 2, Reason: Withdrawn by investigators because their synovial fluid analyses suggested a diagnosis of gout or an unidentified crystal arthritis Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Severe joint pain after injection at 5 months; Group 1: 2/45, Group 2: 1/46; Comments: Severe transient increase in pain and/or swelling in the treated knee as defined by the patient Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: More severe people in the placebo group, worse VAS score on climbing stairs in the placebo group; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Heyworth 2008[192]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed using standard radiographic and clinical criteria: basal joint tenderness, thumb or wrist pain at rest or with activity, joint stiffness, decreased mobility, deformity, instability and decreased manual function
Stratum	Thumb
Subgroup analysis within study	Not applicable
Inclusion criteria	People with clinical and radiographic symptomatic basal joint osteoarthritis; age greater than 40 years
Exclusion criteria	People who had received previous corticosteroid injections if they had not experienced at least mild to moderate pain relief or functional improvement from the injections; if they had received more than 2 such injections in the affected joint in the past; if they had received an injection in the preceding 6 months; pregnancy; prior surgery on the affected thumb or wrist; history of infection in the affected joint; history of inflammatory arthritis; skin disease or eruption at the joint injection site; known allergy to eggs, feathers, avian proteins or HA derivative products.
Recruitment/selection of patients	60 people recruited from the two senior author's medical practices
Age, gender and ethnicity	Age - Mean (SD): 61 (1). Gender (M:F): 8:52. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms: Not stated.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 2 injections of 1mL hylan G-F 20 given over 1 week. Duration 2 injections given over 1 week. Concurrent medication/care: People were given access to splints to wear as needed and standard doses of NSAIDs (ibuprofen 400mg every 4-6 hours as required). Indirectness: No indirectness Comments: Radiographic confirmation of the injection was not believed to be

	necessary due to "the authors' extensive experience" (n=22) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 1 injection of 1mL normal saline placebo (0.9% sodium chloride) at time = 0, and 1 injection of 1mL sodium betamethasone sodium phosphate-betamethasone acetate (Celestone Soluspan) given in 1 week. Duration 1 injection of corticosteroid, 1 injection of saline given over 1 week. Concurrent medication/care: People were given access to splints to wear as needed and standard doses of NSAIDs (ibuprofen 400mg every 4-6 hours as required). Indirectness: No indirectness Comments: Radiographic confirmation of the injection was not believed to be necessary due to "the authors' extensive experience" (n=18) Intervention 3: Placebo. 2 injections of 1mL normal saline placebo (0.9% sodium chloride) given over 2 weeks. Duration 2 injections given over 1 week. Concurrent medication/care: People were given access to splints to wear as needed and standard doses of NSAIDs (ibuprofen 400mg every 4-6 hours as required). Indirectness: No indirectness
Funding	Study funded by industry (Funded with a joint grant from Genzyme Corporation and Wyeth Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Serious adverse events at ≤3- or >3- months
- Actual outcome for Thumb: Adverse events at 26 weeks; Group 1: 0/20, Group 2: 0/22; Comments: Reports that there were no adverse events of the injection observed after the injection or later on during follow up visits
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, dominant hand, treated hand, number of people with bilateral symptoms, range of motion, visual analogue scale pain, grip strength, and DASH score; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Serious adverse events at ≤3- or >3- months
- Actual outcome for Thumb: Adverse events at 26 weeks; Group 1: 0/20, Group 2: 0/18; Comments: Reports that there were no adverse events of the injection observed after the injection or later on during follow up visits
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, dominant hand, treated hand, number of people with bilateral symptoms, range of motion, visual analogue scale pain, grip strength, and DASH score; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Thumb: Adverse events at 26 weeks; Group 1: 0/22, Group 2: 0/18; Comments: Reports that there were no adverse events of the injection observed after the injection or later on during follow up visits Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, dominant hand, treated hand, number of people with bilateral symptoms, range of motion, visual analogue scale pain, grip strength, and DASH score; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Housman 2014[195]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=391)
Countries and setting	Conducted in Canada, France, Germany, United Kingdom, USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fulfilling the American College of Rheumatology criteria for osteoarthritis with Kellgren-Lawrence Grade I to III disease.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged ≥40 years with an active lifestyle in good general health, who were ambulatory and currently meeting American College of Rheumatology criteria for Osteoarthritis. People were required to have primary OA knee pain despite conservative treatment, defined as a score of 1.5-3.5 on the WOMAC likert version 3.1 pain subscore and moderate or severe walking pain.
Exclusion criteria	Modified Kellgren-Lawrence Grade 0 or IV; clinically apparent tense effusion; significant valgus/varus deformities, ligament laxity, or meniscal instability; inflammatory disease, or other condition that affects the joints (e.g. rheumatoid arthritis, metabolic bone disease, gout, active infection); prior or current symptomatic peripheral vascular disease of the study leg; any musculoskeletal condition that would impede assessment of clinical outcomes; significant mechanical problems; viscosupplementation within the prior 12 months; systemic/IA corticosteroids within the prior 3 months; target knee arthroplasty at any time; or other surgery within the prior 6 months.
Recruitment/selection of patients	Recruited from 25 centers in the USA, Canada, France, UK and Germany.
Age, gender and ethnicity	Age - Mean (SD): 60.9 (9.7). Gender (M:F): 130:261. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity of osteoarthritis: Not explicitly stated, majority Kellgren-Lawrence grade II-III Duration of symptoms: 35.8 (40.9) months
Indirectness of population	No indirectness

Interventions	(n=259) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). One or two 4mL hyaluronic acid (hylastan) injections. If receiving only one injection, arthrocentesis two weeks after the first injection.. Duration Those receiving two injections received them over 2 weeks. Those receiving one injection had an injection on day 0 and arthrocentesis on week 2.. Concurrent medication/care: Paracetamol 500mg was provided as rescue medication (with 1-2 to be taken every 4-6 hours as needed, not exceeding 8 tablets in 24 hours) except within 48 hour prior to a study visit.. Indirectness: No indirectness Comments: Reports the 1 injection or 2 injection groups separately. These have been combined for this analysis. There was a repeat phase after this, but this was used in the analysis as it provided not additional information. (n=132) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). One injection of intraarticular methylprednisolone acetate (40mg/mL) on day 0 and arthrocentesis of week 2.. Duration 1 injection on day 0, arthrocentesis on week 2. Concurrent medication/care: Paracetamol 500mg was provided as rescue medication (with 1-2 to be taken every 4-6 hours as needed, not exceeding 8 tablets in 24 hours) except within 48 hour prior to a study visit.. Indirectness: No indirectness Comments: There was a repeat phase after this, but this was used in the analysis as it provided not additional information.
Funding	Study funded by industry (Funded by Genzyme Corp.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain subscale at 24 weeks (6 months); Group 1: mean -0.85 (SD 0.74); n=259, Group 2: mean -0.9 (SD 0.59); n=132; WOMAC pain subscale using a 5 point Likert scale 0-20 Top=High is poor outcome; Comments: Reports confidence intervals on change scores: Reported 2x HA: -0.9 (95% CI -1.0, -0.7). Reported 1x HA: -0.8 (-0.9, -0.7). These were combined in the final value. Reported CS: -0.9 (-1.0, -0.8). Baseline values not reported.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 45, Reason: 5 due to adverse events, 2 due to non-compliance, 18 due to patient requestion, 6 due to lost to follow up, 10 due to lack of efficacy, 4 other; Group 2 Number missing: 20, Reason: 7 due to adverse events, 1 due to patient request, 3 due to lost to follow up, 8 due to lack of efficacy, 1 other

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Serious adverse events at 24 weeks (6 months); Group 1: 1/259, Group 2: 0/131; Comments: 1 person in the steroid group was

randomised in error and did not receive treatment so wasn't included in the safety population. The one adverse event was progressive joint disease; that they judged was unrelated to study treatment/procedure by investigator. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 did not receive the drug and so was not included in the final analysis	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Huang 2011[198]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Taiwan; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 25 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of osteoarthritis of the knee according to the American College of Rheumatology criteria. Eligible patients also had radiographic evidence of osteoarthritis with Kellgren-Lawrence scores of II to III on X-ray with predominance in the tibio-femoral compartment.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Males or females >50 years of age, diagnosed with OA of the knee according to ACR criteria (knee pain with one or more of the following conditions: age >50 years, crepitus, or morning stiffness <30 minutes in duration). Eligible people also had radiographic evidence of OA with Kellgren-Lawrence scores of II to II on x-ray with predominance in the tibio-femoral compartment and visual analog scale pain scores of ≥40 mm on a 50-foot walking test. It was required that any acute disease or trauma leading to secondary osteoarthritis must have occured at least 5 years before study entry.
Exclusion criteria	Severe degeneration of the knee joint with marked joint narrowing, varus or valgus deformity of the knee (>12 degrees) or other joint deformities, or other joint disorders (eg. inflammatory joint disease, specific arthropathy, severe axis deviations or instabilities, joint or skin infections, joint prostheses of the lower limbs or symptomatic hip). Patients were not permitted to have received IA steroid injections within the 2 weeks prior to study entry.
Recruitment/selection of patients	Conducted at 3 hospitals: the National Taiwan University Hospital, the Taipei Medical College Hospital, and the Tri-Service General Hospital.
Age, gender and ethnicity	Age - Mean (SD): 65.0 (8.3). Gender (M:F): 48:152. Ethnicity: Asian population stated in the title
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Mild to moderate by Kellgren-Lawrence grade. Duration of osteoarthritis: 427.0 (1022.5) days.
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 5 weekly injections of sodium hyaluronate (Hyalgan) at 20mg/2mL. Duration 5 injections over 5 weeks. Concurrent medication/care: Paracetamol could be taken for further pain relief, but not exceeding 3g per day. People were not permitted to take paracetamol on the day before the study visit. Oral and parenteral corticosteroids, IA corticosteroid injections, NSAIDs or analgesics other than paracetamol, topical analgesic preparations, rehabilitation, physical therapy and acupuncture were not permitted.. Indirectness: No indirectness (n=100) Intervention 2: Placebo. Intraarticular saline placebo (2mL) with 5 injections over 5 weeks. Duration 5 injections over 5 weeks. Concurrent medication/care: Paracetamol could be taken for further pain relief, but not exceeding 3g per day. People were not permitted to take paracetamol on the day before the study visit. Oral and parenteral corticosteroids, IA corticosteroid injections, NSAIDs or analgesics other than paracetamol, topical analgesic preparations, rehabilitation, physical therapy and acupuncture were not permitted.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Hyalgan provided by Fidia Farmaceutici Spa and Med Pharma Co. Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: VAS pain scale change from week 0 to week 13 at 13 weeks; Group 1: mean -24.75 mm (SD 12.66); n=100, Group 2: mean -20.41 mm (SD 15.38); n=98; Visual analog scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 47.85 (10.76). Baseline placebo: 45.15 (9.75).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: People included in the ITT: 1 lost to follow up, 8 person did not continue, 3 lack of efficacy; Group 2 Number missing: 12, Reason: 2 people excluded from the ITT evaluation due to violation - did not have baseline value of primary outcome. Otherwise, people including in the ITT evaluation: 1 lost to follow up, 7 person did not continue, 4 lack of efficacy.
- Actual outcome for Knee: WOMAC pain change from 0 to 24 weeks, mm (VAS) at 24 weeks (6 months); Group 1: mean -29.28 mm (SD 19.2); n=100, Group 2: mean -21.52 mm (SD 19.2); n=98; WOMAC pain score visual analog scale 0-100 Top=High is poor outcome; Comments: Reported standard errors. Reported HA: 29.28 (1.92). Reported placebo: 21.52 (1.94). Baseline WOMAC pain score HA: 45.3 (11.17). Baseline WOMAC pain score placebo: 45.39 (13.06).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: People included in the ITT: 1 lost to follow up, 8 person did not continue, 3 lack of efficacy; Group 2 Number missing: 12, Reason: 2 people excluded from the ITT evaluation due to violation - did not have baseline value of primary outcome. Otherwise, people including in the ITT evaluation: 1 lost to follow up, 7 person did not continue, 4 lack of efficacy. Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC function change from 0 to 24 weeks, mm (VAS) at 24 weeks (6 months); Group 1: mean 25.16 mm (SD 16.7); n=100, Group 2: mean 18.2 mm (SD 16.7); n=98; WOMAC function subscale visual analog scale 0-100 Top=High is poor outcome; Comments: Reported standard errors. Reported HA: 25.16 (1.67). Reported placebo: 18.20 (1.69). Baseline WOMAC physical function score HA: 46.54 (11.31). Baseline WOMAC physical function score placebo: 45.45 (13.13). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: People included in the ITT: 1 lost to follow up, 8 person did not continue, 3 lack of efficacy; Group 2 Number missing: 12, Reason: 2 people excluded from the ITT evaluation due to violation - did not have baseline value of primary outcome. Otherwise, people including in the ITT evaluation: 1 lost to follow up, 7 person did not continue, 4 lack of efficacy. Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 24 weeks (6 months); Group 1: 3/100, Group 2: 2/98; Comments: Hyaluronic acid group: Forearm fracture, intestinal obstruction and aggravated urinary incontinence. Placebo group: Upper gastrointestinal bleeding and joint sprain. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: People included in the ITT: 1 lost to follow up, 8 person did not continue, 3 lack of efficacy; Group 2 Number missing: 12, Reason: 2 people excluded from the ITT evaluation due to violation - did not have baseline value of primary outcome. Otherwise, people including in the ITT evaluation: 1 lost to follow up, 7 person did not continue, 4 lack of efficacy.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Huang 2019[199]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in China; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic knee osteoarthritis with Kellgren-Lawrence grade 1-2 changes on radiography
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with symptomatic knee osteoarthritis (Kellgren-Lawrence grade 1-2 on radiographs) between the ages of 40 and 65 years, having a body mass index <30, with stable knees without malignment or maltracking of the patella. Additionally, people had to have pain with no relief using antiinflammatory agents even after 3 months, normal blood results and coagulation profile (platelet 150,000-450,000/L), people who had not undergone any surgery on the affected knee within 2 years prior to the first injection and zero, traces or 1+ effusion on the grading scale based on the Stroke test.
Exclusion criteria	People diagnosed with tricompartmental osteoarthritis, rheumatoid arthritis or concomitant hip OA; a previous high tibial osteotomy or cartilage transplantation procedure; grade 2+ and 3+ effusion in the knee joint (requiring aspiration) based on the Stroke test; blood diseases; systemic metabolic disorders; immunodeficiency; hepatitis B or C; HIV positive status; local or systemic infection; ingestion of anti-platelet medication within 7 days prior to the injection and treatment with IA or oral corticosteroids in the 3 months prior to the first injection.
Recruitment/selection of patients	No additional information provided
Age, gender and ethnicity	Age - Mean (SD): 54.5 (1.3). Gender (M:F): 65:55. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity of osteoarthritis not stated. Symptom duration not stated.
Indirectness of population	No indirectness

Interventions	(n=40) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronic acid (molecular weight 500-730kDa) 2mL injection into the knee each week for 3 weeks. Duration 3 injections over 3 weeks. Concurrent medication/care: After injection, people were allowed weight bearing and local ice application was recommended for 20 minutes every 2-4 hours for 24 hours. Vigorous activities of the knee were not recommended for 48 hours.. Indirectness: No indirectness (n=40) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Injection of corticosteroid (type and dose not specified) 1mL. Duration 1 injection. Concurrent medication/care: After injection, people were allowed weight bearing and local ice application was recommended for 20 minutes every 2-4 hours for 24 hours. Vigorous activities of the knee were not recommended for 48 hours.. Indirectness: No indirectness (n=40) Intervention 3: Intra-articular plasma-rich platelets - Intra-articular plasma-rich platelets (non-image guided). Samples of 8mL of blood that were obtained from the cubital vein and centrifuged for 5 mins at 1500g centrifugal force or 3500pm. After centrifugation, platelet recovery was >80% and total leucocyte concentration was below the normal level specific granulocyte depletion >95% in 3mL of PRP. 3 injections given of 4mL every 3 weeks.. Duration 3 injections every 3 weeks. Concurrent medication/care: After injection, people were allowed weight bearing and local ice application was recommended for 20 minutes every 2-4 hours for 24 hours. Vigorous activities of the knee were not recommended for 48 hours.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analog scale pain at 12 months; Group 1: mean 2.14 mm (SD 1.523); n=40, Group 2: mean 2.26 mm (SD 1.707); n=40; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Baseline HA: 4.54 (0.596). Baseline CS: 4.64 (0.543).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Pain and DVT adverse events at 12 months; Group 1: 2/40, Group 2: 3/40; Comments: All adverse events recorded were due to

'pain'. No events due to DVT. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Huskisson 1999[201]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with a diagnosis of osteoarthritis of one or both knees according to the Australian Rheumatology Association criteria. All people had radiographic changes consistent with Kellgren and Lawrence grade II or III on an X-ray taken within the 6 months prior to the study.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Fully ambulant people with a diagnosis of OA of one or both of the knees according to the Australia Rheumatology Association criteria. All people had radiographic changes of OA equal to Kellgren and Lawrence grade II or III on an X-ray taken within 6 months prior to study entry. All people had consistent pain for the 3 months prior to recruitment and moderate or severe pain on walking at both the initial screening visit and at the baseline visit.
Exclusion criteria	X-rays showing grade IV change on the Kellgren and Lawrence scale; serious functional impairment at the knee; associated OA of the hip of sufficient severity to interfere with assessment of the knee or OA of any other joint which might have hindered assessment of the knee; psoriasis; radiographic evidence of sacroiliitis or any other joint disease other than OA; known or suspected joint infection; poor general health or other conditions which would prevent regular hospital attendance; skin conditions overlying the joint which might make injection dangerous; painful knee conditions other than OA like Sudek's atrophy or Paget's disease; severe intercurrent hepatic or renal disease or major general medical conditions; and use of an intra-articular steroid or radiocolloid within the 3 months before the start of treatment.
Recruitment/selection of patients	Recruited from the outpatient clinic
Age, gender and ethnicity	Age - Mean (SD): 65.3 (9.1). Gender (M:F): 33:67. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity of osteoarthritis not stated. Duration of pain was on average between 7-24 months..
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Five weekly intraarticular injections of HA (20mg/2mL, Hyalgan) in a buffered aqueous solution. Duration 5 injections over 5 weeks. Concurrent medication/care: All people were permitted to continue with existing analgesic or antiinflammatory therapy.. Indirectness: No indirectness (n=50) Intervention 2: Placebo. Five weekly intraarticular injections of a buffered aqueous solution. Duration 5 injections over 5 weeks. Concurrent medication/care: All people were permitted to continue with existing analgesic or antiinflammatory therapy.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analog scale (pain) at 2 months; Group 1: mean 32.3 mm (SD 26.6); n=39, Group 2: mean 42.1 mm (SD 29.3); n=41; Visual analog scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 65.8 (18.0). Baseline placebo: 61.9 (22.9).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: 4 withdrew during the initial 4 week treatment period for reasons unrelated to the treatment. 6 withdrew during the follow-up period, two due to non-drug related adverse events (removal or a calf ulcer in one, flare up in the other), two due to lack of efficacy, and two who were lost to follow-up. Unclear why there is one additional missing period.; Group 2 Number missing: 9, Reason: Two withdrew during the initial treatment period due to lack of efficacy. Seven withdrew during the follow up period, six due to lack of efficacy and one for a non-drug related adverse event (flare up).
- Actual outcome for Knee: Visual analog scale (pain) at 6 months; Group 1: mean 39.4 mm (SD 27.8); n=39, Group 2: mean 53.7 mm (SD 39.9); n=41; Visual analog scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 65.8 (18.0). Baseline placebo: 61.9 (22.9).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: 4 withdrew during the initial 4 week treatment period for reasons unrelated to the treatment. 6 withdrew during the follow-up period, two due to non-drug related adverse events (removal or a calf ulcer in one, flare up in the other), two due to lack of efficacy, and two who were lost to follow-up. Unclear why there is one additional missing period.; Group 2 Number missing: 9, Reason: Two withdrew during the initial treatment period due to lack of efficacy. Seven withdrew during the follow up period, six due to lack of efficacy and one for a non-drug related adverse event (flare up).

Protocol outcome 2: Osteoarthritis flares at ≤3- or >3- months

- Actual outcome for Knee: Flare of the knee joint at 6 months; Group 1: 7/50, Group 2: 7/50 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 2/50, Group 2: 1/50; Comments: HA group: 1 developed cutaneous vasculitis spreading from both legs to the abdomen and arms. 1 developed a skin reaction with peeling of the skin on the hands and toes and erythema, which improved over the duration of the study. Placebo: 1 myocardial infarction. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months

Study	Jorgensen 2010[225]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=337)
Countries and setting	Conducted in Denmark; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fulfilling the clinical and laboratory American College of Rheumatology criteria for primary osteoarthritis of the knee. Includes radiographic measures.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Fulfilling the clinical and laboratory ACR criteria for primary osteoarthritis of the knee; outpatients; both men and women; age >18 years; LFI score >10; CRP in normal range; written consent before entering the project
Exclusion criteria	Radiographic attrition >5mm; intraarticular injections previous 3 months; intraarticular hyaluronan injection ever before; secondary osteoarthritis or other inflammatory joint disease no matter what origin, including chondrocalcinosis; significant osteoarthritis in the other knee that might affect the project examinations; infection in the evaluated knee joint; dermatological diseases at knee region contraindicating intraarticular injections; cancer; comorbidity that might make regular control visits for 1 year difficult; regular use of analgesics or anti-inflammatory drugs taken for conditions not related to knee pain; acetaminophene 4g unable to control knee osteoarthritis pain; patients lying in bed, using wheelchair or walker, having hemiparesis, or are one legged; pregnant, breastfeeding women or women who are planning pregnancy in project period; known intolerance or allergy to acetaminophene or avian protein; patients unable to speak or understand Danish; earlier inclusion in this study; present participation in other medical trials or back to 1 month before inclusion in this study.
Recruitment/selection of patients	Multicenter trial. No additional information.
Age, gender and ethnicity	Age - Mean (SD): 62.0 (11.3). Gender (M:F): 77:123. Ethnicity: Almost 100% were white (97.6% in the placebo group, 100% in the HA group).
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity of osteoarthritis not stated. Duration of symptoms: 6.4 (7.5) years..
Indirectness of population	No indirectness
Interventions	(n=165) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 2mL Hyalgan (10mg/mL) injected five times at 1 week intervals.. Duration 5 injections over 5 weeks. Concurrent medication/care: Anaesthetic of the skin with 0.5mL of 1% lidocaine. Synovial fluid was aspirated before injection. Paracetamol was used as escape medication (maximum of 4g daily) during the 2 week washout period and throughout the entire study, but not on the days of examination.. Indirectness: No indirectness (n=170) Intervention 2: Placebo. 5 injections of 2mL saline. Duration 5 injections over 5 weeks. Concurrent medication/care: Anaesthetic of the skin with 0.5mL of 1% lidocaine. Synovial fluid was aspirated before injection. Paracetamol was used as escape medication (maximum of 4g daily) during the 2 week washout period and throughout the entire study, but not on the days of examination.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Nycomed Denmark A/S with blinded hyaluronan/placebo medication free of charge and good clinical practice monitoring. Financial support from the Clinical Institute, Aarhus University and the Danish Rheumatism Association)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analog scale pain after walking 50m (cm) change from baseline at 3 months; MD; -0.07 (95%CI -0.46 to 0.33) Visual analogue scale (after 50m walk) 0-10 Top=High is poor outcome, Units: cm, Comments: Negative sign added to indicate direction of effect.;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 did not receive the initial injection so were not included; Group 2 Number missing: 0
- Actual outcome for Knee: Visual analog scale pain after walking 50m (cm) change from baseline at 12 months; MD; -0.22 (95%CI -1.14 to 0.71) Visual analogue scale (pain after walking 50m) 0-10 Top=High is poor outcome, Units: cm, Comments: Negative sign added to indicate direction of effect.;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 did not receive the initial injection so were not included; Group 2 Number missing: 0

Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Severe or serious adverse events as probably or possibly being related to treatment at 12 months; Group 1: 0/139, Group 2: 0/159 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 did not receive the initial injection so were not included; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Jubb 2003[226]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=408)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Primary osteoarthritis of the Knee as defined by the American College of Rheumatology criteria and radiographic involvement of the medial tibio-femoral compartment associated with grade II or III severity (Kellgren-Lawrence scoring system).
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary osteoarthritis of the knee (American College of Rheumatology criteria) and radiographic involvement of the medial tibio-femoral compartment associated with grade II or III severity (Kellgren-Lawrence scoring system). If bilateral osteoarthritis was present, the more painful knee was treated.
Exclusion criteria	Concurrent treatment with corticosteroids, glucosamine or chondroitin sulphate. People with OA of the hip or other joint disease that was severe enough to prevent adequate assessment of the knee. Any of the following: psoriasis, sacroilitis, other joint disease, known or suspected joint infection, disease of the skin overlying the knee joint that prevented injections, other painful knee conditions (e.g. Sudek's atrophy, intra-articular neoplasm, villonodular pigmented synovitis, Paget's disease), or severe concurrent illnesses (e.g. diabetes, cardiovascular, hepatic or renal disease, and other major illnesses). People who received intraarticular corticosteroid or radiocolloid in the three months before the study, or intraarticular or new/rearrangement surgical procedures on the legs; if there was evidence of clinically important axial deviation of the legs (valgus or varus deformities); if they had history of allergic reactions to avian proteins; or if they were pregnant or breast feeding.
Recruitment/selection of patients	Multicentre trial completed at 17 UK centres
Age, gender and ethnicity	Age - Mean (SD): 64.2 (9.3). Gender (M:F): 129:279. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: People with multimorbidities excluded

Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-3. Duration of symptoms (mean [SD]): 8.2 (7.3) years
Indirectness of population	No indirectness
Interventions	(n=208) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Three injections of 20mg/2mL hyaluronic acid (Hyalgan) over three weeks repeated twice at four monthly intervals. Duration 3 injections over 3 weeks repeated at four month intervals (overall 9 injections). Concurrent medication/care: Free concurrent use of analgesics and NSAIDs, except indomethacin, was allowed. Although in patients taking these treatments the regimens were required to be stable for at least one month before study entry.. Indirectness: No indirectness (n=200) Intervention 2: Placebo. Three injections of 2mL saline vehicle over three weeks repeated twice at four monthly intervals. Duration 3 injections over 3 weeks repeated at four month intervals (overall 9 injections). Concurrent medication/care: Free concurrent use of analgesics and NSAIDs, except indomethacin, was allowed. Although in patients taking these treatments the regimens were required to be stable for at least one month before study entry.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by a grant from Fidia SpA, Abano, Terme, Italy)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 52 weeks; Group 1: 27/208, Group 2: 14/200; Comments: Only states that there was 1 death due to MI in the HA group. No other explanation on what was included in serious adverse events. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Ke 2021[240]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=440)
Countries and setting	Conducted in China; Setting: Outpatient follow up.
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Grade I to III Kellgren Lawrence osteoarthritis of the knee, confirmed by standard X-ray up to three months before screening; people meeting the American College of Rheumatology criteria for knee osteoarthritis
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 40 to 80 years; grade I to III Kellgren Lawrence osteoarthritis of the knee, confirmed by standard X-ray up to three months before screening; people meeting the American College of Rheumatology criteria for knee osteoarthritis; had a WOMAC A1 NRS score of between 4.0 and 8.0 at baseline; failed to respond to non-pharmacologic therapy and/or simple analgesics.
Exclusion criteria	Moderately severe or severe depression as indicated by the Patient Health Questionnaire-9 total score of at least 15 or a score of >0 on item 9, severe anxiety, or severe insomnia as indicated by a score from four questionnaires at the screening visit; people who had prior knee surgery; previous intraarticular treatment with corticosteroids, local anaesthetic agents or viscosupplementation agents to the target knee; scores of contralateral knee pain greater than 3.0 NRS; ipsilateral hip osteoarthritis; concomitant inflammatory disease; other conditions that affected the joints.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 61.6 (7.9). Gender (M:F): 98:342. Ethnicity: Asian = 440
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Kellgren Lawrence grades I-III, median grade II. Duration of symptoms: Not stated/unclear.
Indirectness of population	No indirectness
Interventions	(n=218) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hylan G-F 20 (6mL injection, 48mg hylan polymer) injected into the knee joint. . Duration One injection. Concurrent medication/care: On an as-needed basis in a tiered manner, the following therapies were allowed as rescue medication in case of unbearable pain (eg, worsening of osteoarthritis symptoms in the target knee) during the study period: 1) Paracetamol (500mg, up to 3000mg/day), paracetamol (325mg)/oxycodone (5mg, up to 1 tablet 4 times daily); paracetamol (325mg)/tramadol (37.5mg, up to 1 tablet 6 times daily).

Study
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	However, rescue medication was not to be taken within 48 hours prior to any study visit.. Indirectness: No indirectness (n=220) Intervention 2: Placebo. One placebo injection into the knee (6mL phosphate buffer saline, pH 7.2).. Duration One injection. Concurrent medication/care: On an as-needed basis in a tiered manner, the following therapies were allowed as rescue medication in case of unbearable pain (eg, worsening of osteoarthritis symptoms in the target knee) during the study period: 1) Paracetamol (500mg, up to 3000mg/day), paracetamol (325mg)/oxycodone (5mg, up to 1 tablet 4 times daily); paracetamol (325mg)/tramadol (37.5mg, up to 1 tablet 6 times daily). However, rescue medication was not to be taken within 48 hours prior to any study visit.. Indirectness: No indirectness
Funding	Study funded by industry (This study was sponsored by Sanofi.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC pain at 26 weeks; Group 1: mean -2.146 (SD 1.595); n=218, Group 2: mean -2.271 (SD 1.632); n=220; WOMAC pain 0-10 Top=High is poor outcome; Comments: Baseline hyaluronic acid: 5.3 (1.2). Baseline placebo: 5.2 (1.3). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported gender, age, race, ethnicity, baseline BMI, radiographic grade and baseline values of outcomes; Group 1 Number missing: 6, Reason: 6 lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Treatment emergent adverse events at 26 weeks; Group 1: 134/218, Group 2: 142/220; Comments: Hyaluronic acid: 134. Placebo: 142. Type of events not clear. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported gender, age, race, ethnicity, baseline BMI, radiographic grade and baseline values of outcomes; Group 1 Number missing: 6, Reason: 6 lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

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Study	Khalifeh soltani 2019[242]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Iran; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with knee OA (grades 2-4 based on the Kellgren Lawrence criteria in knee standing anteroposterior and lateral radiographs)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with knee OA (grades 2-4 based on the Kellgren Lawrence criteria in knee standing anteroposterior and lateral radiographs)
Exclusion criteria	Age <35 or >75 years; any acute or chronic infection; visible knee deformity (varus >10 degrees, valgus >20 degrees); pregnant or lactating women; any sort of neoplasia; BMI >35; conditions along with impaired immune system; any inflammation in the joints or secondary osteoarthritis; intraarticular injections during the last 3 months; history of knee surgery; kidney malfunction (creatinine >2.0mg/dL); liver malfunction (bilirubin >2.0mg/dL; AST and ALT >100 IU/L); uncontrolled diabetes mellitus
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Other: Mean: 56.7. Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). Allogenic placental mesenchymal stem cells - cells collected from health mothers who carried to full term and had a normal vaginal delivery with normal complications. Placenta (3-5g) was selected, picked, rinsed and minced into minute pieces. The minced tissue was washed three times with 9% sodium chloride solution to remove the remaining blood, before being incubated with 1mg/mL GMP-grade

	collagenase NB6 at 37 degrees centigrade for 3 hours with shaking every 30 minutes. Then 9% sodium chloride solution was added and the mixture was shaken and centrifuged. The supernatant was discarded and the cell pellet was cultivated in MSC complete medium containing Dulbecco's Modified Eagle's Medium supplemented with 10% pharmaceutical grade Australian-origin fetal bovine serum. Primary cultures were maintained for 1 week in a 37 degree centigrade humidified 5% carbon dioxide incubator in small digested residues; non-adherent cells were removed by changing the culture medium. New medium was added twice weekly. Upon approximately 80% confluence, adherent MSCs were passaged via animal origin-free TrypLE Express enzyme to reach a sufficient number of MSCs for further clinical applications. Each donor placenta was used for 2-3 people. Average passage of cells was 12 passages. The cells were injected via a 10mL syringe. The MSC group received intraarticular injection of MSCs (10mL, 0.5-0.6x10^8 cells).. Duration 1 injection. Concurrent medication/care: All people were allowed to use paracetamol for breakthrough pain.. Indirectness: No indirectness (n=10) Intervention 2: Placebo. 10mL normal saline injected via a 10mL syringe. Duration 1 injection. Concurrent medication/care: All people were allowed to use paracetamol for breakthrough pain.. Indirectness: No indirectness
Funding	Academic or government funding (The study was supported by grant number 943798 of the National Institute For Medical Research Development (NIMAD) granted to M. Vasei. The authors thank the Babak Radiology Center team for their cooperation in performing the MRAs.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Any other clinical adverse effects at 24 weeks; Group 1: 0/10, Group 2: 0/10; Comments: Reports that "four people in the MSC group had increased local pain and mild effusion. Their symptoms were mild and self-limited within 48-72 hours. Re-examination at 2 weeks after treatment showed that the laboratory parameters all were unchanged. In the 24-week clinical and radiological follow-up, there was no ectopic mass formation or any other clinical adverse effects."
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports (in supplementary table) age, gender, BMI, and outcome baseline values (unfortunately does not report the final values for these); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Kuah 2018[257]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Australia; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Kellgren Lawrence grade 1-3 knee osteoarthritis with moderate-severe pain in the study knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Provide written informed consent; males or females aged 40-65 years, inclusive; diagnosed Kellgren Lawrence grade 1, 2 or 3 knee osteoarthirits in the study knee; moderate-severe pain associated with osteoarthritis in the study knee as measured by a VAS pain score of between 35 and 90mm inclusive at the screening visit; BMI of 20-30 inclusive; negative results for virus antibody tests from samples taken at the screening visit; HIV1 and 2 antibody test; HCV antibody test; HBV antibody test; able to read and write in English. Additional criteria for females: not pregnant or breast feeding/lactating; females of non-childbearing potential; females of childbearing potential must agree to use adequate and highly effective methods of contraception throughout the study. Additional criteria for men: males with female partners of childbearing potential must use adequate and highly effective methods of contraception such as double-barrier form for the entire duration of the study
Exclusion criteria	Inability or unwillingness to comply with protocol requirements; evidence, or diagnosis of osteoarthritis in the non-study knee that is of a worse screening visit VAS score than the study knee; joint surgery in the study knee, including arthroscopy, within the last 3 years; consistently occurring major mechanical issues in the study knee including locking, catching and giving way; intraarticular injections into either knee within the last 3 months; current evidence of infection in either knee; diagnosed or symptomatic OA in other major joints (feet, hips, shoulders or spine) that is of greater clinical significance than the study knee; planned hip, knee, ankle or foot surgery including joint replacement within the expected study duration; history or current evidence of other joint diseases (such as gout, rheumatoid arthritis and ankylosing spondylitis), or disease or medication affecting the bone or cartilage metabolism, including systemic corticosteroids and osteoporosis medication; unable to undergo an MRI scan for any reason including severe claustrophobia and metal implants such as

	hip, knee or aortic valve prosthetics; current smoker or have been a regular (daily) smoker in the past 3 months; planned or current participation in any other interventional clinical trials; people who require use of systemic immunosuppressants; any clinically significant condition that is in the opinion of the primary investigator may compromise safety or compliance, interfere with evaluation or preclude completion of the study
Recruitment/selection of patients	Conducted at the Sydney Sportsmed Specialists and Sydney Sports Medicine Centre, Sydney Australia. Investigational product administration was performed at East Sydney Private Hospital, Sydney, Australia and magnetic resonance imaging was performed at Castlereagh Imaging, Sydney, Australia.
Age, gender and ethnicity	Age - Mean (SD): 53.3 (7.6). Gender (M:F): 12:8. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grades 1-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (image guided). Combination of two groups: Progenza 3.9 million and 6.7 million cells. The mesenchymal stem cells were derived from a single human donor, who was qualified according to TGA requirements. Cells were isolated and culture expanded in a good manufacturing practice accredited facility. 2mL of PRG 3.9M or PRG 6.7M was provided by Regeneus Ltd. and stored in a CryoVial and maintained at or below 150 degrees C. The IP was thawed prior to being drawn up into a sterile syringe and administered via ultrasound guided intraarticular injection into the study knee either by an independent, unblinded radiologist or sports and exercise medicine physician trained in the technique.. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness Comments: 8 people received PRG3.9M. 8 people received PRG 6.7M. (n=4) Intervention 2: Placebo. 2mL of placebo (cell culture medium and cryopreservative) was provided by Regeneus Ltd. and stored in a CryoVial and maintained at or below 150 degrees C. The IP was thawed prior to being drawn up into a sterile syringe and administered via ultrasound guided intraarticular injection into the study knee either by an independent, unblinded radiologist or sports and exercise medicine physician trained in the technique.. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness

Funding	Principal author funded by industry (Kuah, D: Receipt of payment from Regeneus Ltd via a Clinical Trial Research Agreement; Sivell, S: Employee of Regeneus Ltd, sponsor of the trial; Longworth, T: Receipt of payment from Regeneus Ltd via a Clinical Trial Research Agreement; James, K: Receipt of payment from Regeneus Ltd via a Clinical Trial Research Agreement; Guermazi, A: Fee for service for MRI analyses from Regeneus Ltd. President of Boston Imaging Core Lab, LLC. Consultant to Merck Serono, OrthoTrophix, Genzyme, Sanofi, TissueGene, Astra Zeneca; Cicuttini, F: Fee for service for MRI analyses from Regeneus Ltd. Other consultancy roles: Mesoblast LTD, Paradigm Biopharmaceuticals LTD; Wang, Y: Fee for service for MRI analyses from Regeneus Ltd. Y.W is the recipient of National Health and Medical Research Council (NHMRC) Career Development Fellowship (Clinical Level 1, APP1065464). Other consultancy roles: Mesoblast LTD, Paradigm Biopharmaceuticals LTD; Craig, S: Employee of Regeneus Ltd, sponsor of the trial; Comin, J: No competing interests to disclose; Robinson, D: Fee for service for providing ultrasound-guided injection from Regeneus Ltd; Wilson, J: Employee of Regeneus Ltd, Sponsor of the trial)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain subscale at 12 months; Group 1: mean -2.36 (SD 2.05); n=16, Group 2: mean -0.73 (SD 2.45); n=4; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Reports change score and 95% confidence intervals. Converted to SD. Reported stem cells: -2.36 (-3.56 to -1.55, p <0.001). Reported placebo: -0.73 (-3.14 to 1.67, p = 0.526). Baseline stem cells: 7.25 (2.7). Baseline placebo: 6.3 (3.86).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, Kellgren Lawrence grade, outcome baseline values, MRI features and biomarker results; Group 1 Number missing: 0, Reason: 1 person was randomised but did not enter the treatment and withdrew (due to patient decision). Unclear whether they were to be an experimental or control participant.; Group 2 Number missing: 0, Reason: 1 person was randomised but did not enter the treatment and withdrew (due to patient decision). Unclear whether they were to be an experimental or control participant.

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Serious adverse events at 12 months; Group 1: 0/16, Group 2: 0/4
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, Kellgren Lawrence grade, outcome baseline values, MRI features and biomarker results; Group 1 Number missing: 0, Reason: 1 person was randomised but did not enter the treatment and withdrew (due to patient decision). Unclear whether they were to be an experimental or control participant.; Group 2 Number missing: 0, Reason: 1 person was randomised but did not enter the treatment and withdrew (due to patient decision). Unclear whether they were to be an experimental

or control participant.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Kullenberg 2004[260]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Sweden; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with hip pain recruited from a waiting list for hip replacement and with hip osteoarthritis that was radiologically graded (by the Ahlback criteria) as grade 2 or worse.
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	Hip pain for more than 4 weeks requiring regular analgesia and pain on weight-bearing and rest (VAS >3). Hip osteoarthritis radiologically graded as Ahlback grade 2 or worse and joint space narrowing with cartilage destruction of 50% or worse.
Exclusion criteria	No exclusion criteria specified
Recruitment/selection of patients	Recruited from a waiting list for hip replacement
Age, gender and ethnicity	Age - Mean (SD): 70.0 (7.6). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Ahlback grade 2 or worse. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (image guided). 80mg triamcinolone acetonide in 2mL. Administered via a 22G needle that was introduced under fluoroscopy by anterior approach. No attempt was made to aspirate the joint prior to injection. . Duration 1 injection. Concurrent medication/care: People were discharged after a short rest and advised to rest for the remainder of the day and start normal activities from the next day.. Indirectness: No indirectness (n=40) Intervention 2: Placebo. Mepivacaine 1% in 2mL. Administered via a 22G needle that was introduced under fluoroscopy by anterior approach. No attempt was made to aspirate the joint prior to injection. . Duration 1 injection. Concurrent medication/care: People were discharged after a short rest and advised to rest for the

	remainder of the day and start normal activities from the next day.. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Hip: Visual analogue score (pain) on activity at 3 weeks; Group 1: mean 2.5 (SD 1.4); n=40, Group 2: mean 7.3 (SD 1.5); n=40; Visual analogue scale (pain on activity) 0-10 Top=High is poor outcome; Comments: Baseline CS: 6.9 (1.3). Baseline placebo: 7.0 (1.0). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age in the text.; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Reports that all people discontinued before 12 weeks (reporting the steroid 12 week data, but not the placebo data) due to no positive effect Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Hip: Functional ability at 3 weeks; Group 1: mean 3.6 (SD 0.6); n=40, Group 2: mean 2 (SD 0.4); n=40; Functional ability (derived by Katz and Akpom) 0-5 Top=High is good outcome; Comments: Baseline CS: 2.0 (0.3). Baseline placebo: 2.2 (0.2). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age in the text.; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Reports that all people discontinued before 12 weeks (reporting the steroid 12 week data, but not the placebo data) due to no positive effect	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Kul-panza 2010[259]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee pain and a diagnosis of osteoarthritis. Have radiographic grades stated in the baseline characteristics.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with uni- or bilateral osteoarthritis presenting to the Physical Medicine and Rehabilitation Outpatient Clinic, Marmara University School of Medicine with complaints of knee pain.
Exclusion criteria	None stated
Recruitment/selection of patients	People presenting to the Physical Medicine and Rehabilitation Outpatient Clinic, Marmara University School of Medicine
Age, gender and ethnicity	Age - Mean (SD): 61.1 (8.5). Gender (M:F): 7:41. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity not stated (mean osteoarthritis radiological Grade 2, ranging from Grade 1-4). Mean duration of symptoms: 7.2 (7.1) years
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hyaluronic acid - 2mL 1.5% (Orthovisc). Given three times in one week.. Duration 3 injections over 1 week. Concurrent medication/care: All people received instruction on quadriceps isometric exercises and range of motion exercises and were advised to practice them regularly at home. People were told not to use any drug for knee pain except paracetamol if required (500mg up to four times a day).. Indirectness: No indirectness (n=23) Intervention 2: Placebo. Intraarticular placebo - 2mL 0.9% saline solution. Given as three injections over one week.. Duration 3 injections over 1 week. Concurrent medication/care: All people received instruction on quadriceps isometric

	exercises and range of motion exercises and were advised to practice them regularly at home. People were told not to use any drug for knee pain except paracetamol if required (500mg up to four times a day).. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC total pain subscale at 14 weeks; Group 1: mean 11.6 (SD 3.2); n=23, Group 2: mean 12.3 (SD 4); n=22; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 15.3 (2.8). Baseline placebo: 14.7 (3.1). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC function subscale at 14 weeks; Group 1: mean 43.6 (SD 11.1); n=23, Group 2: mean 46.3 (SD 13.9); n=22; WOMAC function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 51.2 (9). Baseline placebo: 50 (11.1). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Adverse events at 14 weeks; Group 1: 0/23, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Kwon 2013[261]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with shoulder pain primarily due to glenohumeral osteoarthritis determined by the investigator and confirmed by standard shoulder radiography. This can be supported by MRI, but was not required in all people.
Stratum	Shoulder
Subgroup analysis within study	Not applicable
Inclusion criteria	People with shoulder pain primarily due to glenohumeral osteoarthritis (people could have other diagnoses concurrently) determined clinically by the investigator and confirmed by standard shoulder radiographs. Age 35 years or older, initial visual analogue score for shoulder pain on movement of 50mm or greater, chronic shoulder pain lasting more than 6 months but less than 3 years, willing to discontinue all pain medication for at least 24 hours before each visit, and no modification of the pain medication regimen in the previous 4 weeks.
Exclusion criteria	Severe joint effusion; structural defects requiring surgical management; corticosteroid injection in any joint(s) in the previous 3 months; surgical interventions in the trial shoulder within the previous 2 years; inflammatory arthropathy of the trial shoulder
Recruitment/selection of patients	300 people were recruited. Of these, 72 had one or more protocol deviations, leaving 228 for the per protocol analysis. Of the 300 people, 37 had concomitant shoulder pathologies in addition to glenohumeral osteoarthritis such as full thickness rotator cuff tears.
Age, gender and ethnicity	Age - Mean (SD): 66.1 (11.2). Gender (M:F): 164:136. Ethnicity: 10 identified as hispanic or latino. 290 identified as non-hispanic or latino. Of those 14 identified as black/African American, 1 identified as Native Hawaiian/Pacific Islander, and 1 identified as Asian. The remainder identified as Caucasian.
Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not stated Duration of symptoms: Not stated explicitly. More than 6 months but less than 3 years..
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 3 injections of hyaluronic acid over 3 weeks (no additional information). Duration 3 injections over 3 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=150) Intervention 2: Placebo. 3 injections of phosphate buffered saline over 3 weeks (no additional information). Duration 3 injections over 3 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Principal author funded by industry (Young W. Kwon, MD, PhD and Joseph D. Zuckerman, MD are paid consultant for Smith & Nephew, Inc. The other authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Shoulder: Visual analogue scale (pain) at 26 weeks; MD; -2.84 (P value: 0.112) Visual analogue scale 0-100 Top=High is poor outcome, Comments: Least squares mean difference. Reports the p value as 0.112. Reported as 2.84 favoring the hyaluronic acid group. Calculated SE (from p-value): 1.78.;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, weight, height, BMI, blood pressure, dominant arm, smoking history, presence of diabetes mellitus; Group 1 Number missing: 33, Reason: Reports that 33 people were excluded due to protocol violations. This was mainly due to change in pain medication and the physical therapy regimen; Group 2 Number missing: 39, Reason: Reports that 39 people were excluded due to protocol violations. This was mainly due to change in pain medication and the physical therapy regimen

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Shoulder: Serious adverse events at 26 weeks; Group 1: 11/150, Group 2: 5/150
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, race, ethnicity, weight, height, BMI, blood pressure, dominant arm, smoking history, presence of diabetes mellitus; Group 1 Number missing: 33, Reason: Reports that 33 people were excluded due to protocol violations. This was mainly due to change in pain medication and the physical therapy regimen; Group 2 Number missing: 39,

Reason: Reports that 39 people were excluded due to protocol violations. This was mainly due to change in pain medication and the physical therapy regimen	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Lambert 2007[262]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Canada; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Primary osteoarthritis of the hip according to the American College of Rheumatology criteria, including radiologic evidence of osteoarthritis
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of primary osteoarthritis of the hip according to the American College of Rheumatology criteria, including radiologic evidence of OA; age >40 years; symptomatic disease for at least 6 months prior to enrollment; persistent pain despite receiving the maximum tolerated doses of conventional medical therapy, including paracetamol (4g/day) and/or a nonsteroidal antiinflammatory drug with persistent pain defined as a minimum score of 40mm on the 5 visual analogue scales for pain (0-100mm range for each) that are the first 5 questions of the WOMAC index comprising the WOMAC composite pain subscale, daily pain during the month prior to study enrollment, and ability to attend followup appointments.
Exclusion criteria	Secondary causes of osteoarthritis; local or systemic infection precluding injection; diabetes mellitus; systemic arthritis; allergy to anaesthetic agent or contrast material; coagulopathy; anticoagulant therapy; previous intraarticular steroid injection into the index hip; avascular necrosis of bone
Recruitment/selection of patients	Two hundred and eleven people were referred to the trial from March 2000 to September 2003, but 101 chose not to participate after they were informed of the possibility of receiving placebo. Of the 110 people screened, 52 met all entry criteria. In view of the delayed recruitment, the ethics committee subsequently raised concerns about continuation of the study, since obvious symptomatic responses had been noted in some people; the committee receommended that an interim analysis be performed, when 52 people had been recruited. Since treatment group difference were highly significant, it was deemed unethical to continue further recruitment to the study beyond 4 years.
Age, gender and ethnicity	Age - Mean (SD): 62.1 (11.8). Gender (M:F): 21:31. Ethnicity: Not stated

Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Included people with Kellgren Lawrence grade 1-4 changes. Duration of symptoms: 51 (46.6) months
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (image guided). 10mg of bupivicaine and 40mg of triamcinolone hexacetonide - the maximum volume of fluid injected was 5cc. Administered under sterile conditions using a 22G, 3.5 inch needle. Aspiration of the joint was attempted. Intrasynovial flow was established with an injection of a small dose (≤1cc) of meglumine iothalamate (radiographic contrast material). Conducted under fluoroscopy.. Duration 1 injection. Concurrent medication/care: All people were advised to rest (preferrably in the form of bed rest) for 3 days and to maintain minimal activity. After this period they were advised to refrain from active exercise and (if possible) work for 1 week. No additional information given.. Indirectness: No indirectness (n=21) Intervention 2: Placebo. 10mg of bupivicaine and 2mL normal saline - the maximum volume of fluid injected was 5cc. Administered under sterile conditions using a 22G, 3.5 inch needle. Aspiration of the joint was attempted. Intrasynovial flow was established with an injection of a small dose (≤1cc) of meglumine iothalamate (radiographic contrast material). Conducted under fluoroscopy.. Duration 1 injection. Concurrent medication/care: All people were advised to rest (preferrably in the form of bed rest) for 3 days and to maintain minimal activity. After this period they were advised to refrain from active exercise and (if possible) work for 1 week. No additional information given.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a CHAR/Nycomed Development Award, the MSI foundation, the University of Alberta Hospital Foundation, and the Arthritis Society of Canada. Dr Maksymowych is a Scientist of the Alberta Heritage Foundation for Medical Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Hip: SF-36 physical component at 2 months; Group 1: mean 31.01 (SD 8.59); n=31, Group 2: mean 26.58 (SD 6.78); n=21; SF-36 physical component 0-100 Top=High is good outcome; Comments: Baseline CS: 25.73 (5.28). Baseline placebo: 25.50 (7.07).

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age (different at baseline, lower in the placebo group), time since diagnosis, which hip was affected, number of people taking medication before, Kellgren Lawrence grade and baseline values of outcomes; Group 1 Number missing: 0, Reason: 0 withdrew before 2 months. However, lots withdrew after this point.; Group 2 Number missing: 2, Reason: 2 withdrew before 2 months. 1 entered an open label injection of steroid arm. 1 had a total hip arthroplasty.
- Actual outcome for Hip: SF-36 social functioning at 2 months; Group 1: mean 66.94 (SD 27.87); n=31, Group 2: mean 53.57 (SD 24.73); n=21; SF-36 social functioning subscale 0-100 Top=High is good outcome; Comments: Baseline CS: 55.65 (26.39). Baseline placebo: 55.36 (24.87).
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age (different at baseline, lower in the placebo group), time since diagnosis, which hip was affected, number of people taking medication before, Kellgren Lawrence grade and baseline values of outcomes; Group 1 Number missing: 0, Reason: 0 withdrew before 2 months. However, lots withdrew after this point.; Group 2 Number missing: 2, Reason: 2 withdrew before 2 months. 1 entered an open label injection of steroid arm. 1 had a total hip arthroplasty.

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: WOMAC pain subscale at 2 months; Group 1: mean 157.4 (SD 127.2); n=31, Group 2: mean 306.5 (SD 121.2); n=21; WOMAC pain subscale 0-500 Top=High is poor outcome; Comments: Baseline CS: 310.1 (54.6). Baseline placebo: 314.3 (76.2).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age (different at baseline, lower in the placebo group), time since diagnosis, which hip was affected, number of people taking medication before, Kellgren Lawrence grade and baseline values of outcomes; Group 1 Number missing: 0, Reason: 0 withdrew before 2 months. However, lots withdrew after this point.; Group 2 Number missing: 2, Reason: 2 withdrew before 2 months. 1 entered an open label injection of steroid arm. 1 had a total hip arthroplasty.

Protocol outcome 3: Physical function at ≤3- or >3- months
- Actual outcome for Hip: WOMAC physical function subscale at 2 months; Group 1: mean 538.5 (SD 402); n=31, Group 2: mean 949.1 (SD 350.4); n=21; WOMAC physical function subscale 0-1500 Top=High is poor outcome; Comments: Baseline CS: 969.3 (167.8). Baseline placebo: 970.9 (254.5).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age (different at baseline, lower in the placebo group), time since diagnosis, which hip was affected, number of people taking medication before, Kellgren Lawrence grade and baseline values of outcomes; Group 1 Number missing: 0, Reason: 0 withdrew before 2 months. However, lots withdrew after this point.; Group 2 Number missing: 2, Reason: 2 withdrew before 2 months. 1 entered an open label injection of steroid arm. 1 had a total hip arthroplasty.

Protocol outcome 4: Serious adverse events at ≤3- or >3- months
- Actual outcome for Hip: Deep vein thrombosis post-injection at 2 months; Group 1: 1/31, Group 2: 0/21
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age (different at baseline, lower in the placebo group), time since diagnosis, which hip was affected, number of people taking medication before, Kellgren Lawrence grade and baseline values of outcomes; Group 1 Number missing: 0, Reason: 0 withdrew before 2 months. However, lots withdrew after this point.; Group 2 Number missing: 2, Reason: 2 withdrew before 2 months. 1 entered an open label injection of steroid arm. 1 had a total hip arthroplasty.

Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Lee 2020[268]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=102)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Kellgren-Lawrence grade 3 osteoarthritis of the knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 18 and 70 years; body mass index between 18.5 and 45.5 kg/m²; Kellgren Lawrence grade 3 osteoarthritis of the knee; continuous or intermittent pain for more than 4 consecutive months
Exclusion criteria	Abnormal haematology, serum chemistry, or urinalysis screening laboratory values (i.e., white/red blood cell counts, haemoglobin/haematocrit, creatinine outside of the standard normal ranges); non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days of baseline visit; steroidal anti-inflammatory medications within 2 months of the baseline visit (enough time for appropriate wash-out); drug abuse within 1 year and/or a positive urine drug test at the time of screening; previous injection to the target knee within 2 months of study enrollment (enough time for appropriate washout); contraindication for 3T MRI; currently pregnant or breastfeeding; history of systemic, rheumatic, or inflammatory disease of the knee (including the use of disease modifying antirheumatic drugs); history of ongoing human immunodeficiency virus and Hepatitis B or C infections.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (range): 56.7 (25-71). Gender (M:F): 38:64. Ethnicity: 82 white, 16 black, 4 hispanic
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 3. Duration of symptoms: Not stated
Indirectness of population	No indirectness

Interventions	(n=67) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). 2mL of a 3:1 mixture of nontransduced allogenic human chondrocytes and transduced allogenic human chondrocytes expressing TGF-β. The joint was aspirated prior to administration of either solution, and the synovial fluid was analysed for infection. An 18-gauge needle was used to inject the agent using the inferolateral and inferomedial approach with the knee in 90 degrees of flexion. . Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=35) Intervention 2: Placebo. 2mL of normal saline (0.9%). The joint was aspirated prior to administration of either solution, and the synovial fluid was analysed for infection. An 18-gauge needle was used to inject the agent using the inferolateral and inferomedial approach with the knee in 90 degrees of flexion. . Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Principal author funded by industry (Lee: Kolon TissueGene; Parvizi: Alpheon; CeramTec; Ceribell; ConvaTex; Corentec; Cross Current Business Intelligence; Datatrace; Eastern Orthopaedic Association; Elzevier; Ethicon; Heron; Hip Innovation Technology; Intellijoint; Invisible Sentinelp; Jaypee Publishers; Joint Purification Systems; Journal of Bone and Joint surgery-American; MDValuate; MedAp; MicroGenDx; Muller Foundation; Parvizi Surgical Innovations; Physician Recommended Nutriceuticals; PRN-Vetinary; SLACK Incorporated; Tenor; Kolon TissueGene; Wolters Kluwer Health - Lippincott Williams & Wilkins; Zimmer; Romness: AAOS,Eastern Orthopaedic Assn.,Virginia Orthopaedic Society; Centrexion; Tenex; Kolon Tissuegene; Guermazi; Astra Zeneca; Boston Imaging Core Lab; GE Healthcare; Merck; Norvartis; Orthotrophix; Pfizer; Kolon TissueGene; Noh: Kolon TissueGene; Mont: AAOS, Cymedica, DJ Orthopaedics, Johnson&Johnson, Journal of Arthroplasty, Journal of Knee Surgery, Microport, National Institutes of Health (NIAMS&NICHD), Ongoing Care Solutions, Orthopedics, Orthosensor, Pacira, Peerwell, Performance Dynamics Inc, Sage. Striker: IP royalties, Surgical Technologies International, Kolon TissueGene)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 12 weeks; MD; -14.4 (P value: 0.0119) Visual analogue scale 0-100 Top=High is poor outcome, Comments: Reports least mean square difference and p-values.;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, race and BMI. Does not report baseline values for outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Knee: Visual analogue scale (pain) at 24 months; MD; -12.2 (P-value: 0.0106) Visual analogue scale (pain) 0-100 Top=High is poor outcome, Comments: Reports least mean square difference and p-value; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, race and BMI. Does not report baseline values for outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Severe adverse events at 24 months; Group 1: 0/67, Group 2: 0/35 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, race and BMI. Does not report baseline values for outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Lee 2019[273]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in South Korea; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Osteoarthritis of the knee joint (Kellgren-Lawrence grade 2-4)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People must consent in writing to participate in the study by signing and dating an informed consent document approved by IRB indicating that the patient has been informed by all pertinent aspects of the study prior to completing any of the screening procedures; Male or female at age 18-75; healthy patients with no major history of illness; patients must have a diagnosis of osteoarthritis by radiographic criteria of Kellgren and Lawrence grade 2-4; people must have had more than grade 4 (0-10 point numeric scale) pain at least for 12 weeks
Exclusion criteria	People with measures twice or more than normal in lab test or with any condition that principle investigator considers clinically important; pregnant women or lactating mothers; people who have received any anti-inflammatory drugs including herb-drug within 14 days prior to the investigational drug injection. People with a known, current substance abuse (e.g. alcohol, illegal drugs, ect.) or urine-tested positively for those substances within one year prior to this study; people who received any drug by intra-articular injection for treatment within 2 months prior to this enrollment; people with other disease (no matter the length of time) including systemic or rheumatologic or inflammatory cartilage disease, crystalline disease (gout or pseudogout), haemochromatosis, inflammatory joint disease, femoral head necrosis, Paget disease in the joint of femur or tibia, or related knee joint disease, ochronosis, haemophilia arthropathy, joint infections, joint sarcoidosis, villonodular synovitis, or solitary synovial chondromatosis; people with positive human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening indicative of current or past infection; people with serious conditions which can affect this study, including: cardiovascular diseases, renal diseases, liver diseases, endocrine diseases, cancer or diabetes; people with a body mass index >30; people who had participated in other clinical trials within 12 weeks

	prior to this study; people who the principle investigator considers inappropriate for the clinical trial due to any other reasons than those listed above
Recruitment/selection of patients	Performed in two orthopaedic centers
Age, gender and ethnicity	Age - Mean (SD): 62.7 (5.5). Gender (M:F): 6:18. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: People with multimorbidities excluded
Extra comments	Severity: Not explicitly stated. Majority Kellgren-Lawrence grade 2-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (image guided). 1x10^8 cells of adipose derived-mesenchymal stem cells in 3mL of saline administered intraarticularly under ultrasound guidance. Duration 1 injection. Concurrent medication/care: The rescue analgesic was paracetamol at 4000mg or less per day. Other analgesics were not permitted, and any medications were recorded.. Indirectness: No indirectness (n=12) Intervention 2: Placebo. 3mL of saline administered intraarticularly under ultrasound guidance. Duration 1 injection. Concurrent medication/care: The rescue analgesic was paracetamol at 4000mg or less per day. Other analgesics were not permitted, and any medications were recorded.. Indirectness: No indirectness
Funding	Study funded by industry (This study was supported by the R-Bio Co., Ltd.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 0/12, Group 2: 0/12; Comments: Definition given: an SAE is defined as any undesired medical incident that causes death, life threatening, hospitalisation, disability, congenital abnormality or birth death Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, body mass index, Kellgren Lawrence grade, mechanical axis, baseline WOMAC score and cartilage defect; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Leighton 2014[276]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=442)
Countries and setting	Conducted in Canada, Sweden, United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Unilateral knee pain meeting the American College of Rheumatology criteria for the diagnosis of OA with radiographically verified OA of the study knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 35-80 with a body mass index of ≤40 kg/m², the ability to walk 50m unaided, unilateral knee pain meeting the American College of Rheumatology for the diagnosis of OA, WOMAC pain score of 7-17 in the study knee, and radiographically verified OA of the study knee (Kellgren-Lawrence grade II or III).
Exclusion criteria	Clinically detectable knee effusion; clinically significant contralateral knee OA (WOMAC pain score >3); clinically significant pain in joints other than the knee; IA steroid injection into the study knee within the preceding 3 months; IA HA injection into the study knee within the preceding 9 months; use of systemic glucocorticosteroids (excluding inhaled steroids) within the preceding 3 months and arthroscopy or other surgical procedure in the study knee within the preceding 12 months.
Recruitment/selection of patients	442 participants were enrolled at sites in Canada (15 sites), UK (4 sites), and Sweden (5 sites).
Age, gender and ethnicity	Age - Mean (SD): 61.7 (9.8). Gender (M:F): 220:213. Ethnicity: Majority Caucasian (416 people). 5 people were black. 9 people were Asian. 1 was hispanic. 2 other.
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed without imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated (K-L grade II-III) Duration of symptoms: 4.8 (5.9) years
Indirectness of population	No indirectness
Interventions	(n=221) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). A single injection of NASHA (Durolane) 60mg in 3mL. Duration 1 injection. Concurrent medication/care: Synovial fluid was aspirated as needed and an

	IA injection of lidocaine was performed. Rescue medication with paracetamol was allowed up to 3g per day.. Indirectness: No indirectness (n=221) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 1 injection of methylprednisolone acetate (1mL, 40mg). Duration 1 injection. Concurrent medication/care: Synovial fluid was aspirated as needed and an IA injection of lidocaine was performed. Rescue medication with paracetamol was allowed up to 3g per day.. Indirectness: No indirectness
Funding	Study funded by industry (Q-Med Ali, Uppsala, Sweden and Smith & Nephew, UK Ltd.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Arthralgia at 26 weeks; Group 1: 38/221, Group 2: 7/221 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Lohmander 1996[287]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=240)
Countries and setting	Conducted in Denmark, Finland, Norway, Sweden; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A clinical history of symptomatic, radiologically verified unilateral osteoarthritis of the knee (50-100% obliteration of the medial tibiofemoral joint space without bony erosion on anteroposterior standing films at 10-15 degrees flexion, taken within 6 months of the start of the study).
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 40-75 years at inclusion; symptomatic, radiologically verified knee osteoarthritis (stage I-II according to Ahlbäck); knee pain on the day of examination scoring more than 10mm on a 100mm visual analogue scale (VAS) at baseline; and an algofunctional score of 4 or greater at baseline.
Exclusion criteria	Significant symptoms of osteoarthritis of both knees; previous intra-articular fracture of the knee; rheumatoid arthritis or other inflammatory arthritis as diagnosed by American College of Rheumatology criteria; including C reative protein and serum rheumatoid factor concentrations; intra-articular injections of steroids or any other invasive procedure in the knee within the previous six months; any other condition that might interfere with the efficacy assessment or completion of the trial.
Recruitment/selection of patients	Enrolled from eight orthopaedic or rheumatology clinics in Denmark, Finland, Norway and Sweden.
Age, gender and ethnicity	Age - Mean (SD): 58.3 (8.4). Gender (M:F): 106:134. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity not stated Duration of symptoms not stated
Indirectness of population	No indirectness
Interventions	(n=120) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hyaluronan 25mg (approximate around 1000kDa) (Artzal) - supplied as a sterile 1% solution in 2.5mL phosphate buffered saline, pH 7.. Duration

	1 injection. Concurrent medication/care: Concurrent and escape medication in the form of simple analgesics (for example, paracetamol) in addition to NSAIDs, was allowed during the trial.. Indirectness: No indirectness (n=120) Intervention 2: Placebo. Sterile 1% solution in 2.5mL phosphate buffered saline, pH7.. Duration 1 injection. Concurrent medication/care: Concurrent and escape medication in the form of simple analgesics (for example, paracetamol) in addition to NSAIDs, was allowed during the trial.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by the Medical Faculty of Lund University, the Swedish Medical Research Council, KaroBio AB, and Astra Läkemedel AB)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 20 weeks; Group 1: 0/119, Group 2: 0/120 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 lost to follow up; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Lundsgaard 2008[291]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=251)
Countries and setting	Conducted in Denmark; Setting: Outpatient follow up (referred from primary and secondary care)
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Daily knee pain with radiographic evidence of mild or severe change.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People over 59 years of age with daily knee pain above 20mm on a 100-mm visual analogue scale (VAS-movement) that did not respond satisfactorily to analgesics. Based on radiographic findings, OA patients wre classified into mild (Kellgren-Lawrence grade 1 or 2) or severe (Kellgren-Lawrence grade 3 or 4).
Exclusion criteria	Rheumatoid arthritis or other inflammatory arthritis as diagnosed by the American College of Rheumatolog; intra-articular steroid injections within the previous 2 months; invasive knee procedures within the past 6 months; contraindications to hyaluronate (e.g. allergy); contraindications to injections into the knee (e.g. local dermatological disease); medications that could interfere with the planned interventions; or coexisting diseases (e.g. psychosis, dementia) that could interfere with the investigation; signs of crystals or infection.
Recruitment/selection of patients	Recruited from primary or secondary care at one centre.
Age, gender and ethnicity	Age - Mean (SD): 69.4 (6.8). Gender (M:F): 113:138. Ethnicity: Not stated
Further population details	1. Age: Mixed (Due to SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity not explicitly stated (K-L grade I-IV, majority GRADE III-IV). Duration of symptoms not stated
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Four weekly injections of sodium hyaluronate 2mL (Hyalgan 10.3 mg/mL). Duration 4 injections over 4 weeks. Concurrent medication/care: All people were permitted analgesics of the acetaminophen, aspirin, NSAID (inclusive COX-2

	selective inhibitors), codeine and tramadol.. Indirectness: No indirectness (n=83) Intervention 2: Placebo. Physiological saline 20mL intraarticular injections. Duration 4 injections over 4 weeks. Concurrent medication/care: All people were permitted analgesics of the acetaminophen, aspirin, NSAID (inclusive COX-2 selective inhibitors), codeine and tramadol.. Indirectness: Serious indirectness; Indirectness comment: Much larger volume of saline then used in standard placebo doses Comments: Not extracted for any outcomes due to indirectness. Reported for completeness. (n=84) Intervention 3: Placebo. Placebo 2mL physiological saline intraarticular injections (four in four weeks). Duration 4 injections over 4 weeks. Concurrent medication/care: All people were permitted analgesics of the acetaminophen, aspirin, NSAID (inclusive COX-2 selective inhibitors), codeine and tramadol.. Indirectness: No indirectness
Funding	Academic or government funding (Funding from Glostrup Hospital, The Danish Society of Rheumatism, and the Copenhagen Trial Unit, Centre for Clinical Intervention Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Knee: KOOS quality of life at 26 weeks; MD; -2.72 (95%CI -7.31 to 1.87) (p-value: 0.72) KOOS quality of life subscale 0-100 Top=High is poor outcome, Comments: Baseline HA: 36.6 (16.5). Baseline saline 2mL: 33.6 (16.9).;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: One had a joint replacement after week 8. One was lost to follow up after week 12 due to lack of effect.; Group 2 Number missing: 4, Reason: One discontinued at week 1 due to joint replacement. Two discontinued after week 1 due to death in the family or travel distance. 1 discontinued after week 2 due to cerebral haemorrhage.

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: KOOS pain subscale at 26 weeks; MD; -1.41 (95%CI -5.79 to 2.97) (P-value: 0.63) KOOS pain subscale 0-100 Top=High is poor outcome, Comments: Baseline HA: 53.0 (14.8). Baseline saline 2mL: 52.3 (14.3).;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: One had a joint replacement after week 8. One was lost to follow up after week 12 due to lack of effect.; Group 2 Number missing: 4, Reason: One discontinued at week 1 due to joint replacement. Two discontinued after week 1 due to death in the family or travel distance. 1 discontinued after week 2 due to cerebral haemorrhage.

Protocol outcome 3: Physical function at ≤3- or >3- months - Actual outcome for Knee: KOOS activities subscale at 26 weeks; MD; -3.67 (95%CI -8.54 to 1.2) KOOS activities subscale 0-100 Top=High is poor outcome, Comments: Baseline HA: 55.6 (17.0). Baseline saline 2mL: 53.0 (17.9).; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: One had a joint replacement after week 8. One was lost to follow up after week 12 due to lack of effect.; Group 2 Number missing: 4, Reason: One discontinued at week 1 due to joint replacement. Two discontinued after week 1 due to death in the family or travel distance. 1 discontinued after week 2 due to cerebral haemorrhage. Protocol outcome 4: Osteoarthritis flares at ≤3- or >3- months - Actual outcome for Knee: Post-injection "flares" at 26 weeks; Group 1: 0/82, Group 2: 0/80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: One had a joint replacement after week 8. One was lost to follow up after week 12 due to lack of effect.; Group 2 Number missing: 4, Reason: One discontinued at week 1 due to joint replacement. Two discontinued after week 1 due to death in the family or travel distance. 1 discontinued after week 2 due to cerebral haemorrhage. Protocol outcome 5: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 26 weeks; Group 1: 0/82, Group 2: 0/80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: One had a joint replacement after week 8. One was lost to follow up after week 12 due to lack of effect.; Group 2 Number missing: 4, Reason: One discontinued at week 1 due to joint replacement. Two discontinued after week 1 due to death in the family or travel distance. 1 discontinued after week 2 due to cerebral haemorrhage.	
Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months

Study	Lyons 2005[292]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A clinical diagnosis of osteoarthritis using the criteria of: in the absence of an alternative rheumatological diagnosis, three of the follow six being present: age >50 years; morning stiffness of less than 30 minutes duration; crepitus; bony tenderness; bony enlargement; no palpable warmth. Non-radiological.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People who consulted their general practitioner with a complaint of knee pain every day for at least the prior six weeks.
Exclusion criteria	Marked tenderness in the region of the origin of the medial collateral ligament.
Recruitment/selection of patients	Recruited from general practice
Age, gender and ethnicity	Age - Other: Mean: 59.7. Gender (M:F): 9:11. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed without imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity not stated Duration of symptoms at least six weeks.
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Methylprednisolone 60mg (2mL) with 1% lignocaine (8mL) given as one injection. Duration 1 injection. Concurrent medication/care: Nothing explicitly stated. Indirectness: No indirectness (n=10) Intervention 2: Placebo. 10mL of 1% lignocaine given as one injection. Duration 1 injection. Concurrent medication/care: Nothing explicitly stated. Indirectness: No indirectness
Funding	Academic or government funding (Azeem Majeed holds a Primary Care Scientist Aware funded by the Department of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: VAS improvement at 2 months; Group 1: mean 5.39 (SD 2.67); n=10, Group 2: mean 0.7 (SD 2.67); n=10; Visual analogue scale (pain) - improvement (can have negative added, in which case can flip the scale) 0-10 Top=High is good outcome; Comments: Reported indirectly, calculated standard deviation from p-value (p =0.001). Baseline CS: 7.67. Baseline placebo: 5.91. Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in several parameters, likely due to low sample size. Especially regarding to VAS score at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Matas 2019[301]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in Chile; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic knee osteoarthritis (defined by daily pain at the affected joint for at least 3 months before inclusion) with grade 1-3 Kellgren-Lawrence radiographic changes in the targeted knee, without meniscal rupture
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic osteoarthritis (defined by daily pain at the affected joint for at least 3 months before inclusion) with grade 1-3 Kellgren-Lawrence radiographic changes in the target knee, without meniscal rupture.
Exclusion criteria	Bilateral symptomatic knee osteoarthritis; condylar or tibial plateau generalized bone marrow oedema on MRI; major axial deviation defined by valgus (>10 degrees) or varus (5 degrees) deformity of the involved leg; use of oral or intraarticular steroids or hyaluronic acid in the past 6 months; ipsilateral hip or ankle pain; local or systemic infection; any form of secondary arthritis; previous malignancy; or body mass index ≥30
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 55.9 (5.4). Gender (M:F): 13:16. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 2-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). Two groups combined. One group has two injections of mesenchmal stem cells (at baseline and 6 months). The other has one injection of mesenchymal stem cells at baseline and a placebo injection (of 3cc of saline with 5% AB plasma) at baseline. MSC injections contained 20x10^6 umbilical cord

	mesenchymal stem cells in 3cc of saline with 5% AB plasma.. Duration 2 injections (1 at baseline, 1 at 6 months). Concurrent medication/care: Paracetamol (1g every 8 hours) was allowed as needed in case of pain. Indirectness: No indirectness (n=9) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intra-articular knee injections of hyaluronic acid at baseline and at 6 months. These contained 3cc of Durolane.. Duration 2 injections (1 at baseline, 1 at 6 months). Concurrent medication/care: Paracetamol (1g every 8 hours) was allowed as needed in case of pain. Indirectness: No indirectness
Funding	Principal author funded by industry (C.I., R.T.-L, M.I.C., F.A.-M., P.L.G., and M.K. have declared employment/leadership position with Cells for cells. F.E. has declared employment/leadership position and intellectual property or patent holder with Cells for Cells. The other authors indicated no potential conflicts of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 12 months; Group 1: mean 2.4 (SD 2.4); n=18, Group 2: mean 4.2 (SD 3.8); n=9; WOMAC pain 0-20 Top=High is poor outcome; Comments: Stem cell groups were combined. Reported MSC-1 group: 3.7 (2.6). MSC-2 group: 1.1 (1.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, Kellgren grade and baseline values for outcomes; Group 1 Number missing: 2, Reason: 2 discontinued the intervention; Group 2 Number missing: 0

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC function at 12 months; Group 1: mean 6.1 (SD 6.5); n=18, Group 2: mean 9.2 (SD 9.4); n=9; WOMAC function subscale 0-68 Top=High is poor outcome; Comments: Combined stem cell groups. Reported MSC-1: 9.5 (7.4). Reported MSC-2: 2.6 (2.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, Kellgren grade and baseline values for outcomes; Group 1 Number missing: 2, Reason: 2 discontinued the intervention; Group 2 Number missing: 0

Protocol outcome 3: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Serious adverse events at follow up at 12 months; Group 1: 0/18, Group 2: 0/9; Comments: Defined as serious AEs, deaths, permanent disability, neoplasia or septic arthritis
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, BMI, Kellgren grade and baseline values for outcomes; Group 1 Number missing: 2, Reason: 2 discontinued the intervention; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Mcalindon 2017[303]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=140)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis defined by the American College of Rheumatology through standardised questions and tibiofemoral osteoarthritis evident on posteroanterior weight-bearing semi-flexed radiographs.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	45 years or older with knee osteoarthritis as defined by the American College of Rheumatology classification criteria. Thresholds were placed for knee pain (score ≥2 but ≤8 on weight bearing questions of the WOMAC pain subscale, range 0-12), and radiographic severity (K-L grade 2-3). Clinical examination confirming pain from the knee joint. Had to be willing to discontinue analgesic medication for 48 hours before each pain assessment. Ultrasonographic evidence of effusion synovitis in the study knee, defined according to established protocols by a suprapatellar pouch depth larger than 2mm.
Exclusion criteria	Other disorders affecting the study joint, such as systemic inflammatory joint disease, prior sepsis, osteonecrosis; chronic or recent use of oral corticosteroids, doxycycline, indomethacin, glucosamine or chondroitin; recent (≤3 months) intraarticular corticosteroids or hyaluronic acid; serious medical conditions (like uncontrolled diabetes, HIV infection or hypertension) that could be contraindications to participation; and any contraindications to undergoing an MRI scan.
Recruitment/selection of patients	Recruited through clinics and local advertisements
Age, gender and ethnicity	Age - Mean (SD): 58.2 (8.0). Gender (M:F): 65:75. Ethnicity: 89 people were white. Other ethnicities not specified.
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: People with multimorbidities excluded
Extra comments	Severity not explicitly stated (K-L grade 2-3) Duration of symptoms not stated
Indirectness of population	No indirectness

Interventions	(n=70) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular triamcinolone - 1mL, 40mg/mL for injection. Administered every 12 weeks for 2 years.. Duration 8 injections over 2 years (1 injection every 12 weeks). Concurrent medication/care: Synovial fluid was aspirated prior to injection. Participants were asked to discontinue concomitant analgesics 2 days before each assessment to avoid masking symptoms of pain. Participants were advised to take paracetamol only if needed.. Indirectness: No indirectness (n=70) Intervention 2: Placebo. 1mL of 0.9% sodium chloride for injection, 1 injection every 12 weeks for 2 years. Duration 8 injections over 2 years (1 injection every 12 weeks). Concurrent medication/care: Synovial fluid was aspirated prior to injection. Participants were asked to discontinue concomitant analgesics 2 days before each assessment to avoid masking symptoms of pain. Participants were advised to take paracetamol only if needed.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 2 years; Group 1: mean -1.2 (SD 2.8); n=70, Group 2: mean -1.9 (SD 2.8); n=70; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Reported as mean (95% CIs), transformed into SD. Reported CS: -1.2 (-1.9 to -0.58). Reported saline: -1.9 (-2.52 to -1.23). Baseline CS: 7.50 (6.3 to 8.6). Baseline saline: 8.2 (7.0 to 9.3).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: WOMAC scores at baseline after estimations were made were different; Group 1 Number missing: 11, Reason: Calculated outcomes based on estimates from an effects model estimating results for the missing participants. 6 treatment ineffective, 4 lost to follow-up, 1 died; Group 2 Number missing: 10, Reason: Calculated outcomes based on estimates from an effects model estimating results for the missing participants. 2 treatment ineffective, 3 lost to follow-up, 2 developed a malignancy, 2 disliked injections, 1 died

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function at 2 years; Group 1: mean -4.1 (SD 14); n=70, Group 2: mean -5.1 (SD 12.6); n=70; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Reported as mean (95% CIs), transformed into SD. Reported CS: -4.1 (-7.4 to -0.83). Reported saline: -5.1 (-8.1 to -2.19). Baseline CS: 27.1 (23.1 to 31.0). Baseline saline: 29.2 (25.3 to 33.1).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: WOMAC scores at baseline after estimations were made were different; Group 1 Number missing: 11, Reason: Calculated outcomes based on estimates from an effects model estimating results for the missing participants. 6 treatment ineffective, 4 lost to follow-up, 1 died; Group 2 Number missing: 10, Reason: Calculated outcomes based on estimates from

an effects model estimating results for the missing participants. 2 treatment ineffective, 3 lost to follow-up, 2 developed a malignancy, 2 disliked injections, 1 died Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Cellulitis at 2 years; Group 1: 0/70, Group 2: 1/70 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: WOMAC scores at baseline after estimations were made were different; Group 1 Number missing: 11, Reason: 6 treatment ineffective, 4 lost to follow-up, 1 died; Group 2 Number missing: 10, Reason: 2 treatment ineffective, 3 lost to follow-up, 2 developed a malignancy, 2 disliked injections, 1 died	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Meenagh 2004[310]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic carpometacarpal joint osteoarthritis (of the thumb) satisfying the American College of Rheumatology criteria for hand osteoarthritis
Stratum	Thumb
Subgroup analysis within study	Not applicable
Inclusion criteria	People with symptomatic carpometacarpal joint osteoarthritis (of the thumb) satisfying the American College of Rheumatology criteria for hand osteoarthritis
Exclusion criteria	A history of inflammatory arthritis; previous thumb base trauma; previous steroid joint injection to either carpometacarpal joint
Recruitment/selection of patients	Referred in from primary care
Age, gender and ethnicity	Age - Mean (range): 60.0 (41-71). Gender (M:F): 4:36. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging (Imaging completed before injection). 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated Duration of symptoms (mean): 7.8 years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 0.25mL (5mg) of triamcinolone hexacetonide in an opaque syringe injected with the hand held in a semi-prone position, the joint line identified by palpation, and the needle tip inserted lateral to the abductor pollicis longus tendon. Duration 1 injection. Concurrent medication/care: The injected joint was immobilised in a thumb spica splint for 48 hours after injection. Indirectness: No indirectness (n=20) Intervention 2: Placebo. 0.25mL sterile 0.9% saline in an opaque syringe injected with the hand held in a semi-prone position, the joint line identified by palpation, and the needle tip inserted lateral to the abductor pollicis longus tendon. Duration 1 injection. Concurrent medication/care: The injected joint was immobilised in

	a thumb spica splint for 48 hours after injection. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Thumb: Visual analogue scale (pain) at 12 weeks; Group 1: mean 0 (SD 0); n=20, Group 2: mean 0 (SD 0); n=20; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Reports medians, interquartile range and p-values. Reported CS: 3.5 (-8.5 to 4.9) p=0.31. Reported placebo: 23.3 (6.0 to 29.3) p=0.51. Baseline CS: 52 (40 to 72). Baseline placebo: 56 (50-78). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, mean duration of symptoms, gender, family history of hand osteoarthritis, dominant hand injected, bilateral symptoms, nodal osteoarthritis present and baseline values for outcomes; Group 1 Number missing: 1, Reason: 1 failed to attend the 12 week assessment; Group 2 Number missing: 0 - Actual outcome for Thumb: Visual analogue scale (pain) at 24 weeks; Group 1: mean 0 (SD 0); n=20, Group 2: mean 0 (SD 0); n=20; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Reports medians, interquartile range and p-values. Reported CS: 0.0 (-12.5 to 2.3) p=0.52. Reported placebo: 14.0 (-12.5 to 16.9) p=0.32. Baseline CS: 52 (40 to 72). Baseline placebo: 56 (50-78). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, mean duration of symptoms, gender, family history of hand osteoarthritis, dominant hand injected, bilateral symptoms, nodal osteoarthritis present and baseline values for outcomes; Group 1 Number missing: 2, Reason: 2 failed to attend the 24 week assessment; Group 2 Number missing: 1, Reason: 1 failed to attend the 24 week assessment	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Mendes 2019[311]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=105)
Countries and setting	Conducted in Brazil; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Primary knee osteoarthritis as defined by the American College of Rheumatology. Mild to moderate OA according to the Kellgren-Lawrence classification (grades II or III).
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age over 50 years, the diagnosis of mild to moderate osteoarthritis according to the Kellgren-Lawrence classification (grades II or III), knee pain for more than six months, knee pain at rest (visual analogue scale) between 3 and 8cm, and an agreement to sign the informed consent form for the study.
Exclusion criteria	A diagnosis of secondary osteoarthritis; a cutaneous lesion near the intra-articular injection site; any intra-articular injection in the last three months; the use of systemic corticosteroids in the last 30 days; a prior knee arthroplasty; a history of neuromuscular disease; any peripheral neuropathy; any use of aminoglycoside or curare-like drugs in the preceding 30 days; a suspected infection; any cardiovascular or respiratory disease that interfered with the patient's functional status; a severe coagulation disorder; untreated fibromyalgia; pregnancy; breastfeeding; and any ability to walk.
Recruitment/selection of patients	Recruited by the study's lead investigator, who was not involved in randomisation, intervention or study evaluation
Age, gender and ethnicity	Age - Mean (SD): 64.2 (6.9). Gender (M:F): 9:96. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Mild-to-moderate. Duration of symptoms: 6.3 (7.1) years.
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Triamcinolone hexacetonide - 2mL of 40mg active drug. Inserted into the knee by an intraarticular needle, with access occurring 2cm from the

	superolateral angle of the patella with a 40mm x 8mm needle. In the case of difficult injection only, 2% lidocaine was used in the skin at the time of procedure. In the presence of joint effusion, total aspiration of the synovial fluid was performed.. Duration 1 injection, followed up over 12 weeks. Concurrent medication/care: In all groups, people were advised to rest for 48 hours and to use 750mg of paracetamol every 8 hours as needed.. Indirectness: No indirectness (n=35) Intervention 2: Placebo. Intraarticular saline solution (2mL of sterile saline 0.9%). Inserted into the knee by an intraarticular needle, with access occurring 2cm from the superolateral angle of the patella with a 40mm x 8mm needle. In the case of difficult injection only, 2% lidocaine was used in the skin at the time of procedure. In the presence of joint effusion, total aspiration of the synovial fluid was performed.. Duration 1 injection, followed up over 12 weeks. Concurrent medication/care: In all groups, people were advised to rest for 48 hours and to use 750mg of paracetamol every 8 hours as needed.. Indirectness: No indirectness (n=35) Intervention 3: Other. Intraarticular Botulinum toxin type A in 2mL of sterile saline 0.9%. Inserted into the knee by an intraarticular needle, with access occurring 2cm from the superolateral angle of the patella with a 40mm x 8mm needle. In the case of difficult injection only, 2% lidocaine was used in the skin at the time of procedure. In the presence of joint effusion, total aspiration of the synovial fluid was performed.. Duration 1 injection, followed up over 12 weeks. Concurrent medication/care: In all groups, people were advised to rest for 48 hours and to use 750mg of paracetamol every 8 hours as needed.. Indirectness: No indirectness Comments: Not for use in our analysis, included in this section for completeness.
Funding	Academic or government funding (Supported by the Sao Paulo Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 12 weeks; Group 1: mean 5.3 (SD 4.2); n=35, Group 2: mean 7.4 (SD 5.1); n=35; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline corticosteroid: 10.3 (3.6). Baseline placebo: 10.5 (3.6).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, symptom onset, disease onset, gender, and Kellgren-Lawrence grade; Group 1 Number missing: 4, Reason: 4 lost to follow up (personal problems); Group 2 Number missing: 14, Reason: 14 lost to follow up (personal problems)

Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function at 12 weeks; Group 1: mean 17 (SD 12.4); n=35, Group 2: mean 23.3 (SD 15.1); n=35; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline corticosteroid: 32.7 (11.9). Baseline placebo: 32.5 (11.4). Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, symptom onset, disease onset, gender, and Kellgren-Lawrence grade; Group 1 Number missing: 4, Reason: 4 lost to follow up (personal problems); Group 2 Number missing: 14, Reason: 14 lost to follow up (personal problems) Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Adverse events at 12 weeks; Group 1: 0/35, Group 2: 0/35 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, symptom onset, disease onset, gender, and Kellgren-Lawrence grade; Group 1 Number missing: 4, Reason: 4 lost to follow up (personal problems); Group 2 Number missing: 14, Reason: 14 lost to follow up (personal problems)	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Migliore 2009[315]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Italy; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months (5 months after the last injection)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hip osteoarthritis as defined by the American College of Rheumatology radiographic criteria
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >40 years; ambulant without assistance; hip OA by American college of Rheumatology radiographic criteria; baseline VAS ≥4cm; persistence of hip pain for at least 1 month before baseline; and signed informed consent
Exclusion criteria	Comorbidities (for example, rheumatoid arthritis, avascular necrosis, fibromyalgia); infection around the injection site; treatment with oral, parenteral or intraarticular steroids within 3 months; use of anticoagulants or history of thrombocytopenia; allergy to local anesthetics; history of adverse reaction to intraarticular hyaluronic acid; pending hip replacement surgery; use of a purported osteoarthritis disease modifying agent
Recruitment/selection of patients	Consecutive people
Age, gender and ethnicity	Age - Mean (SD): 70 (8.9). Gender (M:F): 22:20. Ethnicity: Not stated
Further population details	1. Age: Mixed (Include some people over the age of 75 years). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Radiological grade 2-4. Duration of symptoms (mean [SD]): 4.71 (3.93) years
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Ultrasound guided intraarticular 4mL (60mg) hyaluronic acid (Hyalubrix, high molecular weight >1500kDa) once a month for two injections. Performed by inserting a 20 gauge, 0.9 x 90mm spinal needle into the biopsy guide. Advanced with real time guidance. After contact with the femoral head, the needle was retracted 1mm before injection. IA localisation was monitored by real time ultrassound visualisation and Doppler signal.. Duration 2 injections over 2 months. Concurrent

	medication/care: Not explicitly stated. However, NSAIDs were permitted as NSAID usage was an outcome. (n=20) Intervention 2: Placebo. Ultrasound guided intraarticular 2% mepivacaine (4mL) once a month for two injections. Performed by inserting a 20 gauge, 0.9 x 90mm spinal needle into the biopsy guide. Advanced with real time guidance. After contact with the femoral head, the needle was retracted 1mm before injection. IA localisation was monitored by real time ultrassound visualisation and Doppler signal.. Duration 2 injections over 2 months. Concurrent medication/care: Not explicitly stated. However, NSAIDs were permitted as NSAID usage was an outcome.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Fidia S.p.A (Padova, Italy) provided Hyalubrix and the local anaesthetic necessary to perform the study but were not involved in the collection, analysis, or interpretation of the data, in the writing of the manuscript or decision for publication)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: Pain visual analogue scale at 3 months; Group 1: mean 4.3 (SD 2.58); n=17, Group 2: mean 4.5 (SD 2.63); n=17; Visual analogue scale pain 0-10 Top=High is poor outcome; Comments: Baseline HA: 6.4 (1.94). Baseline placebo: 6.0 (1.34).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, smoking history, height, BMI, side of osteoarthritis, type of osteoarthritis (primary or secondary), duration of osteoarthritis, radiographic grade, presence of knee osteoarthritis and baseline characteristics of outcomes; Group 1 Number missing: 5, Reason: Reports the overall reasons. 1 treatment failure in each groups, 4 lost to follow up, 2 not evaluated at 6 months due to comorbidities appearing in their 4th month; Group 2 Number missing: 3, Reason: Reports the overall reasons. 1 treatment failure in each groups, 4 lost to follow up, 2 not evaluated at 6 months due to comorbidities appearing in their 4th month
- Actual outcome for Hip: Pain visual analogue scale at 6 months; Group 1: mean 4.5 (SD 1.96); n=17, Group 2: mean 5 (SD 2.41); n=17; Visual analogue scale pain 0-10 Top=High is poor outcome; Comments: Baseline HA: 6.4 (1.94). Baseline placebo: 6.0 (1.34).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, smoking history, height, BMI, side of osteoarthritis, type of osteoarthritis (primary or secondary), duration of osteoarthritis, radiographic grade, presence of knee osteoarthritis and baseline characteristics of outcomes; Group 1 Number missing: 5, Reason: Reports the overall reasons. 1 treatment failure in each groups, 4 lost to follow up, 2 not evaluated at 6 months due to comorbidities appearing in their 4th month; Group 2 Number missing: 3, Reason: Reports the overall reasons. 1 treatment failure in each groups, 4 lost to follow up, 2 not evaluated at 6 months due to comorbidities appearing in their 4th month

Protocol outcome 2: Serious adverse events at ≤3- or >3- months

- Actual outcome for Hip: Serious adverse events at 6 months; Group 1: 0/22, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, smoking history, height, BMI, side of osteoarthritis, type of osteoarthritis (primary or secondary), duration of osteoarthritis, radiographic grade, presence of knee osteoarthritis and baseline characteristics of outcomes; Group 1 Number missing: 5, Reason: Reports the overall reasons. 1 treatment failure in each groups, 4 lost to follow up, 2 not evaluated at 6 months due to comorbidities appearing in their 4th month; Group 2 Number missing: 3, Reason: Reports the overall reasons. 1 treatment failure in each groups, 4 lost to follow up, 2 not evaluated at 6 months due to comorbidities appearing in their 4th month	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Monfort 2015[323]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A previous diagnosis of thumb carpometacarpal joint osteoarthritis as defined by criteria of the American College of Rheumatology provided they had clinical symptoms in the affected thumb for at least 90 days prior to the study, required treatment with analgesics or NSAIDs on a routine basis, and had an available confirmatory X-ray diagnosis (Kellgren-Lawrence grade I-III) within the previous 6 months.
Stratum	Thumb
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18 years or older who received a diagnosis of thumb carpometacarpal joint osteoarthritis between January 2005 and December 2009, as defined by criteria of the American College of Rheumatology were eligible, provided that they had clinical symptoms in the affected thumb for at least the 90 days prior to the start of the study, required treatment with analgesics of NSAIDs on a routine basis, had an available confirmatory X-ray diagnosis (Kellgren Lawrence grade 1-3) within the previous 6 months, gave written informed consent, and were able to understand and follow the study procedures. Negative pregnancy test and appropriate use of a safe contraceptive method were required for women of childbearing age.
Exclusion criteria	Pregnant or lactating women; liver dysfunction (serum aminotransferases >3 times the upper limit of normal); hemodialysis or renal dysfunction (serum creatinine concentration >1.5mg/dL); physical therapy performed by a physiotherapist at home or in a specialised center; history of any surgical procedure in the trapeziometacarpal joint; diagnosis of OA of the trapezioscaphoid joint or microcrystalline arthritis; participation in a clinical trial in the previous three months; and presence of any medical condition judged by the investigator to preclude the patient's inclusion in the study; known allergy to corticosteroids, paracetamol or low molecular weight hyaluronic acid; concomitant treatment with antiepileptic drugs, oral anticoagulants, acetylsalicylic acid >325mg/day, lithium, potassium-sparing diuretics, digoxin, minocycline, metalloprotease inhibitors, methotrexate, or regular use of analgesic and/or NSAIDs; treatment with chondroitin sulphate, glucosamine sulphate, diacerein,

	oral or parenteral corticosteroids, or corticosteroid injection in any other joint during the previous 3 months.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 62.8 (8.7). Gender (M:F): 11:77. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 1-3. Duration of symptoms: Not stated. At least 90 days.
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). One cycle of three injections of 0.5cm³ of hyaluronic acid (5mg) (Suplasyn). Duration Three injections over three weeks. Concurrent medication/care: Instructed to discontinue any systemic or topical treatment. Paracetamol (maximum 3g/day) was allowed but all medication use during the trial needed to be recorded.. Indirectness: No indirectness (n=40) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). One cycle of three injections of 0.5cm³ betamethasone disodium phosphate (1.5mg) and betamethasone acetate (1.5mg).. Duration Three injections over three weeks. Concurrent medication/care: Instructed to discontinue any systemic or topical treatment. Paracetamol (maximum 3g/day) was allowed but all medication use during the trial needed to be recorded.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Thumb: SF-36 PCS at 3 months; Group 1: mean 0.51 (SD 7.02); n=48, Group 2: mean 1.7 (SD 9.32); n=40; SF-36 physical component summary subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 38.9 (8.1). Baseline CS: 37.7 (10.3).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those

were finally evaluable: 5 did not carry out the washout period due to they were taking ant
- Actual outcome for Thumb: SF-36 PCS at 6 months; Group 1: mean -1.66 (SD 9.6); n=48, Group 2: mean 1.31 (SD 9.42); n=40; SF-36 physical component score subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 38.9 (8.1). Baseline CS: 37.7 (10.3).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking ant
- Actual outcome for Thumb: SF-36 MCS at 3 months; Group 1: mean -0.46 (SD 6.77); n=48, Group 2: mean 1.73 (SD 10.75); n=40; SF-36 mental component score subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 45.4 (13.3). Baseline CS: 48.9 (10.8).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking ant
- Actual outcome for Thumb: SF-36 MCS at 6 months; Group 1: mean 2.79 (SD 11.78); n=48, Group 2: mean 2.17 (SD 9.64); n=40; SF-36 mental component score subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 45.4 (13.3). Baseline CS: 48.9 (10.8).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking ant

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Thumb: Visual analogue scale (pain) at 3 months; Group 1: mean -1.61 (SD 2.54); n=48, Group 2: mean -1.55 (SD 2.14); n=40; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Baseline HA: 6.0 (1.8). Baseline CS: 6.4 (1.3).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those

were finally evaluable: 5 did not carry out the washout period due to they were taking ant - Actual outcome for Thumb: Visual analogue scale (pain) at 6 months; Group 1: mean -1.97 (SD 2.73); n=48, Group 2: mean -1.42 (SD 2.35); n=40; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Baseline HA: 6.0 (1.8). Baseline CS: 6.4 (1.3). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking ant Protocol outcome 3: Physical function at ≤3- or >3- months - Actual outcome for Thumb: Functional Index for Hand Osteoarthritis (median and interquartile range only) at 3 months; Group 1: mean 0 (SD 0); n=48, Group 2: mean 0 (SD 0); n=40; Functional Index for Hand Osteoarthritis 0-30 Top=High is poor outcome; Comments: Reports median and interquartile ranges. Reported HA: -4 (-8 to -1). Reported CS: -1 (-3 and -1). Baseline HA: 11.0 (7 and 14.7). Baseline CS: 11.5 (8 and 14). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking ant - Actual outcome for Thumb: Functional Index for Hand Osteoarthritis (median and interquartile range only) at 6 months; Group 1: mean 0 (SD 0); n=48, Group 2: mean 0 (SD 0); n=40; Functional Index for Hand Osteoarthritis 0-30 Top=High is poor outcome; Comments: Reports median and interquartile ranges. Reported HA: -3 (-8.7 to -1). Reported CS: -1 (-3 and -3). Baseline HA: 11.0 (7 and 14.7). Baseline CS: 11.5 (8 and 14). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age and states that sex distribution was similar between groups. Baseline outcomes were similar.; Group 1 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking antiinflammatory drugs, 3 were asymptomatic and the remaining 4 did not fulfill radiological criteria. Unclear which group these participants belonged to. Attrition rate could have been significant (if 50 in both arms, potentially a 20% loss in the control group).; Group 2 Number missing: , Reason: Reports that 100 people were randomised to treatment and only 88 of those were finally evaluable: 5 did not carry out the washout period due to they were taking ant	
Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study (subsidiary papers)	Munteanu 2011[330] (Munteanu 2009[329])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Australia; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Pain during motion or rest and stiffness of the first metatarsophalangeal joint with radiographic evidence (score of 1 or 2 for either osteophytes or joint space narrowing using the radiographic classification described by Menz et al. 2007) of osteoarthritis
Stratum	Toes
Subgroup analysis within study	Not applicable
Inclusion criteria	i) be aged at least 18 years; ii) report having symptoms of pain during motion or rest, and stiffness in the first metatarsophalangeal joint for at least 3 months; iii) report having pain rated at least 20mm on a 100mm visual analogue pain scale (VAPS); iv) have pain upon palpation of the dorsal aspect of the first metatarsophalangeal joint; v) Radiographic evidence of osteoarthritis (score 1 or 2 for either osteophytes or joint space narrowing using radiographic classification described by Menz et al.[2007]) at the first metatarsophalangeal joint; vi) be normally active and able to walk household distances (>50 meters) without the aid of a walker, crutches or cane; vii) be willing to attend the La Trobe University Medical Centre for treatment with either Synvisc® or placebo (single intra-articular injection) and attend the Health Sciences Clinic of La Trobe University for the initial assessment and the outcome measurements (at baseline and 1, 3 and 6 months post-treatment); viii) not receive other intra-articular injections into the first metatarsophalangeal joint, apart from the study intervention, during the course of the study; (ix) be willing to discontinue taking all pain-relieving medications (analgesics and non-steroidal anti-inflammatory medications, except paracetamol up to 4g/day, taken by mouth or applied topically): - for at least 14 days prior to the initial assessment; - during the study period (6 months after the final treatment with Synvisc®). Participants who do take paracetamol need to discontinue its use at least 24 hours

	prior to the: - initial assessment; - follow-up assessments at 1, 3 and 6 months after the treatment with Synvisc®; (x) be willing to not receive any physical therapy on the involved first metatarsophalangeal joint or trial of shoe modifications or orthotics during the study period.
Exclusion criteria	i) No radiographic evidence of osteoarthritis (score 0 for osteophytes and joint space narrowing using radiographic classification described by Menz et al.[2007]), or severe radiographic evidence of osteoarthritis (score 3 for either osteophytes or joint space narrowing using radiographic classification described by Menz et al.[2007]) at the first metatarsophalangeal joint; ii) previous surgery on the first metatarsophalangeal joint; iii) intra-articular steroid, or any other intra-articular injection at the first metatarsophalangeal joint, in the previous 6 months; iv) treatment with systemic steroid (excluding inhalation or topical steroids), immunosuppressives or anticoagulants (except for acetylsalicylic acid at dosages of up to 325 mg/day); v) presence of joint infections of the foot; vi) significant deformity of the first metatarsophalangeal joint including hallux abducto valgus; vii) presence of peripheral vascular disease; viii) presence of one or more conditions that can confound pain and functional assessments of the first metatarsophalangeal joint, such as significant hallux abducto valgus, metatarsalgia, plantar fasciitis, pre-dislocation syndrome, sprains of the foot, Achilles tendinopathy, degenerative joint disease of the foot (other than the first metatarsophalangeal joint) or painful corns and callus; ix) planning to undergo any surgical procedure or receive any injections at the involved first metatarsophalangeal joint during the study period; x) presence of systemic inflammatory condition or infection, such as inflammatory arthritis, diagnosed with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, septic arthritis, gout/acute pseudogout, or any other connective tissue disease; xi) Evidence of gout or other musculoskeletal disease other than osteoarthritis within the feet. Gout will be screened for using clinical history and physical assessment (painful joint, abrupt onset, swelling), radiographic assessment (asymmetrical joint swelling, subcortical cysts without erosion and tophi) as well as serum uric acid levels; xii) active skin disease or infection in the area of the injection site; xiii) any medical condition that, in the opinion of the investigators, makes the

	participant unsuitable for inclusion (e.g., severe progressive chronic disease, malignancy, bleeding disorder, clinically important pain in a part of the musculoskeletal system other than the first metatarsophalangeal joint, or fibromyalgia); xiv) pregnant or lactating women, or women who are of child bearing age or have not undergone menopause (Synvisc® has not been tested in pregnant women or women who are nursing); xv) cognitive impairment (defined as a score of <7 on the Short Portable Mental Status Questionnaire); xvi) known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations, or to avian proteins, feathers, and egg products; xvii) Involvement in any clinical research study in the previous 3 months that could be considered to affect the results of this study.
Recruitment/selection of patients	People with hallux limitus will be recruited from a number of sources: 1) advertisements in relevant Melbourne newspapers; 2) mail-out advertisements to health-care practitioners in Melbourne; 3) advertisements using relevant internet websites (including http://www.bigtoearthritis.com); 4) posters displayed in local retirement villages, community centres and universities located in Melbourne
Age, gender and ethnicity	Age - Mean (SD): 54.5 (11.3). Gender (M:F): 95:56. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Severe (based on radiographic score) Duration of symptoms (mean [SD]): 42.9 (48.9) months. Inclusion and exclusion criteria taken from the Australian and New Zealand clinical trials register (mentioned in the protocol)
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). 1mL of hylan G-F 20 (Synvisc) injected into the first metatarsal phalangeal joint. The injections were performed by an interventional radiologist guided by fluoroscopy. If the person had bilateral symptoms, the more painful side was treated. Participants were given the option of a second and final intraarticular injection (of HA for the intervention group, of saline for the control group) at month 1 or 3 if there was no improvement in first metatarsophalangeal joint pain.. Duration 1 injection (potential for additional injections at month 1 or 3). Concurrent medication/care: No additional information. Indirectness: No indirectness (n=76) Intervention 2: Placebo. 1mL of sterile saline (0.9%) injected into the first

	metatarsal phalangeal joint. The injections were performed by an interventional radiologist guided by fluoroscopy. If the person had bilateral symptoms, the more painful side was treated. Participants were given the option of a second and final intraarticular injection (of HA for the intervention group, of saline for the control group) at month 1 or 3 if there was no improvement in first metatarsophalangeal joint pain.. Duration 1 injection (potential for additional injections at month 1 or 3). Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Study funded by industry (This study was funded by the Australian Podiatry Education and Research Foundation and the La Trobe University Faculty of Health Sciences. Genzyme Australasia Pty. Ltd. (North Ryde, NSW, Australia) provided the hylan G-F 20 (Synvisc) product and partially funded the costs associated with advertising, radiographs, assessment of serum uric acid of participants and fluoroscopic injections. HBM is currently a National Health and Medical Research Council fellow (Clinical Career Development Award, ID: 433049).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Toes: SF-36 physical function subdomain at 3 months; Group 1: mean 82.3 (SD 21.9); n=75, Group 2: mean 81.1 (SD 17.7); n=76; SF-36 physical function subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 79.5 (20.3). Baseline placebo: 79.6 (16.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 physical function subdomain at 6 months; Group 1: mean 82.5 (SD 19); n=75, Group 2: mean 81.1 (SD 17.7); n=76; SF-36 physical function subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 79.5 (20.3). Baseline placebo: 79.6 (16.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 role physical subdomain at 3 months; Group 1: mean 89.3 (SD 14.5); n=75, Group 2: mean 82.3 (SD 18.5); n=76; SF-36 role physical subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 88.5 (16.5). Baseline placebo: 81.3 (20.4).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be

contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 role physical subdomain at 6 months; Group 1: mean 86 (SD 17.7); n=75, Group 2: mean 83.4 (SD 19.1); n=76; SF-36 role physical subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 88.5 (16.5). Baseline placebo: 81.3 (20.4).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 bodily pain subdomain at 3 months; Group 1: mean 72.4 (SD 19.5); n=75, Group 2: mean 69.8 (SD 22); n=76; SF-36 bodily pain subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 68.2 (17.7). Baseline placebo: 63.5 (20.1).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 bodily pain subdomain at 6 months; Group 1: mean 65.8 (SD 21.8); n=75, Group 2: mean 70.7 (SD 20.9); n=76; SF-36 bodily pain subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 68.2 (17.7). Baseline placebo: 63.5 (20.1).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 general health subdomain at 3 months; Group 1: mean 77 (SD 20.3); n=75, Group 2: mean 75.9 (SD 18.7); n=76; SF-36 general health 0-100 Top=High is good outcome; Comments: Baseline HA: 76.2 (18.7). Baseline placebo: 75.3 (18.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 general health subdomain at 6 months; Group 1: mean 76.2 (SD 19.8); n=75, Group 2: mean 76.8 (SD 18.3); n=76; SF-36 general health subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 76.2 (18.7). Baseline placebo: 75.3 (18.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 vitality subdomain at 3 months; Group 1: mean 68.3 (SD 16.6); n=75, Group 2: mean 63.7 (SD 18.5); n=76; SF-36 vitality

subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 65.3 (18.5). Baseline placebo: 61.4 (18.1).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 vitality subdomain at 6 months; Group 1: mean 67.1 (SD 17.1); n=75, Group 2: mean 61.1 (SD 19.9); n=76; SF-36 vitality subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 65.3 (18.5). Baseline placebo: 61.4 (18.1).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 social functioning subdomain at 3 months; Group 1: mean 90.2 (SD 16.7); n=75, Group 2: mean 86.2 (SD 20.3); n=76; SF-36 social functioning subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 89.8 (16.7). Baseline placebo: 85.2 (20.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 social functioning subdomain at 6 months; Group 1: mean 87.3 (SD 19.9); n=75, Group 2: mean 89.1 (SD 18); n=76; SF-36 social functioning subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 89.8 (16.7). Baseline placebo: 85.2 (20.5).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 role emotional subdomain at 3 months; Group 1: mean 91 (SD 15.4); n=75, Group 2: mean 90.4 (SD 14.9); n=76; SF-36 role emotional subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 91.4 (16.5). Baseline placebo: 89.9 (13.8).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 role emotional subdomain at 6 months; Group 1: mean 92.4 (SD 13.1); n=75, Group 2: mean 91.5 (SD 13); n=76; SF-36 role emotional subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 91.4 (16.5). Baseline placebo: 89.9 (13.8).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of

symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 mental health subdomain at 3 months; Group 1: mean 82.9 (SD 13.5); n=75, Group 2: mean 79.9 (SD 13.9); n=76; SF-36 mental health subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 81.1 (14.7). Baseline placebo: 81.0 (18.9).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: SF-36 mental health subdomain at 6 months; Group 1: mean 82.7 (SD 12.9); n=75, Group 2: mean 81.5 (SD 14.3); n=76; SF-36 mental health subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 81.1 (14.7). Baseline placebo: 81.0 (18.9).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted

Protocol outcome 2: Pain reduction at ≤3- or >3- months
- Actual outcome for Toes: Foot pain dimension of the Foot Health Status Questionnaire at 3 months; Group 1: mean 68.2 (SD 22.5); n=75, Group 2: mean 72.5 (SD 17); n=76; Foot Health Status Questionnaire pain dimension 0-100 Top=High is good outcome; Comments: Baseline HA: 56.2 (19.3). Baseline placebo: 57.0 (17.8).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted
- Actual outcome for Toes: Foot pain dimension of the Foot Health Status Questionnaire at 6 months; Group 1: mean 68 (SD 21.4); n=75, Group 2: mean 71.4 (SD 18.7); n=76; Foot Health Status Questionnaire foot pain dimension 0-100 Top=High is good outcome; Comments: Baseline HA: 56.2 (19.3). Baseline placebo: 57.0 (17.8).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 10, Reason: 5 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 6, Reason: 5 were unable to be contacted. 1 discontinued the study due to lack of treatment effect.

Protocol outcome 3: Physical function at ≤3- or >3- months
- Actual outcome for Toes: Foot function (assessed via the FHSQ) at 3 months; Group 1: mean 85 (SD 21.3); n=75, Group 2: mean 83.4 (SD 17.4); n=76;

FHSQ 0-100 Top=High is good outcome; Comments: Baseline HA: 78.4 (20.5). Baseline placebo: 73.1 (19.1). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 14, Reason: 9 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 10, Reason: 10 were unable to be contacted - Actual outcome for Toes: Foot function (assessed via the FHSQ) at 6 months; Group 1: mean 84.2 (SD 21.8); n=75, Group 2: mean 84 (SD 17.3); n=76; FHSQ 0-100 Top=High is good outcome; Comments: Baseline HA: 78.4 (20.5). Baseline placebo: 73.1 (19.1). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 10, Reason: 5 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 6, Reason: 5 were unable to be contacted. 1 discontinued the study due to lack of treatment effect. Protocol outcome 4: Serious adverse events at ≤3- or >3- months - Actual outcome for Toes: Cellulitis attributed to the injection at 6 months; Group 1: 1/75, Group 2: 0/76 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, height, weight, BMI, duration of symptoms, side affected, side treated, severity of osteoarthritis and baseline values of outcomes; Group 1 Number missing: 10, Reason: 5 unable to be contacted. 5 discontinued the study - 1 due to a motor vehicle accident, 2 due to lack of treatment effect, 1 due to anxiety, 1 due to surgery: other foot complaint; Group 2 Number missing: 6, Reason: 5 were unable to be contacted. 1 discontinued the study due to lack of treatment effect.	
Protocol outcomes not reported by the study	Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Neustadt 2005[338]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=372)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 22 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of knee osteoarthritis according to the American College of Rheumatology criteria, a Kellgren Lawrence grade of 1-3 in accord with radiographic evidence of knee osteoarthritis, and a summed WOMAC pain score ≥200mm and <400mm (maximum possible score 500mm) in the index (treated) knee and <150mm in the contralateral (untreated) knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	All people were ≥40 years of age and were willing to discontinue all analgesics and NSAID 7 days before the first injection and for the duration of the study. Diagnosis of knee osteoarthritis according to the American College of Rheumatology criteria, a Kellgren Lawrence grade of 1-3 in accord with radiographic evidence of knee osteoarthritis, and a summed WOMAC pain score ≥200mm and <400mm (maximum possible score 500mm) in the index (treated) knee and <150mm in the contralateral (untreated) knee.
Exclusion criteria	People who initiated an exercise or physical therapy program within 3 months; oral or parenteral corticosteroid use within 30 days; IA injection of steroids into the index knee within 90 days; IA injection of any hyaluronic substance within the past 9 months, or operative arthroscopy within 6 months; treatment with anticoagulants; clinically significant comorbidities (fibromyalgia, peripheral neuropathy, vascular insufficiency, or hemiparesis) severe enough to interfere with accurate evaluation
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 58.8 (8.7). Gender (M:F): 175:161. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 1-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness

Interventions	(n=248) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Two groups: One had four weekly injections of of high molecular weight hyaluronic acid (2mL, 30mg, Orthovisc, molecular weight 1-2.9 million Da) administered by intraarticular injection after arthrocentesis. The other had three weekly injections of hyaluronic acid after arthrocentesis, and one arthrocentesis only.. Duration 4 injections over 4 weeks. Concurrent medication/care: Paracetamol up to 4g/day was the only rescue medication allowed. Paracetamol was not permitted for at least 24 hours prior to each study assessment session.. Indirectness: No indirectness Comments: Combination of two groups. (n=124) Intervention 2: Placebo. Four arthrocentesis only sessions. Arthrocentesis was conducted leaving the needle in for enough time to simulate injection.. Duration 4 injections over 4 weeks. Concurrent medication/care: Paracetamol up to 4g/day was the only rescue medication allowed. Paracetamol was not permitted for at least 24 hours prior to each study assessment session.. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by a grant from Anika Therapeutics Inc., Woburn, Massachusetts, USA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Pain on standing (visual analogue scale) at 12 weeks; Group 1: mean -32.4 (SD 29.5); n=194, Group 2: mean -26.2 (SD 27.9); n=100; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Combination of two groups to make the HA group. Reported 4HA injection group: -38.8 (28.4). Reported 3HA1A group: -25.0 (29.1). Baseline 4HA: 65.2 (17.9). Baseline 3HA1A: 65.7 (16.1). Baseline placebo: 65.5 (16.1).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, BMI, radiographic grade and outcome baseline values; Group 1 Number missing: 54, Reason: Reported incompletely. Worsening of symptoms occurred in 9 people in the 4HA group, 8 in the 3HA1A group, 15 in the placebo group. 16 people were lost to follow up. 8 discontinued for non compliance.; Group 2 Number missing: 24, Reason: Reported incompletely. Worsening of symptoms occurred in 9 people in the 4HA group, 8 in the 3HA1A group, 15 in the placebo group. 16 people were lost to follow up. 8 discontinued for non compliance.
- Actual outcome for Knee: Pain on standing (visual analogue scale) at 22 weeks; Group 1: mean -27.6 (SD 30.9); n=194, Group 2: mean -24.6 (SD 29.9); n=100; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Combination of two groups to make the HA group. Reported 4HA injection group: -29.5 (31.4). Reported 3HA1A group: -25.5 (30.2). Baseline 4HA: 65.2 (17.9). Baseline 3HA1A: 65.7 (16.1). Baseline placebo: 65.5 (16.1).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, BMI, radiographic grade and outcome baseline values; Group 1 Number missing: 54, Reason: Reported incompletely. Worsening of symptoms occurred in 9 people in the 4HA group, 8 in the 3HA1A group, 15 in the placebo group. 16 people were lost to follow up. 8 discontinued for non compliance.; Group 2 Number missing: 24, Reason: Reported

incompletely. Worsening of symptoms occurred in 9 people in the 4HA group, 8 in the 3HA1A group, 15 in the placebo group. 16 people were lost to follow up. 8 discontinued for non compliance. Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 22 weeks; Group 1: 4/248, Group 2: 3/124; Comments: These events included angina, myocardial infarction, gastrointestinal haemorrhage, and GI tract cancer Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, BMI, radiographic grade and outcome baseline values; Group 1 Number missing: 54, Reason: Reported incompletely. Worsening of symptoms occurred in 9 people in the 4HA group, 8 in the 3HA1A group, 15 in the placebo group. 16 people were lost to follow up. 8 discontinued for non compliance.; Group 2 Number missing: 24, Reason: Reported incompletely. Worsening of symptoms occurred in 9 people in the 4HA group, 8 in the 3HA1A group, 15 in the placebo group. 16 people were lost to follow up. 8 discontinued for non compliance.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study (subsidiary papers)	Petrella 2002[369] (Cubbage 2002[94])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Canada; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiographic evidence of medial compartment unilateral knee osteoarthritis
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with radiographic evidence of grades 1 to 3 medial compartment unilateral knee OA
Exclusion criteria	Non-OA arthritides; previous NSAID intolerance; gastrointestinal haemorrhage; peptic ulcer disease; avian allergy; regular consumption of "herbal" OA products (ie. glucosamine sulfate); intraarticular injections of HA or corticosteroid given in the previous 6 months.
Recruitment/selection of patients	People were recruited from a large primary care referral center for assessment of knee OA.
Age, gender and ethnicity	Age - Mean (SD): 65.5 (9.0). Gender (M:F): 65:55. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Low comorbidity score (Mean number of chronic disease diagnoses on medical history: 1 (1.1).).
Extra comments	Severity: Not explicitly stated. Radiographic OA grade 2.2 (0.3). Duration of symptoms: Not stated.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Two millilitres of intraarticular sodium hyaluronate solution at a concentration of 10mg/mL (Suplasyn). Injection under a sterile field using a medial approach at baseline and weeks 2 and 3. Given with oral placebo twice daily.. Duration 12 weeks. Concurrent medication/care: People were also given 325mg acetaminophen as rescue medications to be taken as needed up to 650mg four times a day.. Indirectness: No indirectness

	(n=30) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Two millilitres of intraarticular sodium hyaluronate solution at a concentration of 10mg/mL (Suplasyn). Injection under a sterile field using a medial approach at baseline and weeks 2 and 3. Given with oral placebo twice daily. Given with 75mg diclofenac twice a day.. Duration 12 weeks. Concurrent medication/care: People were also given 325mg acetaminophen as rescue medications to be taken as needed up to 650mg four times a day.. Indirectness: No indirectness Comments: Not used in our analysis. Included for completeness. (n=30) Intervention 3: Placebo. Two millilitres of intraarticular isotonic sodium chloride solution. Injection under a sterile field using a medial approach at baseline and weeks 2 and 3. Given with oral placebo twice daily.. Duration 12 weeks. Concurrent medication/care: People were also given 325mg acetaminophen as rescue medications to be taken as needed up to 650mg four times a day.. Indirectness: No indirectness (n=30) Intervention 4: Placebo. Two millilitres of intraarticular isotonic sodium chloride solution. Injection under a sterile field using a medial approach at baseline and weeks 2 and 3. Given with oral placebo twice daily.. Duration 12 weeks. Concurrent medication/care: People were also given 325mg acetaminophen as rescue medications to be taken as needed up to 650mg four times a day.. Indirectness: No indirectness Comments: Not in our analysis. Reported for completeness.
Funding	Study funded by industry (Unrestricted educational grant from Bioniche Life Sciences Inc. Dr Petrella is a Canadian Institutes of Health Research investigator.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 4 weeks; Group 1: mean 2.42 (SD 2.34); n=25, Group 2: mean 3.19 (SD 2.81); n=28; VAS-WOMAC pain subscale 0-10 Top=High is poor outcome; Comments: Baseline HA: 3.32 (2.42). Baseline placebo: 3.62 (2.71).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, OA grade, chronic diseases, and BMI; Group 1 Number missing: 5, Reason: Does not report for individual groups. Overall: 12 people failed to complete follow up: 1 was lost to follow up, 2 had moderate gastrointestinal irritation, 1 failed to comply with the study tablet protocol, and 8 dropped out without reason prior to treatment; Group 2 Number missing: 2, Reason: Does not report for individual groups. Overall: 12 people failed to complete follow up: 1 was lost to follow up, 2 had moderate gastrointestinal irritation, 1 failed to comply with the study tablet protocol, and 8 dropped out without reason prior to treatment

Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function at 4 weeks; Group 1: mean 2.45 (SD 2.24); n=25, Group 2: mean 3.73 (SD 2.99); n=28; VAS-WOMAC disability 0-10 Top=High is poor outcome; Comments: Baseline HA: 4.10 (2.71). Baseline placebo: 4.72 (3.03). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, OA grade, chronic diseases, and BMI; Group 1 Number missing: 5, Reason: Does not report for individual groups. Overall: 12 people failed to complete follow up: 1 was lost to follow up, 2 had moderate gastrointestinal irritation, 1 failed to comply with the study tablet protocol, and 8 dropped out without reason prior to treatment; Group 2 Number missing: 2, Reason: Does not report for individual groups. Overall: 12 people failed to complete follow up: 1 was lost to follow up, 2 had moderate gastrointestinal irritation, 1 failed to comply with the study tablet protocol, and 8 dropped out without reason prior to treatment Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 4 weeks; Group 1: 0/25, Group 2: 0/28 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, OA grade, chronic diseases, and BMI; Group 1 Number missing: 5, Reason: Does not report for individual groups. Overall: 12 people failed to complete follow up: 1 was lost to follow up, 2 had moderate gastrointestinal irritation, 1 failed to comply with the study tablet protocol, and 8 dropped out without reason prior to treatment; Group 2 Number missing: 2, Reason: Does not report for individual groups. Overall: 12 people failed to complete follow up: 1 was lost to follow up, 2 had moderate gastrointestinal irritation, 1 failed to comply with the study tablet protocol, and 8 dropped out without reason prior to treatment	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Petterson 2019[373]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=369)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of idiopathic knee osteoarthritis defined by the American College of Rheumatology with Kellgren Lawrence grade II or III changes in the index knee
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People between 35 and 75 years old, with a BMI between 20 and 40 kg/m², with a diagnosis of idiopathic knee osteoarthritis as defined by the American College of Rheumatology. Other criteria: symptom duration of at least 6 months; confirmed radiographic evidence of osteoarthritis within 6 months of study enrollment; Kellgren Lawrence grade II or III OA in the index knee; and a baseline summed WOMAC VAS pain score greater than 200mm and less than 400mm out of a maximum 500mm scoring system.
Exclusion criteria	Intraarticular crystals; neoplasms; rheumatoid arthritis; fibromyalgia; peripheral neuropathy; vascular insufficiency; immunocompromised or immunosuppresive disorder; systemic bleeding disorder; symptomatic pes anserine bursitis; clinically significant knee deformity that could interfere with the ability to evaluate the effectiveness of the treatment on pain and function; intraarticular hyaluronic acid injection in the index knee within 6 months; intraarticular steroid injection or knee arthroscopy in the index knee within 3 months; open surgical procedure in the index knee within 12 months; synovial fluid aspirate greater than 20mL; range of motion less than 90 degrees in the index knee; people with K-L grade II or IV OA in the contralateral knee with a baseline summed WOMAC VAS pain score greater than 150mm in the contralateral knee; and people who underwent an open surgical procedure within 3 months in the contralateral knee
Recruitment/selection of patients	Conducted in 31 sites across the US between January 2008 and December 2009.
Age, gender and ethnicity	Age - Mean (SD): 59.1 (8.6). Gender (M:F): 154:215. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade II or III. Duration of symptoms: Not explicitly stated. Inclusion criteria was that it should have been at least 6 months.
Indirectness of population	No indirectness
Interventions	(n=184) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronic acid (Monovisc) given approximately 1 week after the screening visit and following a 7 day analgesic/NSAID washout period. 4mL of hyaluronic acid given with a 5mL syringe using either a medial or lateral approach. Prior to the administration of the injection, an 18-21 gauge needle was used to aspirate the knee if effusion was present.. Duration 1 injection. Concurrent medication/care: Oral glucosamine and chondroitin sulphate were permitted if subjects maintained a constant dosage throughout the duration of the study. Daily paracetamol consumption of up to 4g (8-500mg tablets) was permitted as rescue medication starting 7 days prior to the randomisation visit). People were not allowed to take paracetamol 24 hours prior to each follow up appointment.. Indirectness: No indirectness (n=185) Intervention 2: Placebo. Intraarticular sodium chloride given approximately 1 week after the screening visit and following a 7 day analgesic/NSAID washout period. 4mL of 0.9% saline given with a 5mL syringe using either a medial or lateral approach. Prior to the administration of the injection, an 18-21 gauge needle was used to aspirate the knee if effusion was present.. Duration 1 injection. Concurrent medication/care: Oral glucosamine and chondroitin sulphate were permitted if subjects maintained a constant dosage throughout the duration of the study. Daily paracetamol consumption of up to 4g (8-500mg tablets) was permitted as rescue medication starting 7 days prior to the randomisation visit). People were not allowed to take paracetamol 24 hours prior to each follow up appointment.. Indirectness: No indirectness
Funding	Study funded by industry (Study sponsored by Anika Therapeutics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function at 12 weeks; Group 1: mean 24.7 (SD 26.2); n=181, Group 2: mean 31.7 (SD 25.3); n=184; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Baseline HA: 55.7 (15.9). Baseline saline: 54.1 (17.3).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, index knee, K-L grade, baseline WOMAC pain, WOMAC physical function, evaluator global asesssment, patient global assessment and total knee range of motion; Group 1 Number missing: 3, Reason: Adverse events: 4, need for continued therapy: 2, withdrew consent: 4, lost to follow up: 7, other: 5. Ultimately included 181 in their ITT analysis.; Group 2 Number missing: 1, Reason: Adverse event: 1, need for continued therapy: 1, withdrew consent: 5, lost to follow up: 6, other: 3. Ultimately 184 were included in their ITT analysis. - Actual outcome for Knee: WOMAC physical function at 26 weeks; Group 1: mean 32.5 (SD 24.8); n=181, Group 2: mean 33.1 (SD 25.2); n=184; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Baseline HA: 55.7 (15.9). Baseline saline: 54.1 (17.3). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, index knee, K-L grade, baseline WOMAC pain, WOMAC physical function, evaluator global asesssment, patient global assessment and total knee range of motion; Group 1 Number missing: 3, Reason: Adverse events: 4, need for continued therapy: 2, withdrew consent: 4, lost to follow up: 7, other: 5. Ultimately included 181 in their ITT analysis.; Group 2 Number missing: 1, Reason: Adverse event: 1, need for continued therapy: 1, withdrew consent: 5, lost to follow up: 6, other: 3. Ultimately 184 were included in their ITT analysis. Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Total serious adverse events at 26 weeks; Group 1: 9/184, Group 2: 5/185; Comments: No definition of serious adverse events given Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, index knee, K-L grade, baseline WOMAC pain, WOMAC physical function, evaluator global asesssment, patient global assessment and total knee range of motion; Group 1 Number missing: , Reason: Adverse events: 4, need for continued therapy: 2, withdrew consent: 4, lost to follow up: 7, other: 5. Included all people in their safety evaluation.; Group 2 Number missing: , Reason: Adverse event: 1, need for continued therapy: 1, withdrew consent: 5, lost to follow up: 6, other: 3. Included all people in their safety evaluation.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Pham 2004[374]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=301)
Countries and setting	Conducted in France; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic medial femorotibial knee osteoarthritis with radiographic evidence of medial joint space width >2mm.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of a symptomatic primary painful medial femorotibial knee osteoarthritis defined by a daily pain visual analogue scale score >30mm in the previous month. If both knees were symptomatic, only the most painful one was taken into account. The radiographic inclusion criterion was medial joint space width (JSW) >2mm. The radiographic evidence of knee OA, eligibility criteria, and the quality of radiographic films were verified by a central reader before inclusion of a patient in the study.
Exclusion criteria	Evidence of secondary knee OA (possibly due to injury, inflammatory, or metabolic rheumatic disease, osteonecrosis, Paget's disease, villonodular synovitis, haemophilia); prior intra-articular hyaluronic acid treatment; other IA injection, including lavage and corticosteroids within the previous 3 months; treatment with diacerein in the 3 months before inclusion and use of any other anti-osteoarthritic drugs in the 2 months before inclusion; contraindication to IA injection (anticoagulants, haematological anomalies); and severe knee OA (JSW <2mm, surgery required on the evaluated knee in the year).
Recruitment/selection of patients	Recruited from 46 rheumatology departments in France
Age, gender and ethnicity	Age - Mean (SD): 64.8 (8.0). Gender (M:F): 97:204. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. K-L grades 0-4, median grade: 3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=131) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Three courses of three weekly intraarticular hyaluronic acid (NRD

	101) injections with daily placebo capsules. The Ia injection procedure was the following: subcutaneous lidocaine local anaesthesia, aspiration of synovial fluid (if present), and injection of the 2.5mL contained in pre-filled syringes.. Duration 3 courses of 3 weekly injections. Concurrent medication/care: People were allowed to take analgesics as rescue drugs. However, before each evaluation visit, they were required to undergo a 2 day washout period. Aspirin at an antiplatelet dose (<500mg/day) was allowed. If NSAIDs were required, the drugs used were those with an equivalent dosage available, and a 7 day washout period was required before each evaluation visit. No systemic corticosteroid, IA treatment (lavage, HA, corticosteroid), or any potential symptom modifying drug was allowed during the study.. Indirectness: No indirectness (n=85) Intervention 2: Placebo. Three courses of three weekly saline injections with daily placebo capsules. The IA injection procedure was the following: subcutaneous lidocaine local anaesthesia, aspiration of synovial fluid (if present), and injection of the 2.5mL contained in pre-filled syringes.. Duration 3 courses of 3 weekly injections. Concurrent medication/care: People were allowed to take analgesics as rescue drugs. However, before each evaluation visit, they were required to undergo a 2 day washout period. Aspirin at an antiplatelet dose (<500mg/day) was allowed. If NSAIDs were required, the drugs used were those with an equivalent dosage available, and a 7 day washout period was required before each evaluation visit. No systemic corticosteroid, IA treatment (lavage, HA, corticosteroid), or any potential symptom modifying drug was allowed during the study.. Indirectness: No indirectness (n=85) Intervention 3: Placebo. Three courses of three weekly saline injections with daily diacerein capsules. The IA injection procedure was the following: subcutaneous lidocaine local anaesthesia, aspiration of synovial fluid (if present), and injection of the 2.5mL contained in pre-filled syringes.. Duration 3 courses of 3 weekly injections. Concurrent medication/care: People were allowed to take analgesics as rescue drugs. However, before each evaluation visit, they were required to undergo a 2 day washout period. Aspirin at an antiplatelet dose (<500mg/day) was allowed. If NSAIDs were required, the drugs used were those with an equivalent dosage available, and a 7 day washout period was required before each evaluation visit. No systemic corticosteroid, IA treatment (lavage, HA, corticosteroid), or any potential symptom modifying drug was allowed during the study.. Indirectness: No indirectness Comments: Not included in this analysis. Included in this statement for completeness.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: Pain (0-100 VAS) at 1 year; Group 1: mean -33.5 (SD 28.5); n=131, Group 2: mean -34.5 (SD 27.4); n=85; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 61.7 (13.6). Baseline placebo: 57.3 (18.5). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, weight, height, knee affected, baseline outcomes, joint space width, osteophyte score, and Kellgren and Lawrence score; Group 1 Number missing: 9, Reason: 9 withdrew - 1 for personal reasons, 2 lost to follow up, 4 adverse events, 1 inefficacy, 1 other; Group 2 Number missing: 5, Reason: 5 withdrew - 1 for personal reasons, 2 adverse events, 2 inefficacy	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Pons 2007[377]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 84 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Painful osteoarthritis of the first metatarsophalangeal joint with or without deviation diagnosed by clinical examination and radiography (grade 1 according to the classification of Karasick and Wapner)
Stratum	Toes
Subgroup analysis within study	Not applicable
Inclusion criteria	People between ages 40 and 80 years with painful osteoarthritis of the first metatarsophalangeal joint with or without deviation (hallux valgus) diagnosed by clinical examination and radiography (grade 1 according to the classification of Karasick and Wapner). Pain on dorsiflexion or plantarflexion of the first metatarsophalangeal joint of more than 30 mm as measured on a 100mm visual analogue scale.
Exclusion criteria	People with grade 2 or 3 osteoarthritis changes; foot deformities; pain that might interfere with the clinical assessment of the first MTP joint; people who had infections or previous surgery; people who had been treated with intraarticular injections; people who were hypersensitivity to sodium hyaluronate or corticosteroids
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 62.0 (12.1). Gender (M:F): 6:31. Ethnicity: Not stated
Further population details	1. Age: <75 years (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Grade 1 according to the classification of Karasick and Wapner Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). A single intraarticular injection of 1mL sodium hyalruonate (Ostenil® mini) with the person supine. The foot was prepared in a sterile fashion, and a 25-gauge needle was placed into the joint lateral to the extensor hallucis longus. No

	topical anaesthesia of image intensification were used.. Duration 1 injection. Concurrent medication/care: People were encouraged to refrain from strenuous activity for a day after the injections. As rescue medications people were permitted to take only paracetamol tablets (500mg) for severe pain or symptomatic deterioration (not more than 2 grams per day).. Indirectness: No indirectness (n=19) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). A single intraarticular injection of 1mL triamcinolone acetonide with the person supine. The foot was prepared in a sterile fashion, and a 25-gauge needle was placed into the joint lateral to the extensor hallucis longus. No topical anaesthesia of image intensification were used.. Duration 1 injection. Concurrent medication/care: People were encouraged to refrain from strenuous activity for a day after the injections. As rescue medications people were permitted to take only paracetamol tablets (500mg) for severe pain or symptomatic deterioration (not more than 2 grams per day).. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Toes: Visual analogue scale (pain on walking 20 meters) at 84 days; Group 1: mean 24.2 (SD 24.1); n=17, Group 2: mean 36.9 (SD 19.7); n=19; Visual analogue scale (pain at rest) 0-100 Top=High is poor outcome; Comments: Baseline HA: 61.4 (13.0). Baseline CS: 59.3 (12.2).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in pain at baseline. Reports age and gender.; Group 1 Number missing: 0, Reason: Reports that 37 people were recruited. 3 dropped out from the SH group and 1 from the TA group. Therefore, 17 people were in the SH group and 19 in the TA group. This number doesn't add up (it reports that 40 joints were included, so likely they used the wrong numbers). There isn't an obvious distribution of people to groups beforehand. However, the rate appears lower than 20% for each arm.; Group 2 Number missing: 0, Reason: Reports that 37 people were recruited. 3 dropped out from the SH group and 1 from the TA group. Therefore, 17 people were in the SH group and 19 in the TA group. This number doesn't add up (it reports that 40 joints were included, so likely they used the wrong numbers). There isn't an obvious distribution of people to groups beforehand. However, the rate appears lower than 20% for each arm.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Toes: AOFAS-hallux function subscale at 84 days; Group 1: mean 35.7 (SD 6.5); n=17, Group 2: mean 31.2 (SD 8.3); n=17; Comments: Baseline HA: 27.4 (7.6). Baseline CS: 27.1 (7.5).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender and outcome at baseline; Group 1 Number missing: 0, Reason: Reports that 37 people were recruited. 3 dropped out from the SH group and 1 from the TA group. Therefore, 17 people

were in the SH group and 19 in the TA group. This number doesn't add up (it reports that 40 joints were included, so likely they used the wrong numbers). There isn't an obvious distribution of people to groups beforehand. However, the rate appears lower than 20% for each arm.; Group 2 Number missing: 0, Reason: Reports that 37 people were recruited. 3 dropped out from the SH group and 1 from the TA group. Therefore, 17 people were in the SH group and 19 in the TA group. This number doesn't add up (it reports that 40 joints were included, so likely they used the wrong numbers). There isn't an obvious distribution of people to groups beforehand. However, the rate appears lower than 20% for each arm.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Qvistgaard 2006[383]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in Denmark; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 90 days (3 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hip osteoarthritis as defined by the American College of Rheumatology criteria, with radiological changes of hip osteoarthritis
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	Hip osteoarthritis as defined by the American College of Rheumatology criteria, radiographic changes of hip osteoarthritis, age above 18 years, stable medication for at least 3 weeks before inclusion, and written informed consent
Exclusion criteria	Radiographic signs of osteonecrosis of the hip, pain demanding morphine or incompatability with long-term observation, pain-free at randomisation, participation in other medical trials, previous intra-articular injection in the hip joint within the last 3 months; defects or other skin changes in the injection area with resultant increased risk of infection; inflammatory or neurological diseases; poultry allergy; anticoagulation treatment; pregnancy; language or intellectual problems; suspected potential for non-compliance with protocol
Recruitment/selection of patients	Referred by general practitioners and specialists in rheumatology to the department of Rheumatology
Age, gender and ethnicity	Age - Mean (SD): 66 (12). Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Included people with Kellgren Lawrence grade 1-4 changes. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (image guided). One injection of 1mL methylprednisolone (40mg Depo-medrol®) followed by two sham injections (2mL of saline). All injections were given with 1mL of

	1% lidocaine. Administered under ultrassound guidance. Given by a non-touch technique with the person in a supine position, given by a 21G needle inserted anteriorly 8-10cm under the inguinal ligament towards the anterior/inferior capsule below the femoral head. The needle was traces from 1cm below the skin surface all the way to the joint. Joint fluid was aspirated if present. Thereafter, a small amount of air (0.3-0.5mL) was injected into the joint to confirm placement).. Duration 1 injection (followed by 2 sham injections). All injections given at 14 days intervals.. Concurrent medication/care: People were asked to continue their usual analgesic consumption throughout the study. If the pain demanded change in therapy, the person was secondarily excluded.. Indirectness: No indirectness (n=33) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Three injections of 2mL HA (Hyalgan). All injections were given with 1mL of 1% lidocaine. Administered under ultrassound guidance. Given by a non-touch technique with the person in a supine position, given by a 21G needle inserted anteriorly 8-10cm under the inguinal ligament towards the anterior/inferior capsule below the femoral head. The needle was traces from 1cm below the skin surface all the way to the joint. Joint fluid was aspirated if present. Thereafter, a small amount of air (0.3-0.5mL) was injected into the joint to confirm placement).. Duration 3 injections given with 14 day intervals between each other. Concurrent medication/care: People were asked to continue their usual analgesic consumption throughout the study. If the pain demanded change in therapy, the person was secondarily excluded.. Indirectness: No indirectness (n=36) Intervention 3: Placebo. 3 sham injections (2mL of saline) given in 14 day intervals. All injections were given with 1mL of 1% lidocaine. Administered under ultrassound guidance. Given by a non-touch technique with the person in a supine position, given by a 21G needle inserted anteriorly 8-10cm under the inguinal ligament towards the anterior/inferior capsule below the femoral head. The needle was traces from 1cm below the skin surface all the way to the joint. Joint fluid was aspirated if present. Thereafter, a small amount of air (0.3-0.5mL) was injected into the joint to confirm placement).. Duration 3 injections given with 14 day intervals between each other. Concurrent medication/care: People were asked to continue their usual analgesic consumption throughout the study. If the pain demanded change in therapy, the person was secondarily excluded.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The study was supported by the Oak Foundation and The Ema Hamilton Foundation. The hyaluronic acid for the study was donated by Fidia Inc., Italy.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED) versus INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: Pain on walking at 3 months; Group 1: mean -9 (SD 23.8); n=32, Group 2: mean -11 (SD 23.5); n=33; Visual analogue scale (pain on walking) 0-100 Top=High is poor outcome; Comments: Reports change score (95% CI). Reported CS: -9 (-19 to -3). Reported HA: -11 (-19 to -3). Baseline CS: 44.0 (19.7). Baseline HA: 49.2 (24.8).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 6, Reason: 4 lost to follow up (2 for no improvement, 1 for hip arthroplasty, 1 no reason given), 2 discontinued (due to dissatisfaction with the result of 2 given injections); Group 2 Number missing: 4, Reason: 1 lost to follow up (no reason given), 3 discontinued (2 due to pain flare after treatment, 1 for erroneous inclusion)

Protocol outcome 2: Osteoarthritis flares at ≤3- or >3- months
- Actual outcome for Hip: Pain flare after injection at 3 months; Group 1: 0/32, Group 2: 2/33; Comments: Not well defined (all that is stated is "pain flare after treatment")
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 6, Reason: 4 lost to follow up (2 for no improvement, 1 for hip arthroplasty, 1 no reason given), 2 discontinued (due to dissatisfaction with the result of 2 given injections); Group 2 Number missing: 4, Reason: 1 lost to follow up (no reason given), 3 discontinued (2 due to pain flare after treatment, 1 for erroneous inclusion)

Protocol outcome 3: Serious adverse events at ≤3- or >3- months
- Actual outcome for Hip: Hip infection or other serious adverse events at 3 months; Group 1: 0/32, Group 2: 0/33
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 6, Reason: 4 lost to follow up (2 for no improvement, 1 for hip arthroplasty, 1 no reason given), 2 discontinued (due to dissatisfaction with the result of 2 given injections); Group 2 Number missing: 4, Reason: 1 lost to follow up (no reason given), 3 discontinued (2 due to pain flare after treatment, 1 for erroneous inclusion)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: Pain on walking at 3 months; Group 1: mean -9 (SD 23.8); n=32, Group 2: mean -5 (SD 23); n=36; Visual analogue scale (pain on

walking) 0-100 Top=High is poor outcome; Comments: Reports change score (95% CI). Reported CS: -9 (-19 to -3). Reported placebo: -5 (-13 to 2). Baseline CS: 44.0 (19.7). Baseline placebo: 42.4 (19.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 6, Reason: 4 lost to follow up (2 for no improvement, 1 for hip arthroplasty, 1 no reason given), 2 discontinued (due to dissatisfaction with the result of 2 given injections); Group 2 Number missing: 3, Reason: 1 lost to follow up (hip arthroplasty). 2 discontinued (after dissatisfaction with the result of 2 given injections).

Protocol outcome 2: Osteoarthritis flares at ≤3- or >3- months
- Actual outcome for Hip: Pain flare after injection at 3 months; Group 1: 0/32, Group 2: 0/36; Comments: Not well defined (all that is stated is "pain flare after treatment")
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 6, Reason: 4 lost to follow up (2 for no improvement, 1 for hip arthroplasty, 1 no reason given), 2 discontinued (due to dissatisfaction with the result of 2 given injections); Group 2 Number missing: 3, Reason: 1 lost to follow up (hip arthroplasty). 2 discontinued (after dissatisfaction with the result of 2 given injections).

Protocol outcome 3: Serious adverse events at ≤3- or >3- months
- Actual outcome for Hip: Hip infection or other serious adverse events at 3 months; Group 1: 0/32, Group 2: 0/36
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 6, Reason: 4 lost to follow up (2 for no improvement, 1 for hip arthroplasty, 1 no reason given), 2 discontinued (due to dissatisfaction with the result of 2 given injections); Group 2 Number missing: 3, Reason: 1 lost to follow up (hip arthroplasty). 2 discontinued (after dissatisfaction with the result of 2 given injections).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: Pain on walking at 3 months; Group 1: mean -11 (SD 23.4); n=33, Group 2: mean -5 (SD 23); n=36; Visual analogue scale (pain at rest) 0-100 Top=High is poor outcome; Comments: Reports change score (95% CI). Reported HA: -11 (-19 to -3). Reported placebo: -5 (-13 to 2). Baseline HA: 49.2 (24.8). Baseline placebo: 42.4 (19.7).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 4, Reason: 1 lost to follow up (no reason given), 3 discontinued (2 due to pain flare after treatment, 1 for erroneous inclusion); Group 2 Number missing: 3, Reason: 1 lost to follow up (hip arthroplasty). 2 discontinued (after dissatisfaction with the result of 2 given injections).

Protocol outcome 2: Osteoarthritis flares at ≤3- or >3- months - Actual outcome for Hip: Pain flare after injection at 3 months; Group 1: 2/33, Group 2: 0/36; Comments: Not well defined (all that is stated is "pain flare after treatment") Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 4, Reason: 1 lost to follow up (no reason given), 3 discontinued (2 due to pain flare after treatment, 1 for erroneous inclusion); Group 2 Number missing: 3, Reason: 1 lost to follow up (hip arthroplasty). 2 discontinued (after dissatisfaction with the result of 2 given injections). Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Hip: Hip infection or other serious adverse events at 3 months; Group 1: 0/33, Group 2: 0/36 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, outcome baseline values, Kellgren Lawrence grade, and the presence of intraarticular effusion. Pain on walking was different between the HA and saline group.; Group 1 Number missing: 4, Reason: 1 lost to follow up (no reason given), 3 discontinued (2 due to pain flare after treatment, 1 for erroneous inclusion); Group 2 Number missing: 3, Reason: 1 lost to follow up (hip arthroplasty). 2 discontinued (after dissatisfaction with the result of 2 given injections).	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months

Study	Raynauld 2003[391]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Canada; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical and radiological diagnosis fulfilled by the American College of Rheumatology criteria for knee osteoarthritis
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Males and females were eligible for the study if they were between 40 and 80 years old, fulfilled by ACR criteria for knee OA, had symptomatic knee osteoarthritis requiring treatment, and had not responded adequately to treatment with paracetamol or traditional NSAIDs. They were required to have radiologic evidence of osteoarthritis of the affected knee on a radiograph obtained within 6 months of the start of the study. In addition they were required to have a severity grade of 2 or 3 on the Kellgren-Lawrence scale for joint space narrowing, osteophytes or sclerosis. For people in whom both knees were symptomatic chose the more symptomatic knee for injection or, when symptoms were similar bilaterally, tossed a coin to determine which knee would be studied.
Exclusion criteria	Chondrocalcinosis; isolated patellofemoral OA, if their knee OA was secondary to other conditions (including inflammation, sepsis, metabolic abnormalities, and trauma); if they had acute or chronic infection (including tuberculosis); history of gastrointestinal ulceration; IA corticosteroid injection in the study knee within the previous 6 months; radiologic grade 4 OA; people with severe functional disability; candidates for imminent knee joint surgery; people with contralateral total joint replacement.
Recruitment/selection of patients	Recruited from outpatient rheumatology clinics affiliated with the University of Montreal. Most of the patients were provided by the 10 rheumatologists at the Arthritis Division, Hôpital Notre-Dame in Montreal
Age, gender and ethnicity	Age - Mean (SD): 63.2 (9.1). Gender (M:F): 65:135. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Not stated / Unclear 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-3. Duration of symptoms: 9.3 (7.0) years
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular triamcinolone acetonide 40mg (1cc) in the affected knee every 3 months. Lidocaine 2% without epinephrine was used to anaesthetize the skin but was not injected into the joint.. Duration Injections every 3 months (24 months, therefore, 8 injections over the study period). Concurrent medication/care: People in both treatment groups were permitted to receive simple analgesics and NSAIDs, and analgesic regimens could be changed according to the rheumatologist's preferences and the patient's clinical course. The use of indomethacin was not permitted.. Indirectness: No indirectness (n=34) Intervention 2: Placebo. Intraarticular saline (1cc) in the affected knee every 3 months. Lidocaine 2% without epinephrine was used to anaesthetize the skin but was not injected into the joint.. Duration Injections every 3 months (24 months, therefore, 8 injections over the study period). Concurrent medication/care: People in both treatment groups were permitted to receive simple analgesics and NSAIDs, and analgesic regimens could be changed according to the rheumatologist's preferences and the patient's clinical course. The use of indomethacin was not permitted.. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by a grant from the Fonds de la Recherche en Santédu Québec)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 2 years; Group 1: mean -11.4 (SD 19.2); n=33, Group 2: mean -13.8 (SD 21.5); n=33; WOMAC pain subscale (VAS) 0-100 Top=High is poor outcome; Comments: Baseline steroid: 40.1 (25.6). Baseline saline: 47.7 (28.2).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, years in education, duration of knee OA, weight, Kellgren and Lawrence grade, concomitant medication use, baseline outcome values, minimum joint space width; Group 1 Number missing: 1, Reason: 1 protocol violation (corticosteroid injection out of the allocated time period); Group 2 Number missing: 1, Reason: 1 refusal to continue due to lack of efficacy

Protocol outcome 2: Physical function at ≤3- or >3- months

- Actual outcome for Knee: WOMAC physical function at 2 years; Group 1: mean -10.9 (SD 32.6); n=33, Group 2: mean -13.1 (SD 34.1); n=33; WOMAC physical function subscale (VAS) 0-100 Top=High is poor outcome; Comments: Baseline steroid: 32.9 (21.7). Baseline saline: 39.3 (26.8). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, years in education, duration of knee OA, weight, Kellgren and Lawrence grade, concomitant medication use, baseline outcome values, minimum joint space width; Group 1 Number missing: 1, Reason: 1 protocol violation (corticosteroid injection out of the allocated time period); Group 2 Number missing: 1, Reason: 1 refusal to continue due to lack of efficacy	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Richette 2009[398]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in France; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People fulfilling the American College of Rheumatology criteria for the diagnosis of hip osteoarthritis
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	People fulfilling the American College of Rheumatology criteria for the diagnosis of hip osteoarthritis; ages 30-80 years; radiographically confirmed hip osteoarthritis; Kellgren Lawrence grades 2 or 3; have had symptoms of hip osteoarthritis for at least 1 month, defined as daily pain score between 40 and 80mm on a 100mm visual analogue scale despite treatment with paracetamol (4 grams/day) and/or nonsteroidal antiinflammatory drugs taken regularly in adequate doses
Exclusion criteria	Pregnancy; Kellgren Lawrence grade 1 or 4; major acetabular dysplasia of the target joint; inflammatory joint disease; chondrocalcinosis of the hip; history of allergy or intolerance to hyaluronic acid; skin changes in the injection area with risk of infection; surgery on the target hip within the last 6 months; intermittent claudication; current anticoagulant therapy or viscosupplementation within the last 6 months; oral corticosteroid treatment or intraarticular corticosteroid injection into the hip or knee joint within the last month.
Recruitment/selection of patients	Recruited from 26 rheumatology departments
Age, gender and ethnicity	Age - Mean (SD): 60.1 (11.5). Gender (M:F): 35:50. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stages. Kellgren Lawrence grade 2-3. Duration of symptoms: 4.4 (5.4) years
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). A single injection of hyaluronic acid (2.5mL, Adant, 900,000 Da) inserted under fluoroscopic guidance. Arthrocentesis was performed before each injection. The needle placement was verified by the injection of 0.1-1mL sodium and meglumine ioxaglate (Hexabrix)

	before the intervention injection. Duration 1 injection. Concurrent medication/care: Paracetamol was allowed throughout the study. Use of NSAIDs or step 2 analgesics for the affected hip was only permitted if symptoms did not respond to optimal doses of paracetamol. Washout was not performed before any assessment.. Indirectness: No indirectness (n=43) Intervention 2: Placebo. A single injection of placebo (2.5mL saline water) inserted under fluoroscopic guidance. Arthrocentesis was performed before each injection. The needle placement was verified by the injection of 0.1-1mL sodium and meglumine ioxaglate (Hexabrix) before the intervention injection. Duration 1 injection. Concurrent medication/care: Paracetamol was allowed throughout the study. Use of NSAIDs or step 2 analgesics for the affected hip was only permitted if symptoms did not respond to optimal doses of paracetamol. Washout was not performed before any assessment.. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Daiichi Sankyo France. Dr. Ravaud has received consulting fees, speaking fees, and/or honoraria from Servier, Roche, Daiichi Sankyo, Pfizer, Sanofi, Schering-Plough, and Almirall (less than $10,000 each). Dr. Conrozier has received consulting fees, speaking fees, and/or honoraria from Genome and Bristol-Myers Squibb (less than $10,000 each) and from PfizerandSmith&Nephew(morethan$10,000each).Dr.Clersonhas received consulting fees, speaking fees, and/or honoraria from Daiichi Sankyo, Actelion, Janssen, Takeda, and Bayer Schering (more than $10,000 each). Dr. Chevalier has received consulting fees, speaking fees, and/or honoraria from Expanscience, Pfizer, Genzyme, Servier, Sankyo, Rottapharma, and Fidia (less than $10,000 each).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: WOMAC pain score at 3 months; Group 1: mean -8.6 (SD 22.3); n=42, Group 2: mean -7.5 (SD 24.6); n=43; WOMAC pain subscale 0-100 Top=High is poor outcome; Comments: Baseline HA: 49.8 (15.6). Baseline placebo: 51.4 (13).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, weight, height, BMI, duration of disease, Kellgren Lawrence grade, and baseline values of outcomes; Group 1 Number missing: 3, Reason: 2 lost for inefficacy. 1 lost for personal reasons.; Group 2 Number missing: 2, Reason: 1 withdrew. 1 lost due to adverse events.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Hip: WOMAC function score at 3 months; Group 1: mean -6.7 (SD 22.7); n=42, Group 2: mean -5.7 (SD 19.9); n=43; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Baseline HA: 51.3 (16.8). Baseline placebo: 49.7 (13.4).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, weight, height, BMI, duration of disease,

Kellgren Lawrence grade, and baseline values of outcomes; Group 1 Number missing: 3, Reason: 2 lost for inefficacy. 1 lost for personal reasons.; Group 2 Number missing: 2, Reason: 1 withdrew. 1 lost due to adverse events. Protocol outcome 3: Osteoarthritis flares at ≤3- or >3- months - Actual outcome for Hip: Pain flares at 3 months; Group 1: 3/42, Group 2: 0/43; Comments: Reports that 3 people had "pain flares" Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, weight, height, BMI, duration of disease, Kellgren Lawrence grade, and baseline values of outcomes; Group 1 Number missing: 3, Reason: 2 lost for inefficacy. 1 lost for personal reasons.; Group 2 Number missing: 2, Reason: 1 withdrew. 1 lost due to adverse events. Protocol outcome 4: Serious adverse events at ≤3- or >3- months - Actual outcome for Hip: Rapidly destructive hip osteoarthritis (needing to undergo total hip replacement) at 3 months; Group 1: 1/42, Group 2: 0/43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, weight, height, BMI, duration of disease, Kellgren Lawrence grade, and baseline values of outcomes; Group 1 Number missing: 3, Reason: 2 lost for inefficacy. 1 lost for personal reasons.; Group 2 Number missing: 2, Reason: 1 withdrew. 1 lost due to adverse events.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months

Study	Rolf 2005[407]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=272)
Countries and setting	Conducted in Sweden; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Osteoarthritis of the knee, primarily affecting one knee with grade 1-3 chondral changes (as assessed by the Outerbridge criteria and verified by arthroscopy)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 35 years or older; OA of the knee, primarily affecting one knee; GRADE 1-3 chondral changes of osteoarthritis, as assessed by the Outerbridge criteria and verified by diagnostic arthroscopy performed >6 months before the baseline visit; pain ≥40mm on VAS, after the washout period, on at least 1 of the WOMAC osteoarthritis index part A, question 1, 2 or 5; was willing to provide informed consent and able to communicate appropriately with the investigator
Exclusion criteria	Had bilateral symptomatic osteoarthritis of the knee requiring simultaneous bilateral treatment; had severe symptomatic osteoarthritis requiring knee replacement surgery; had rheumatoid arthritis, active gout, or crystalline or other systemic inflammatory arthropathy; had significant osteoarthritis in joints other than the study knee, or other painful disease considered likely to warrant use of analgesics or NSAIDs; took an analgesic or NSAID within 6 days before baseline, with the exception of paracetamol rescue medication; had chondromalacia or chondrocalcinosis, or requiring joint replacement surgery; had venous or lymphatic stasis of the leg; had acute infectious synovitis or infectious arthritis; had a medical history notable for any clinically significant hepatic, renal or haematological disorder; was clinicall obese (body mass index >40); received local intraarticular steroid injection or had surgery, including diagnostic arthroscopy, for the affected joint within 6 months before baseline; experienced a new major trauma after diagnostic arthroscopy; had major knee surgery, including debridement or ligament repairs and all larger procedures, within 2 years before baseline; experienced a new major trauma after diagnostic arthroscopy; had major knee surgery, including debridement or ligament repairs and all larger procedures, within 2 years before faseline; had previous treatment with Artzal or Synvisc within 12 months before baseline; had excessive exudates with an

	approximate volume >20mL; use systemic corticosteroids within 3 months before baseline; used anticoagulant treatment within 1 week before baseline; used any investigational drug within 12 weeks before baseline, or was simultaneously participating in another clinical study; had a history of hypersensitivity to paracetamol, hyaluronans, eggs, or chicken products; had mobility limitations requiring support from a walker to walk at least 50 steps; was a female of childbearing potential who was not using an accepted form of birth control, or was pregnant or lactating; people who abused drugs or alcohol; had a history of current psychological or sensory illness or condition that might have interfered with the subject's ability to understand the requirements of the study, participate in the study, or give informed consent; was unwilling to meet the requirements of the protocol
Recruitment/selection of patients	Recruited from two centers
Age, gender and ethnicity	Age - Mean (SD): 53.8 (9.4). Gender (M:F): 162:110. Ethnicity: Majority Caucasian (270), with 1 black person and 1 "other"
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Outerbridge grade 1-3 chondral changes. Ahlback grade 0-3. Duration of symptoms: 7.8 (6.5) years
Indirectness of population	No indirectness
Interventions	(n=181) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Two groups combined. Intraarticular injections of Synvisc (90 people, 2.0mL) or Artzal (91 people, 2.5mL) once weekly for three weeks. . Duration 3 injections over 3 weeks. Concurrent medication/care: Paracetamol (500-2000mg/day) was the only oral treatment allowed for knee pain up to the 26 week visit. Indirectness: No indirectness Comments: Results from these two groups will be combined together as agreed in the protocol (n=91) Intervention 2: Placebo. Intraarticular injections of placebo (2.0mL of sterile physiological buffered saline) once weekly for three weeks. . Duration 3 injections over 3 weeks. Concurrent medication/care: Paracetamol (500-2000mg/day) was the only oral treatment allowed for knee pain up to the 26 week visit. Indirectness: No indirectness

Funding	Study funded by industry (This study was initially funded by Biomatrix, Inc (USA) and Roche AB (Sweden). Subsequent to data collection, Biomatrix merged with companies of the Genzyme Corporation, who funded the completion of the study)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 26 weeks; Group 1: 0/181, Group 2: 0/91; Comments: Reports "None of the patients had a serious adverse event judged to be treatment related by the treated physicians" Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports duration of symptoms, affected knee side, compartment of disease, Outerbridge grade, Ahlback grade, features on examination, age, race, gender, and body mass index; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study (subsidiary papers)	Salk 2005[416] (Salk 2006[417])
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinically diagnosed osteoarthritis of the ankle by clinical examination and radiographic procedures
Stratum	Ankle
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinically diagnosed osteoarthritis of the ankle of Kellgren Lawrence classification grades 2-4 who were 18 years of age or older, had chronic ankle pain for 3 months or longer but less than 5 years, and had a current total Ankle Osteoarthritis Scale score of greater than 30 and less than 90 (range, 0-100); were able to walk 50m without using a walker, crutches or a cane; signed and understood the informed consent; were willing to discontinue all NSAIDs or other analgesic medication for the duration of the study (except for rescue medication); were able to complete efficacy measurements questionnaires; were not on any research protocol for 30 days; and (if a woman) were postmenopausal or using effective contraception.
Exclusion criteria	Bilateral ankle osteoarthritis requiring treatment for both ankles other than simple analgesics such as paracetamol; IA injection of corticosteroids within the last 3 months; use of systemic steroids (excluding inhalation or topical steroids) within the last 3 months; any IA injection within the last month; surgery to signal joint in the prior 6 months; dosage of glucosamine or chondroitin sulfate that has been stable over the preceding 3 months, with the dosage remaining constant during the study; planned arthroscopy or any other surgical procedure to the study ankle during the study period; diagnosis of rheumatoid arthritis; systemic active inflammatory condition or infection, such as inflammatory arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, septic arthritis, gout/acute pseudogout, or any other connective tissue disease; active skin disease or infection in the area of the injection site; significant venous or lymphatic stasis present in the legs; any medical condition that in the opinion of the investigator makes the patient unsuitable for inclusion (e.g. severe progressive chronic disease, malignancy, bleeding disorder, clinically significant pain from part of the musculoskeletal system other than the ankle, fibromyalgia); treatment with anticoagulant (except for acetylsalicylic acid up to 325mg/day); pregnant or

	breastfeeding woman or woman of child-bearing potential not practicing adequate contraception; conditions that can confound pain and function assessments in the ankle, such as plantar fasciitis, tendonitis of foot and ankle, sciatica, osteoarthritis of other joints; sprains of foot, and so forth.
Recruitment/selection of patients	People were recruited from private practice.
Age, gender and ethnicity	Age - Mean (SD): 58.8 (14.4). Gender (M:F): 7:10. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grades 2-4. Duration of symptoms: Not explicitly stated. At least 3 months but less than 5 months..
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Five weekly intraarticular injections of hyaluronic acid - 1mL of sodium hyaluronate, 10mg/mL (on days 0, 7, 14, 21 and 28).. Duration 5 injections over 5 weeks. Concurrent medication/care: All were supplied 500mg paracetamol tablets and were allowed to take up to 4000mg/day for rescue analgesia. People were instructed to not take other NSAIDs, narcotic analgesics, non-narcotic analgesics, or corticosteroids.. Indirectness: No indirectness (n=10) Intervention 2: Placebo. Five weekly intraarticular injections of phosphate buffered saline - 1mL (on days 0, 7, 14, 21 and 28).. Duration 5 injections over 5 weeks. Concurrent medication/care: All were supplied 500mg paracetamol tablets and were allowed to take up to 4000mg/day for rescue analgesia. People were instructed to not take other NSAIDs, narcotic analgesics, non-narcotic analgesics, or corticosteroids.. Indirectness: No indirectness
Funding	Study funded by industry (Conducted under Investigational Device Exemption grant G020019S1 to Northern California Foot and Ankle Center by the Food and Drug Administration. support for portions of the study received from Sanofi-Synthelabo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Serious adverse events at ≤3- or >3- months
- Actual outcome for Ankle: Serious adverse events at 6 months; Group 1: 0/9, Group 2: 0/8; Comments: No serious adverse events. One person (receiving HA) experienced an "anxiety attack" but this was deemed unrelated to the study medication and associated with the stress of anticipating an injection. 5/17 had injection site pain that lasted for no more than 3 days. No soft tissue or IA infections were reported.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, height, weight and affected side; Group 1 Number missing: 1, Reason: Gives the overall reason for withdrawal. Two withdrew for a lack of efficacy. One was lost to follow up.; Group 2 Number missing: 2, Reason: Gives the overall reason for withdrawal. Two withdrew for a lack of efficacy. One was lost to follow up.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Sezgin 2005[430]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of primary gonarthrosis based on the modified American College of Rheumatology criteria with grade II or III disease on plain X-ray of the knee according to Kellgren-Lawrence grading
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of primary gonarthrosis based on the modified American College of Rheumatology criteria; grade II or III disease on plain X-ray of the knee according to Kellgren-Lawrence grading; presence of effusion in the painful and swollen knee; total pain score of 15 or over on the WOMAC index; total pain score of 15 or over on the WOMAC index; not receiving NSAIDs
Exclusion criteria	In the previous year, injection of HA or application of physiotherapy to the knees included in the study or exposure to trauma in the previous 3 months; oral or intramuscular administration of corticosteroids in the previous 2 months; pregnancy or lactation; history of allergy and the presence of infectious, inflammatory, metabolic or malignant disease; presence of OA on the hip and the opposite knee severe enough to affect the evaluation of functions
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 59.7 (10.0). Gender (M:F): 10:31. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade II or III. Duration of symptoms: 36.7 (37.5) months
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Evacuation of any effusion and then injection with 2mL hyaluronic acid (15mg/mL) three times at 1 week intervals. Contains 15 mg/mL of NaHA with a molecular mass over 1,000,000 Da.. Duration 3 injections over 3 weeks. Concurrent

	medication/care: All people were instructed to do isometric quadriceps exercises. They were not given any analgesics or NSAIDs except for paracetamol.. Indirectness: No indirectness (n=19) Intervention 2: Placebo. Intraarticular 2mL 0.9% sodium chloride administered at the same frequency.. Duration 3 injections over 3 weeks. Concurrent medication/care: All people were instructed to do isometric quadriceps exercises. They were not given any analgesics or NSAIDs except for paracetamol.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC pain subscale at 3 weeks; Group 1: mean 8.9 (SD 3.28); n=22, Group 2: mean 11.1 (SD 3.49); n=19; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Reports final values and standard errors. Standard deviation calculated. Reported HA: 8.9 (0.7). Reported placebo: 11.1 (0.8). Baseline HA: 18.9 (2.7). Baseline control: 17.2 (1.7). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, duration of disease, BMI and outcome baseline values.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: WOMAC physical function subscale at 3 weeks; Group 1: mean 32.2 (SD 12.2); n=22, Group 2: mean 39 (SD 12.6); n=19; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Reports final values and standard errors. Standard deviation calculated. Reported HA: 32.2 (2.6). Reported placebo: 39 (2.9). Baseline HA: 64.1 (11.2). Baseline control: 50.0 (8.7). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, duration of disease, BMI and outcome baseline values.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Shimizu 2010[438]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in Japan; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Tibiofemoral and/or patellofemoral joint pain with osteoarthritis findings on radiography (Kellgren Lawrence grade 2 or 3)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥60 years; pain in the tibiofemoral and/or patellofemoral joint persisting ≥6 months; hydroarthrosis; OA findings on radiography and Kellgren-Lawrence grade 2 or 3; no treatment including NSAId administration within 3 months
Exclusion criteria	Intraarticular injection into the knee within 1 year; knee arthritis associated with collagen diseases including rheumatoid arthritis, pseudogout, or infection; arthroplasty in the affected lower limb; surgery including arthroscopy of the knee joint due to injury or meniscus injury within 1 year; marked instability associated with knee ligament dysfunction.
Recruitment/selection of patients	Multicenter. People visited the outpatient clinic between April 2006 and December 2007.
Age, gender and ethnicity	Age - Mean (SD): 75.6 (5.4). Gender (M:F): 38:13. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on SD). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 2 or 3. Duration of symptoms: Not stated explicitly. At least greater than 6 months..
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 25mg of sodium hyaluronate injected into the knee joint once a week for 5 weeks. Duration 1 injection per week for 5 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=29) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular corticosteroid - 4mg injected into the knee joint

	once, with a single additional injection permitted depending on the degree of pain and inflammatory symptoms. Duration 1 injection (potentially 2 depending on symptoms). Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: Visual analogue scale score (pain) at 5 weeks; Group 1: mean 37.4 (SD 12.7); n=26, Group 2: mean 35.2 (SD 13.3); n=25; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 69.0 (11.5). Baseline CS: 68.0 (9.9). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, BMI, Kellgren-Lawrence grade and outcome baseline values; Group 1 Number missing: 6, Reason: 1 developed pseudogout, 2 desired additional analgesic treatment, 3 lost to follow up; Group 2 Number missing: 4, Reason: 1 desired additional analgesic treatment, 3 lost to follow up - Actual outcome for Knee: Visual analogue scale score (pain) at 6 months; Group 1: mean 21.5 (SD 19.3); n=26, Group 2: mean 22.6 (SD 18.3); n=25; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 69.0 (11.5). Baseline CS: 68.0 (9.9). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, BMI, Kellgren-Lawrence grade and outcome baseline values; Group 1 Number missing: 6, Reason: 1 developed pseudogout, 2 desired additional analgesic treatment, 3 lost to follow up; Group 2 Number missing: 4, Reason: 1 desired additional analgesic treatment, 3 lost to follow up	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Shrestha 2018[441]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=171)
Countries and setting	Conducted in Nepal
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinically diagnosed osteoarthritis of the knees by the criteria of the American College of Rheumatology (unclear if radiography was used)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with clinically diagnosed osteoarthritis of the knees by the criteria of the American College of Rheumatology. People who would be available to follow up evaluation, either by visiting the health center/hospital or consenting to provide information on telephone about the condition of their knees
Exclusion criteria	People diagnosed with other diseases (rheumatoid arthritis or gouty arthritis etc.) and osteoarthritis already under medications and people with a known history of allergy to steroids
Recruitment/selection of patients	People presenting to health camps in the community
Age, gender and ethnicity	Age - Mean (SD): 67.3 (5.3). Gender (M:F): 45:72. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Not stated / Unclear 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not stated Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular triamcinolone acetonide (no additional information). Duration 1 injection and 1 week of aceclofenac treatment. Concurrent medication/care: After the injection, all received oral aceclofenac 100mg once a day for seven days and physiotherapy by a trained physiotherapist. Indirectness: No indirectness (n=60) Intervention 2: Placebo. Intraarticular normal saline (no additional information

	provided). Duration 1 injection, followed by 1 week of aceclofenac treatment. Concurrent medication/care: After the injection, all received oral aceclofenac 100mg once a day for seven days and physiotherapy by a trained physiotherapist. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: Visual analogue scale (pain) at 12 weeks; Group 1: mean 6.8 (SD 1.2); n=57, Group 2: mean 6.9 (SD 1.1); n=60; Visual analogue scale (pain) 0-10 Top=High is poor outcome; Comments: Baseline CS: 7 (1.4). Baseline placebo: 6.7 (1.4). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender and age; Group 1 Number missing: 2, Reason: States that only 117 out of 171 people could be traced to the final follow up with complete information with 55 receiving triamcinolone and 58 receiving placebo. Overall unclear description.; Group 2 Number missing: 2 Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: KOOS Physical function shortform at 12 weeks; Group 1: mean 47.1 (SD 11.3); n=57, Group 2: mean 53.2 (SD 12.5); n=60; 0-100 KOOS Physical function shortform Top=High is poor outcome; Comments: Baseline CS: 52.6 (13.8). Baseline placebo: 54.9 (14). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender and age; Group 1 Number missing: 2, Reason: States that only 117 out of 171 people could be traced to the final follow up with complete information with 55 receiving triamcinolone and 58 receiving placebo. Overall unclear description.; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Skwara 2009[445]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Germany; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiographically verified unilateral degenerative osteoarthritis of the knee grade 2 or 3 according to the Kellgren and Lawrence classification
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women between 50 and 75 years of age; radiographically verified unilateral degenerative osteoarthritis of the knee grade 2 or 3 according to the Kellgren and Lawrence classification; pain of at least 40mm on a 100mm visual analogue scale at the time of examination; persisting pain for at least 6 months; a Lequesne-Score of at least 10 points; good physical and mental status; good compliance; and agreement to participate in this study
Exclusion criteria	People with non-degeneratively induced osteoarthritis; rheumatoid arthritis; ligamentous instability or complete resection of the meniscus; Sudeck's disease; operations of the affected knee within the last three months; varus or valgus deformity of more than 15 degrees; patellofemoral arthritis; intraarticular therapy of the affected joint within the last 6 months with hyaluronan and three months with glucocorticoids; severe systemic diseases (tumour, exacerbated diabetes mellitus, hyperthyroidism); anti-thrombotic medication or regular medication with NSAID/psychiatric pharmaceuticals; infectious diseases; alcohol abuse; drugs; psychiatric diseases or suicidal tendencies; involvement in an other study; non-compliance; acute hemarthros or joint effusion; allergic predisposition; skin infections or skin diseases about the knee
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 61.1 (6.9). Gender (M:F): 17:25. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren and Lawrence grade 2-3. Duration of symptoms: Not stated

Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular sodium hyaluronate (1%) - Ostenil 2mL, molecular weight of 1.2x10^6 Da. - 20mg in 2mL. Duration 5 injections over 5 weeks. Concurrent medication/care: People are allowed to use paracetamol up to 2g per day and 100mg/day acetylsalicylic acid (for people with cardiovascular diseases). Indirectness: No indirectness (n=21) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Triamcinolone acetonide 10mg in 1mL given as five injections over one week. Duration 5 injections over 5 weeks. Concurrent medication/care: People are allowed to use paracetamol up to 2g per day and 100mg/day acetylsalicylic acid (for people with cardiovascular diseases). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 12 weeks; Group 1: mean 33.6 (SD 22.9); n=20, Group 2: mean 32 (SD 22); n=15; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 53.1 (11.3). Baseline CS: 57.9 (10.7).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, and osteoarthritis grade. Reports baseline values of outcomes, which are different at baseline (corticosteroid group has worse baseline scores).; Group 1 Number missing: 1, Reason: 1 terminated their participation because of persistent knee pain; Group 2 Number missing: 5, Reason: 5 terminated the participation because of persistent knee pain (1 after 1 infiltration, 4 after 5 infiltrations). 1 was excluded because of a stroke before the follow up visit.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: Knee society score - function at 12 weeks; Group 1: mean 75.25 (SD 14.8); n=20, Group 2: mean 80.3 (SD 10.8); n=15; Knee society score - function 0-100 Top=High is good outcome; Comments: Baseline HA: 73.75 (14.6). Baseline CS: 72.0 (10.7).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, and osteoarthritis grade. Reports baseline values of outcomes, which are different at baseline (corticosteroid group has worse baseline scores).; Group 1 Number missing: 1, Reason: 1 terminated their participation because of persistent knee pain; Group 2 Number missing: 5, Reason: 5 terminated the participation because of persistent knee pain (1 after 1 infiltration, 4 after 5 infiltrations). 1 was excluded because of a stroke before the follow up visit.

Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Withdrawal due to persistent knee pain at 12 weeks; Group 1: 1/21, Group 2: 5/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, height, weight, BMI, and osteoarthritis grade. Reports baseline values of outcomes, which are different at baseline (corticosteroid group has worse baseline scores).; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Skwara 2009[446]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Germany; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiographically verified degenerative osteoarthritis of the knee (grade II or III according to the Kellgren and Lawrence classification)
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women between 35 and 80 years of age, radiographically verified degenerative osteoarthritis of the knee (grade 2 or 3 according to the Kellgren and Lawrence classification); pain of at least 40mm on a 100mm visual analogue scale at initial examination; persistent pain for at least 6 months; a Lequesne-Score of at least 10 points; good physical and mental status; good compliance and agreement to participate in the study.
Exclusion criteria	People with non-degeneratively induced osteoarthritis; rheumatoid arthritis; ligamentous instability or complete resection of the meniscus; Sudeck's disease; operations of the affected knee within the last three months; varus or valgus deformity of more than 15 degrees; patellofemoral arthritis; intraarticular therapy of the affected joint within the last 6 months with hyaluronan and three months with glucocorticoids; severe systemic diseases (tumour, exacerbated diabetes mellitus, hyperthroidism); anti-thrombotic medications or regular medication with NSAID/psychiatric pharmaceuticals; infectious diseases; alcohol abuse; drugs; psychiatric diseases or suicidal tendencies; involvement in another study; non-compliance; acute hemarthros or joint effusion; allergic predisposition; skin infections or skin diseases around the knee.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 61.4 (10.5). Gender (M:F): 27:23. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not explicitly stated. Kellgren and Lawrence grade 2-3. Duration of symptoms: Not stated, pain for at least 6 months
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronan (3mL, Durolane, 20mg/mL non-animal stabilised hyaluronic acid) in buffered physiological sodium chloride solution pH7 in one pre-filled glass syringe in a sterile pack. Duration 1 injection. Concurrent medication/care: No additional information. As stated in the inclusion criteria other intraarticular therapy was not permitted, and regular antithrombotic or NSAIDs/psychiatric pharmaceuticals were not permitted.. Indirectness: No indirectness (n=30) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). One injection of triamcinolone acetonide (1mL of 10mg triamcinolone acetonide, 10mg/mL) give in one pre-filled glass syringe. Duration 1 injection. Concurrent medication/care: No additional information. As stated in the inclusion criteria other intraarticular therapy was not permitted, and regular antithrombotic or NSAIDs/psychiatric pharmaceuticals were not permitted.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 12 weeks; Group 1: mean 44 (SD 22.3); n=24, Group 2: mean 45.8 (SD 27.8); n=26; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 54.9 (15.2). Baseline TA: 52.9 (10.8).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, height, weight, BMI, gender and baseline values for outcomes.; Group 1 Number missing: 6, Reason: 6 people excluded due to persistent knee pain without benefit after injection or a necessity of another therapy; Group 2 Number missing: 4, Reason: 2 people excluded because of persistent knee pain and the necessity of other therapy, one person excluded because of disc prolapse with the need of non-allowed medication and a need for hospital treatment, and one excluded because of persistent pain and knee effusion and the necessity of non-study conforming therapy (infection ruled out).

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: Knee Society Score - Function subscale at 12 weeks; Group 1: mean 72.7 (SD 7.7); n=24, Group 2: mean 73.5 (SD 12.6); n=26; Knee Society Score - Function subscale 0-100 Top=High is good outcome; Comments: Baseline HA: 70.2 (9.1). Baseline TA: 71.9 (8.4).

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, height, weight, BMI, gender and baseline values for outcomes.; Group 1 Number missing: 6, Reason: 6 people excluded due to persistent knee pain without benefit after injection or a necessity of another therapy; Group 2 Number missing: 4, Reason: 2 people excluded because of persistent knee pain and the necessity of other therapy, one person excluded because of disc prolapse with the need of non-allowed medication and a need for hospital treatment, and one excluded because of persistent pain and knee effusion and the necessity of non-study conforming therapy (infection ruled out). Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Adverse reactions at 12 weeks; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, height, weight, BMI, gender and baseline values for outcomes.; Group 1 Number missing: 0; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Spitzer 2010[452]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=313)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Primarily unilateral, primary, symptomatic osteoarthritis of radiographically confirmed Kellgren Lawrence grade 2 or Kellgren Lawrence grade 3 disease
Stratum	Hip
Subgroup analysis within study	Not applicable
Inclusion criteria	Ambulatory men and women age ≥35 years who had primarily unilateral, primary, symptomatic osteoarthritis of radiographically confirmed Kellgren Lawrence grade 2 or Kellgren Lawrence grade 3 disease. People were required to have moderate hip pain due to OA while walking on a flat surface (defined as a score of 50-80mm on a 100mm visual analogue scale) and had to have taken analgesics/NSAIDs for hip OA pain
Exclusion criteria	Rapidly progressive osteoarthritis in the past 26 weeks; pain associated with lower back disorders that could not be differentiated from target hip pain; major dysplasia or congenital abnormality; primary inflammatory arthropathy or any other condition affecting the target joint; any musculoskeletal condition that would impede efficacy measurement of the target hip; any major surgery, arthroplasty or arthroscopy in the target hip or lower extremities in the past 26 weeks; planned surgery in the lower extremities during the study duration; infection of the injection site area; chronic skin disorders that could interfere with injection site evaluation; acute disease or trauma leading to secondary OA of the target hip in the past 5 years; pregnant women; people with asthma who may require the use of systemic corticosteroids; those with septic arthritis in any joint in the past 12 weeks; the presence of any other condition that the investigator considered to interfere with study participation; people with known hypersensitivity to avian protein or any components of hyaluronan-based injection devices, corticosteroids, lidocaine, injected dye at a previous radiological examination, shellfish or iodine and paracetamol; people who received intraarticular viscosupplementation or corticosteroid injection of the target hip within 26 weeks of screening; systemic corticosteroids within 12 weeks; glucosamine and/or chondroitin sulfate within 4 weeks; or any investigational drug, device or biologic

Recruitment/selection of patients	No additional information given
Age, gender and ethnicity	Age - Mean (SD): 59 (11.5). Gender (M:F): 151:161. Ethnicity: Reports that 90-96% of people were Caucasian in the study
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 2-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (image guided). Two intraarticular 2mL injections of hylan G-F 20 (administered 2 weeks apart) under fluoroscopic guidance with 0.5-1.0mL of water-soluble radiopaque solution to confimr IA needle placement. Sterile drapes were used to block the person's view of the procedure, overhead lights were dimmed and the fluoroscopy monitor was turned away from the person. All injection kits were packaged to look identical.. Duration 2 injections spaced 2 weeks apart. Concurrent medication/care: No additional analgesia during injection. Paracetamol use of <4000mg/day was allowed for breakthrough pain or postinjection pain. Any medications had to be discontinued 48 hours priro to each study visit. Other analgesics or NSAIDs, systemic corticosteroids, IA viscosupplementation or corticosteroid injections in any nontarget joint (other than the intervention in the trial), other investigational treatments and chronic narcotics were not allowed.. Indirectness: No indirectness (n=155) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (image guided). One intraarticular injection of 2mL methylprednisolone (40mg) followed by a sham injection (deep tissue injection of lidocaine HCl - not intraarticular) two weeks later. Completed under fluoroscopic guidance with 0.5-1.0mL of water-soluble radiopaque solution to confimr IA needle placement. Sterile drapes were used to block the person's view of the procedure, overhead lights were dimmed and the fluoroscopy monitor was turned away from the person. All injection kits were packaged to look identical.. Duration 1 injection (followed by a sham deep tissue injection 2 weeks later). Concurrent medication/care: No additional analgesia during injection. Paracetamol use of <4000mg/day was allowed for breakthrough pain or postinjection pain. Any medications had to be discontinued 48 hours priro to each study visit. Other analgesics or NSAIDs, systemic corticosteroids, IA viscosupplementation or corticosteroid injections in any nontarget joint (other than the intervention in the trial), other investigational treatments and chronic narcotics were not allowed.. Indirectness: No indirectness

Funding	Principal author funded by industry (Andrew I. Spitzer, MD discloses conflicts of interest with Alpharma, DePuy Orthopaedics, Genzyme Biosurgery, and sanofi-aventis. Barry I. Bockow, MD, Daryl K. Macarter, Garland K. Gudger, MD, James W. Yates, MD, Stephanie Haller, Stephen L. Lake, and Daniel B. Magilavy, MD disclose conflicts of interest with Genzyme Biosurgery. Victoria A. Brander, MD discloses conflicts of interest with Genzyme Biosurgery and Pfizer.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Hip: WOMAC pain subscale (WOMAC A) at 26 weeks; Group 1: mean -16.62 (SD 30); n=156, Group 2: mean -13.59 (SD 29.7); n=156; WOMAC pain subscale 0-100 Top=High is poor outcome; Comments: Reports change scores and standard error, converted to standard deviation. Reported HA: -16.62 (2.40). Reported CS: -13.59 (2.38). Baseline HA: 63.06 (1.14). Baseline CS: 63.35 (1.12). Reports that there were 156 people in each intervention arm, but earlier states that the ITT population was 150 in the HA arm, 155 in the CS arm. Likely calculated the mean for all of the people at the end point and subtracted that from the baseline mean with all people (including those not in the ITT population).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, race, Kellgren-Lawrence grade, which knee had symptomatic disease and baseline values for outcomes; Group 1 Number missing: 48, Reason: 313 people randomised. Of those the ITT population forms 305 people with 150 using hylan G-F 20. Of those 48 discontinued: 9 due to adverse events, 3 due to noncompliance, 24 due to wishes to withdraw, 2 were lost to follow up, and 10 for other reasons.; Group 2 Number missing: 61, Reason: 313 people randomised. Of those the ITT population forms 305 people with 155 using methylprednisolone acetate. Of those, 61 discontinued. 11 due to adverse events. 1 due to noncompliance. 41 due to wishes to withdraw. 2 were lost to follow up. 6 for other reasons.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Hip: WOMAC physical function subscale (WOMAC C) at 26 weeks; Group 1: mean -13.8 (SD 29); n=156, Group 2: mean -11.53 (SD 28.7); n=156; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Reports change scores and standard error, converted to standard deviation. Reported HA: -13.80 (2.32). Reported CS: -11.53 (2.30). Baseline HA: 64.42 (1.40). Baseline CS: 63.03 (1.37). Reports that there were 156 people in each intervention arm, but earlier states that the ITT population was 150 in the HA arm, 155 in the CS arm. Likely calculated the mean for all of the people at the end point and subtracted that from the baseline mean with all people (including those not in the ITT population).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, race, Kellgren-Lawrence grade, which knee had symptomatic disease and baseline values for outcomes; Group 1 Number missing: 48, Reason: 313 people randomised. Of those the ITT population forms 305 people with 150 using hylan G-F 20. Of those 48 discontinued: 9 due to adverse events, 3 due to noncompliance, 24 due to wishes to withdraw, 2 were lost to follow up, and 10 for other reasons.; Group 2 Number missing: 61, Reason: 313 people randomised. Of those the ITT population forms 305 people with 155 using methylprednisolone acetate. Of those, 61 discontinued. 11 due to adverse events. 1 due to noncompliance. 41 due to wishes to withdraw. 2 were lost to follow up. 6 for other reasons.
- Actual outcome for Hip: WOMAC physical function subscale (WOMAC C) at 4 weeks; Group 1: mean -18.19 (SD 22.4); n=156, Group 2: mean -26.58 (SD

21.6); n=156; WOMAC physical function subscale 0-100 Top=High is poor outcome; Comments: Reports change scores and standard error, converted to standard deviation. Reported HA: -18.19 (1.79). Reported CS: -26.57 (1.73). Baseline HA: 64.42 (1.40). Baseline CS: 63.03 (1.37). Reports that there were 156 people in each intervention arm, but earlier states that the ITT population was 150 in the HA arm, 155 in the CS arm. Likely calculated the mean for all of the people at the 4 week point and subtracted that from the baseline mean with all people (including those not in the ITT population). Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, race, Kellgren-Lawrence grade, which knee had symptomatic disease and baseline values for outcomes; Group 1 Number missing: 48, Reason: 313 people randomised. Of those the ITT population forms 305 people with 150 using hylan G-F 20. Of those 48 discontinued: 9 due to adverse events, 3 due to noncompliance, 24 due to wishes to withdraw, 2 were lost to follow up, and 10 for other reasons.; Group 2 Number missing: 61, Reason: 313 people randomised. Of those the ITT population forms 305 people with 155 using methylprednisolone acetate. Of those, 61 discontinued. 11 due to adverse events. 1 due to noncompliance. 41 due to wishes to withdraw. 2 were lost to follow up. 6 for other reasons. Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Hip: Serious adverse events at 26 weeks; Group 1: 5/150, Group 2: 4/155; Comments: Reports that "5 people in the hylan G-F 20 group and 4 in the MPA group experienced a serious adverse event. Of these, 1 in each group (hylan G-F 20: spontaneous abortion; MPA: choroidal dystrophy) was considered remotely/unlikely due to treatment; all others were considered unrelated to treatment. There were no deaths or serious adverse events during the study." Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, BMI, gender, race, Kellgren-Lawrence grade, which knee had symptomatic disease and baseline values for outcomes; Group 1 Number missing: 48, Reason: 313 people randomised. Of those the ITT population forms 305 people with 150 using hylan G-F 20. Of those 48 discontinued: 9 due to adverse events, 3 due to noncompliance, 24 due to wishes to withdraw, 2 were lost to follow up, and 10 for other reasons.; Group 2 Number missing: 61, Reason: 313 people randomised. Of those the ITT population forms 305 people with 155 using methylprednisolone acetate. Of those, 61 discontinued. 11 due to adverse events. 1 due to noncompliance. 41 due to wishes to withdraw. 2 were lost to follow up. 6 for other reasons.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Spolidoro paschoal nde 2015[454]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Brazil; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A diagnosis of hand osteoarthritis involving the proximal interphalangeal joints or distal interphalangeal joints according to the American College of Rheumatology criteria
Stratum	Finger
Subgroup analysis within study	Not applicable
Inclusion criteria	People had to fulfill the following inclusion criteria: age older than 40 years; a diagnosis of hand osteoarthritis involving the proximal interphalangeal joints or distal interphalangeal joints according to the American College of Rheumatology criteria; radiographs showing osteophytes in the studied joint; pain between 3cm and 8cm on the visual analogue scale (VAS) for pain (VAS pain at rest 0-10cm) in at least 1 proximal interphalangeal or distal interphalangeal hand joint
Exclusion criteria	People with change in the corticosteroid or nonsteroidal antiinflammatory drugs dosage in the last 30 days; change in drugs for the osteoarthritis treatment (glucosamine, chondroitin, chloroquine, methotrexate) in the last 2 months; intraarticular injectin with corticosteroids in the studied joint in the last 3 months; any change in nonpharmacological hand osteoarthritis treatment in the last 2 months (rehabilitation, acupuncture and others); suspicion of local or systemic infection; clinical or hand radiographs suggesting another cause of hand arthropathy (inflammatory arthritis, psoriatic arthritis, microcrystalline arthropathy, deposit disease) and severe coagulation disorder
Recruitment/selection of patients	Recruited from the outpatient clinic of the Universidade Federal de São Paulo from August 2011 to August 2012.
Age, gender and ethnicity	Age - Mean (SD): 60.7 (8.25). Gender (M:F): 2:58. Ethnicity: Mixed. 42 people were white, 18 were non-white.
Further population details	1. Age: ≥75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear

Extra comments	Severity: Not stated Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular injection with triamcinolone hexacetonide (20mg/mL) and 2% lidocaine without epinephrine (0.3mL dose 6mg of triamcinolone hexacetonide for the PIP, and 0.2mL dose 4mg of triamcinolone hexacetonide for the DIP. Always with 0.1mL of 2% lidocaine.). Both groups only had 1 intraarticular injection in the most symptomatic joint and on a single occasion.. Duration 12 weeks. Concurrent medication/care: Paracetamol (750mg per tablet) were used if required during the follow up period (up to three tablets per day).. Indirectness: No indirectness (n=30) Intervention 2: Placebo. Intraarticular injection with only 2% lidocaine (0.1mL) without epinephrine in its most symptomatic interphalangeal joint.. Duration 12 weeks. Concurrent medication/care: Paracetamol (750mg per tablet) were used if required during the follow up period (up to three tablets per day).. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Finger: AUSCAN pain subscale at 12 weeks; Group 1: mean 5.3 (SD 4.7); n=30, Group 2: mean 7 (SD 4.8); n=30; AUSCAN pain subscale 0-20 Top=High is poor outcome; Comments: Baseline IA corticosteroid: 8.8 (4.8). Baseline IA placebo: 9.2 (4.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: KL grade is worse overall for the placebo group (KL grade (intervention:control), I (4:5), II (7:4), III (8:3); IV (11:18)). People in the placebo group are using more medication on overage. More white people in the placebo group.; Blinding details: Injection performed blindly by covering the needle with opaque adhesives. The observer responsible for patient assessment was completely "blinded". Caregivers may be aware of the amount of liquid injected being different between the groups.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Finger: AUSCAN function subscale at 12 weeks; Group 1: mean 12.3 (SD 9.8); n=30, Group 2: mean 16.7 (SD 9.8); n=30; AUSCAN function subscale 0-36 Top=High is poor outcome; Comments: Baseline IA corticosteroid: 15.4 (10.4). Baseline placebo: 17.9 (8.9).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: KL grade is worse overall for the placebo group (KL grade (intervention:control), I (4:5), II (7:4), III (8:3); IV (11:18)). People in the placebo group are using more medication on overage. More white people in the placebo

group.; Blinding details: Injection performed blindly by covering the needle with opaque adhesives. The observer responsible for patient assessment was completely "blinded". Caregivers may be aware of the amount of liquid injected being different between the groups.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Stahl 2005[455]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Israel; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic trapeziometacarpal joint grade II arthritis, that was diagnosed by clinical presentation and radiographic evaluation of the first carpometacarpal joint
Stratum	Thumb
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic trapeziometacarpal joint grade II arthritis that was diagnosed by clinical presentation and radiographic evaluation of the first carpometacarpal joint
Exclusion criteria	No additional information
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (range): 62 (37-91). Gender (M:F): 6:46. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on range). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Eaton and Littler grade II Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 40mg methylprednisolone acetate (given as a 1mL intraarticular injection). The injection into the joint was performed by the direct dorsal approach after the joint line was identified by palpation.. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=27) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 15mg sodium hyaluronate (Orthovisc) (given as a 1mL intraarticular injection). The injection into the joint was performed by the direct dorsal approach after the joint line was identified by palpation.. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness

Funding	Equipment / drugs provided by industry (The sodium hyaluronate (OrthoVisc) was supplied with courtesy by the RAFA Laboratories, Ltd.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Thumb: Visual analogue scale (pain after activity) at 3 months; Group 1: mean -2.5 (SD 2); n=25, Group 2: mean -2.2 (SD 1.8); n=27; Visual analogue scale (pain after activity) 0-10 Top=High is poor outcome; Comments: Baseline CS: 7.7. Baseline HA: 7.9. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender and states that there was no significant difference in baseline outcome values; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Thumb: Visual analogue scale (pain after activity) at 6 months; Group 1: mean -2.7 (SD 2.2); n=25, Group 2: mean -2.2 (SD 1.9); n=27; Visual analogue scale (pain after activity) 0-10 Top=High is poor outcome; Comments: Baseline CS: 7.7. Baseline HA: 7.9. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender and states that there was no significant difference in baseline outcome values; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Thumb: Adverse events at 6 months; Group 1: 0/25, Group 2: 0/27; Comments: Reports that "there were no side effects of injections in either study group" Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender and states that there was no significant difference in baseline outcome values; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study (subsidiary papers)	Strand 2012[460] (Strand 2016[462], Takamura 2018[466], Takamura 2019[467])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=379)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 13 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis with pain and Kellgren-Lawrence grade 1-3 changes seen by X-ray
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People were 40-80 years of age, with knee osteoarthritis, and pain in the affected knee of more than or equal to 4 weeks of duration while standing or walking; Kellgren-Lawrence grade 1-3 by X-ray; WOMAC pain subscores more than or equal to 40mm in the affected knee and less than or equal to 20mm in the contralateral knee by 100mm visual analogue scale; willing to discontinue current osteoarthritis treatments other than allowed medications
Exclusion criteria	Kellgren Lawrence grade 4 of the treated knee; inflammatory diseases of the knee other than osteoarthritis; severe knee joint effusion; severe malalignment of the knee; history of joint replacement of knee or hip within the previous 12 months; arthroscopy of either knee within 3 months; intraarticular injections with corticosteroids within the past 6 months; and/or serious systemic diseases or infectious/inflammatory skin diseases in the area of the affected knee
Recruitment/selection of patients	Conducted at 28 sites in the US
Age, gender and ethnicity	Age - Mean (SD): 60.7 (10.2). Gender (M:F): 15:224. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 1-3. Duration of symptoms (mean [SD]): 38.3 (48.4) months.
Indirectness of population	No indirectness
Interventions	(n=251) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). A single intraarticular injection of Gel-200 (30mg cross-linked hyaluronic acid in 3.0mL). Duration 1 injection. Concurrent medication/care: NSAIDs, nonprescription herbal therapies, and chondroprotective agents (e.g. oral HA,

	glucosamine, chondroitin sulfate, minocycline) were allowed if people did not change their treatment regimen and continued regular administration at stable doses from 4 weeks prior to randomization throughout the protocol participation. Intermittent use of short-acting oral opiates was also permitted.. Indirectness: No indirectness (n=128) Intervention 2: Placebo. One intraarticular injection of phosphate buffered saline. Duration 1 injection. Concurrent medication/care: NSAIDs, nonprescription herbal therapies, and chondroprotective agents (e.g. oral HA, glucosamine, chondroitin sulfate, minocycline) were allowed if people did not change their treatment regimen and continued regular administration at stable doses from 4 weeks prior to randomization throughout the protocol participation. Intermittent use of short-acting oral opiates was also permitted.. Indirectness: No indirectness
Funding	Study funded by industry (The study was conducted by the Seikagaku Corporation (Japan))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain subscores (mean difference) at 13 weeks; MD; -6.39 (95%CI -12.41 to -0.37) (P-value: 0.037) WOMAC pain subscale (visual analogue scale) 0-100 Top=High is poor outcome, Comments: Appears to use final scores to calculate difference. Negative sign added to indicate direction of effect.;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, study knee, Kellgren-Lawrence X-ray scores, duration of osteoarthiritis, and baseline values for outcomes; Group 1 Number missing: 20, Reason: 2 had no treatment as they did not meet the eligibility criteria, 1 had no post-injection visit, 1 withdrew consent (with no data at all). They then analysed with the other people, of which 16 discontinued. 6 had other treatments, 4 withdrew consent, 2 were lost to follow up, 4 others.; Group 2 Number missing: 9, Reason: 9 discontinued after the trial had started. 1 had other treatments, 5 withdrew consent, 3 were lost to follow up.

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function subscores (mean difference) at 13 weeks; MD; -5.42 (95%CI -11.31 to 0.47) (P-value: 0.071) WOMAC physical function subscale (visual analogue scale) 0-100 Top=High is poor outcome, Comments: Appears to use final values in calculation. Negative sign added to indicate direction of effect.;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, study knee, Kellgren-Lawrence X-ray scores, duration of osteoarthiritis, and baseline values for outcomes; Group 1 Number missing: 20, Reason: 2 had no treatment as they did not meet the eligibility criteria, 1 had no post-injection visit, 1 withdrew consent (with no data at all). They then analysed with the other people, of which 16 discontinued. 6 had other treatments, 4 withdrew consent, 2 were lost to follow up, 4 others.; Group 2 Number missing: 9, Reason: 9 discontinued after the trial had started. 1

had other treatments, 5 withdrew consent, 3 were lost to follow up. Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 13 weeks; Group 1: 8/249, Group 2: 0/128; Comments: 8 people had serious adverse events - these included patient 1: ductal carcinoma (right breast); patient 2: cardiac arrest, respiratory arrest, cryptogenic cirrhosis, acute bilateral pulmonary oedema, respiratory failure, acute renal failure, hypokalaemia; patient 3: transient ischaemic attack; patient 4: exertional dyspnoea, transient blurry vision, dizziness; patient 5: incarcerated right femoral hernia, abdominal pain left side, abdominal pain; patient 6: basal cell carcinoma of the face (left eyelid and cheek), malignant melanoma; patient 7: prostate cancer; patient 8: squamous cell carcinoma Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, study knee, Kellgren-Lawrence X-ray scores, duration of osteoarthiritis, and baseline values for outcomes; Group 1 Number missing: 20, Reason: 2 had no treatment as they did not meet the eligibility criteria. All other people were included in the safety analysis. 1 had no post-injection visit, 1 withdrew consent (with no data at all). 6 had other treatments, 4 withdrew consent, 2 were lost to follow up, 4 others.; Group 2 Number missing: 9, Reason: 9 discontinued after the trial had started. 1 had other treatments, 5 withdrew consent, 3 were lost to follow up.	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Tamir 2001[469]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in Israel; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Idiopathic symptomatic clinical osteoarthritis of the knee as classified according to the Altman criteria and radiologically verified osteoarthritis of the knee (stages 2-4) according to the Kellgren and Lawrence grading system
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults of either sex, between the ages of 60 and 85, with evidence of idiopathic symptomatic clinical OA of the knee as classified according to the Altman criteria and radiologically verified OA of the knee (stages 2-4) according to the Kellgren and Lawrence grading system, but otherwise in good general health as determined by a complete medical history and physical examination, with no previous history of surgical treatment of the joint or of arthroscopy or injections to the knee in the 6 months prior to initiation of the study.
Exclusion criteria	People with knee osteoarthritis originating from an intraarticular fracture; rheumatoid arthritis; joint infection; other inflammatory and metabolic arthritis; OA of the hip joint; people with significant systemic diseases; allergy or atopy; skin conditions that could cause the administration of injections to be problematic; people with copious joint exudates.
Recruitment/selection of patients	Outpatients of the orthopaedic clinic Assaf Harofeh Medical Centre
Age, gender and ethnicity	Age - Other: Mean: 71 years. Gender (M:F): 13:36. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on inclusion criteria). 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grades 2-4. Duration of symptoms: Not explicitly stated
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). BioHy (10mg/mL sodium hyaluronate (average molecular weight

	of 3.0 (0.6) MDa, manufactured by bacterial fermentation). Supplied as a sterile 1% solution in 2mL phosphate buffered saline (pH 6.5-7.5).. Duration 5 weekly injections. Concurrent medication/care: Analgesic or NSAID medications were not deprived before or during the trial. Indirectness: No indirectness (n=24) Intervention 2: Placebo. 2mL of phosphate buffered saline. Duration 5 weekly injections. Concurrent medication/care: Analgesic or NSAID medications were not deprived before or during the trial. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Severe pain due to pain from the needle (leading to withdrawal from the study) at 20 weeks; Group 1: 1/25, Group 2: 0/24 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Appear comparable for sex, age and stage of osteoarthritis. However, no standard deviations.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Tammachote 2016[470]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Thailand; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A diagnosis of knee osteoarthritis by clinical and radiographic evaluations at an orthopaedic clinic
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of symptomatic primary knee osteoarthritis according to the American Rheumatism Association classification criteria for knee osteoarthritis, dissatisfaction with conservative treatment (NSAIDs, oral analgesic drugs, physical therapy, or brace), no lumbar spondylosis with radiculopathy, good cognition, and the ability to understand the study protocol and the agreement to participate
Exclusion criteria	An allergy to any of the medications used in this study; bone-on-bone arthritis appearing on any radiograph; varus or valgus deformity of >5 degrees from the mechanical axis of the knee; previous fracture of surgical procedure of the investigational knee; previous intraarticular injection in the ipsilateral knee in the past 6 months; and current infection in the affected knee.
Recruitment/selection of patients	Performed at Thammasat University Hospital from May 2012 to November 2013
Age, gender and ethnicity	Age - Other: Mean: 61.8 years. Gender (M:F): 20:79. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grades 1-4. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Single injection of Hylan G-F 20 (6mL). The knee was flexed approximately 60 degrees with the person in the supine position with the eyes blinded. The skin was infiltrated with 1mL of 2% lidocaine hydrochloride with 1:80,000 epinephrine. A 21-gauge needle was inserted into the joint capsule. Any effusion was aspirated. A prefilled needle with the study medication was then injected.. Duration 1

	injection. Concurrent medication/care: All people with post-infection pain were provided with a prescription of 35mg orphenadrine citrate and 500mg paracetamol. They were advised to not take any other medication relevant to the treatment of osteoarthritis. (n=55) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Single injection of 1mL 40mg triamcinolone acetonide plus 5mL of 1% lidocaine with epinephrine (6mL in total). The knee was flexed approximately 60 degrees with the person in the supine position with the eyes blinded. The skin was infiltrated with 1mL of 2% lidocaine hydrochloride with 1:80,000 epinephrine. A 21-gauge needle was inserted into the joint capsule. Any effusion was aspirated. A prefilled needle with the study medication was then injected.. Duration 1 injection. Concurrent medication/care: All people with post-infection pain were provided with a prescription of 35mg orphenadrine citrate and 500mg paracetamol. They were advised to not take any other medication relevant to the treatment of osteoarthritis.. Indirectness: No indirectness
Funding	Academic or government funding (Received an internal grant from Thammasat University, but no third party funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 3 months; Group 1: mean 25 (SD 19); n=50, Group 2: mean 20 (SD 21); n=49; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 53 (18). Baseline CS: 51 (15).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported sex, age, BMI, Kellgren-Lawrence grade, and outcome baseline values; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 6, Reason: 6 lost to follow up
- Actual outcome for Knee: Visual analogue scale (pain) at 6 months; Group 1: mean 24 (SD 22); n=50, Group 2: mean 21 (SD 22); n=49; Visual analogue scale (pain) 0-100 Top=High is poor outcome; Comments: Baseline HA: 53 (18). Baseline CS: 51 (15).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported sex, age, BMI, Kellgren-Lawrence grade, and outcome baseline values; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 6, Reason: 6 lost to follow up

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Knee pain and swelling at 6 months; Group 1: 1/50, Group 2: 0/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported sex, age, BMI, Kellgren-Lawrence grade, and

outcome baseline values; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 6, Reason: 6 lost to follow up	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Tasciotaoglu 2003[473]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Idiopathic osteoarthritis according to the American College of Rheumatology criteria with grade II to III radiographic changes according to the Kellgren-Lawrence grading system
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Idiopathic osteoarthritis according to American College of Rheumatology criteria with grade 2-3 knee osteoarthritis confirmed radiologically according to the Kellgren-Lawrence grading system. In all people pain under weight-bearing was more than 40mm on a horizontal visual analogue scale.
Exclusion criteria	Kellgren-Lawrence grade IV radiological changes; knee joint disease other than osteoarthritis; osteoarthritis of the hip joint; osteoarthritic involvement of the foot joints; serious concomitant systemic diseases; intraarticular injections within the 3 months prior to study; skin infections overlying the joint; intraarticular fluid effusion; history of allergy or hypersensitivity to drugs; treatment with anticoagulants; previous knee surgery.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 58.8 (7.8). Gender (M:F): 0:60. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grades 2-3. Duration of symptoms (mean [SD]): 6.4 (4.4) years
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular hyaluronic acid - 3 weekly injections of 2mL sodium hyaluronate (15mg/mL, Orthovisc, high molecular weight of 1-2.9 million Da). Duration 3 injections over 3 weeks. Concurrent medication/care: People were allowed to use paracetamol (to a maximum of 3 grams daily) during the study period. None was

	permitted for at least 48 hours before each injection and clinical assessment.. Indirectness: No indirectness (n=30) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). 1mL 6-methylprednisolone acetate (40mg/mL) given by intraarticular injection weekly for 3 weeks. Duration 3 injections over 3 weeks. Concurrent medication/care: People were allowed to use paracetamol (to a maximum of 3 grams daily) during the study period. None was permitted for at least 48 hours before each injection and clinical assessment.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: Pain on walking (visual analogue scale) at 3 months; Group 1: mean 32.03 (SD 22.15); n=28, Group 2: mean 50.46 (SD 18.46); n=27; Visual analogue scale (pain at rest) 0-100 Top=High is poor outcome; Comments: Baseline HA: 67.60 (21.03). Baseline CS: 69.00 (21.96). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, disease duration, BMI, Kellgren-Lawrence grade and baseline values for outcomes; Group 1 Number missing: 2, Reason: 1 withdrew due to adverse event (pain). 1 not available for follow up.; Group 2 Number missing: 3, Reason: 1 withdrew due to adverse event (pain). 2 not available for follow up. - Actual outcome for Knee: Pain on walking (visual analogue scale) at 6 months; Group 1: mean 51.16 (SD 20.81); n=28, Group 2: mean 66.06 (SD 20.83); n=27; Visual analogue scale (pain on walking) 0-100 Top=High is poor outcome; Comments: Baseline HA: 67.60 (21.03). Baseline CS: 69.00 (21.96). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, disease duration, BMI, Kellgren-Lawrence grade and baseline values for outcomes; Group 1 Number missing: 2, Reason: 1 withdrew due to adverse event (pain). 1 not available for follow up.; Group 2 Number missing: 3, Reason: 1 withdrew due to adverse event (pain). 2 not available for follow up. Protocol outcome 2: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Increased pain leading to discontinuation from the study at 6 months; Group 1: 1/30, Group 2: 1/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, disease duration, BMI, Kellgren-Lawrence grade and baseline values for outcomes; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Tekeoglu 1998[475]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Kellgren Lawrence stage 1-4 and presence of knee pain
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of radiographic osteoarthritis (Kellgren scale) and presence of pain
Exclusion criteria	Knee joint disease other than OA; history of allergy; skin infections; other intraarticular treatments in the three weeks prior to the study
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 58 (5.8). Gender (M:F): 0:40. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Moderate to severe. Kellgren-Lawrence grade 2-3. Duration of symptoms: 54.0 (24.9) weeks.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 3 intraarticular injections of 20mg of sodium hyaluronate in phosphate buffer (Orthovisc).. Duration 3 injections over 3 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=20) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Three intraarticular betamethasone injections (3mg/mL) - Celestone choronodose.. Duration 3 injections over 3 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus

INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Adverse local or systemic reactions at 12 weeks; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports sex, age, weight, height, duration of the disease, presence of effusion, radiological severity, clinical severity; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Pain reduction at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Trueba davalillo 2015[485]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis diagnosed with an applicable medical history and proven on radiography
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women from 40 years to 85 years of age suffering from knee OA, with radiographic OA grade II-III according to Kellgren and Lawrence with a body mass index (BMI) <35kg/m²
Exclusion criteria	History of trauma or surgery on the target knee, inflammatory arthritis, microcrystalline arthropathies, previous unspecific knee synovitis, knee infection, angular deformity >10 degrees, and neoplasia, as well as other conditions where the administration of corticosteroids would be specifically contraindicated such as diabetes mellitus, and metabolic syndrome
Recruitment/selection of patients	Recruited between April 2008 and February 2011
Age, gender and ethnicity	Age - Mean (SD): 62.8 (0.6). Gender (M:F): 84:116. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-3. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Intraarticular injections of 2.5mL of 1% hyaluronic acid with a mean molecular weight of 900,000 Da, obtained by a fermentation process from Streptococcus zoopidemicus strains - five injections over five weeks. Duration 5 injections over 5 weeks. Concurrent medication/care: Concomitant treatment with glucosamine sulfate1500mg and meloxicam 15mg for 1 month. Once completed people were prescribed glucosamine 1500mg and chondroitic sulfate 1200mg for an additional month. In case of continued pain during follow up, paracetamol was allowed

	for up to 3g/day. Indirectness: No indirectness (n=100) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). IA injections of betametasone dipropionate 5.0mg and betamethasone sodium phosphate 2.0mg in 1mL (Diprospan Hypack) as two injections (on day 0 and in the fourth week). Duration 2 injections, 1 on day 0, 1 on week 4. Concurrent medication/care: Concomitant treatment with glucosamine sulfate1500mg and meloxicam 15mg for 1 month. Once completed people were prescribed glucosamine 1500mg and chondroitic sulfate 1200mg for an additional month. In case of continued pain during follow up, paracetamol was allowed for up to 3g/day. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED)

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 3 months; Group 1: mean 2.4 (SD 2.3); n=97, Group 2: mean 7.4 (SD 2.2); n=98; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 15.3 (2.7). Baseline CS: 14.8 (3.1).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, Kellgren-Lawrence grade and painful knee side; Group 1 Number missing: 3, Reason: 3 people excluded for no efficacy data at follow up. They included data for the other people who did not complete the study: 5 lost at follow up, 2 had knee arthroplasty and 1 died; Group 2 Number missing: 2, Reason: 2 had no efficacy data at follow up. They included data for the other people who did not complete the study: 3 had lost at follow up, 1 had knee arthroplasty, 1 died, 2 used drugs not permitted
- Actual outcome for Knee: WOMAC pain at 12 months; Group 1: mean 8.3 (SD 2.5); n=97, Group 2: mean 12.8 (SD 3.1); n=98; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Baseline HA: 15.3 (2.7). Baseline CS: 14.8 (3.1).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, Kellgren-Lawrence grade and painful knee side; Group 1 Number missing: 3, Reason: 3 people excluded for no efficacy data at follow up. They included data for the other people who did not complete the study: 5 lost at follow up, 2 had knee arthroplasty and 1 died; Group 2 Number missing: 2, Reason: 2 had no efficacy data at follow up. They included data for the other people who did not complete the study: 3 had lost at follow up, 1 had knee arthroplasty, 1 died, 2 used drugs not permitted

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function at 3 months; Group 1: mean 19.1 (SD 4.6); n=97, Group 2: mean 24.9 (SD 4.8); n=98; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 53.2 (4.0). Baseline CS: 48.4 (4.8).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, Kellgren-Lawrence grade and painful knee side; Group 1 Number missing: 3, Reason: 3 people excluded for no efficacy data at follow up. They included data for the other people

who did not complete the study: 5 lost at follow up, 2 had knee arthroplasty and 1 died; Group 2 Number missing: 2, Reason: 2 had no efficacy data at follow up. They included data for the other people who did not complete the study: 3 had lost at follow up, 1 had knee arthroplasty, 1 died, 2 used drugs not permitted - Actual outcome for Knee: WOMAC physical function at 12 months; Group 1: mean 27.8 (SD 4.6); n=97, Group 2: mean 41.9 (SD 4.9); n=98; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Baseline HA: 53.2 (4.0). Baseline CS: 48.4 (4.8). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, Kellgren-Lawrence grade and painful knee side; Group 1 Number missing: 3, Reason: 3 people excluded for no efficacy data at follow up. They included data for the other people who did not complete the study: 5 lost at follow up, 2 had knee arthroplasty and 1 died; Group 2 Number missing: 2, Reason: 2 had no efficacy data at follow up. They included data for the other people who did not complete the study: 3 had lost at follow up, 1 had knee arthroplasty, 1 died, 2 used drugs not permitted Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Pain at 12 months; Group 1: 4/100, Group 2: 2/100 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, Kellgren-Lawrence grade and painful knee side; Group 1 Number missing: 0, Reason: 3 people excluded for no efficacy data at follow up. They included data for the other people who did not complete the study: 5 lost at follow up, 2 had knee arthroplasty and 1 died; Group 2 Number missing: 0, Reason: 2 had no efficacy data at follow up. They included data for the other people who did not complete the study: 3 had lost at follow up, 1 had knee arthroplasty, 1 died, 2 used drugs not permitted	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Vaishya 2017[494]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=82)
Countries and setting	Conducted in India; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Moderate OA knee with Kellgren Lawrence grade 2-3 changes
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People with moderate OA knee, Kellgren-Lawrence grade 2 and 3
Exclusion criteria	People with systemic disorders such as diabetes and thyroid disorder; inflammatory arthritis; major axial deviation at the knee joint (varus >5, valgus >5), haematological diseases (e.g. coagulopathy); severe cardiovascular diseases; any infective foci anywhere in the body; immunosuppression; malignancy; age >80 years; previous IA injection use
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): Not stated. States that people with an age >80 years were excluded. Gender (M:F): 28:54. Ethnicity: Not stated
Further population details	1. Age: Not stated / Unclear 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Moderate Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). IA hyaluronate (6mL, 48mg) (Synvisc-one, Sanofi, Genzyme). Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=40) Intervention 2: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Intraarticular 30mg triamcinolone hexacetate (THA). Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness

Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) Protocol outcome 1: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: KSS pain score at 12 weeks; Group 1: mean 80.24 (SD 19.6); n=42, Group 2: mean 68.82 (SD 19.6); n=40; Knee society score 0-100 Top=High is good outcome; Comments: Reports means and p values. Reported HA: 80.24. Reported CS: 68.82. P=<0.01. Baseline HA: 60.14. Baseline CS: 55.92. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, unilateral/bilateral status, and Kellgren Lawrence grade; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Knee: KSS pain score at 24 weeks; Group 1: mean 76.8 (SD 25.8); n=42, Group 2: mean 61.75 (SD 25.8); n=42; Knee society score pain subscale 0-100 Top=High is good outcome; Comments: Reports means and p values. Reported HA: 76.8. Reported CS: 61.75. P=<0.01. Baseline HA: 60.14. Baseline CS: 55.92. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, unilateral/bilateral status, and Kellgren Lawrence grade; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Physical function at ≤3- or >3- months - Actual outcome for Knee: KSS function score at 12 weeks; Group 1: mean 73.9 (SD 14.8); n=42, Group 2: mean 65.25 (SD 14.8); n=40; Knee society score function subscale 0-100 Top=High is good outcome; Comments: Reports means and p values. Reported HA: 73.9. Reported CS: 65.25. P=<0.01. Baseline HA: 52.92. Baseline CS: 50.62. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, unilateral/bilateral status, and Kellgren Lawrence grade; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Knee: KSS function score at 24 weeks; Group 1: mean 70.6 (SD 22.5); n=42, Group 2: mean 57.5 (SD 22.5); n=40; Knee society score function subscale 0-100 Top=High is good outcome; Comments: Reports means and p values. Reported HA: 70.6. Reported CS: 57.5. P=<0.01. Baseline HA: 52.92. Baseline CS: 50.62. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, unilateral/bilateral status, and Kellgren Lawrence grade; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months; Serious adverse events at ≤3- or >3- months

Study	Van der weegen 2015[496]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=196)
Countries and setting	Conducted in Netherlands; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Mild to moderate knee osteoarthritis according to the American College of Rheumatology diagnostic criteria. Confirmed by a standard anteroposterior radiograph.
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People in good general health with knee OA according to the American College of Rheumatology diagnostic criteria
Exclusion criteria	People with bilateral knee osteoarthritis if they had a ≤25mm difference in VAS pain score on the 50m walk test; people with a VAS score <30 or >89; people with hip OA or any other condition interfering with the assessment of effectiveness; people with prior HA treatment and people who had within the previous 3 months had intraarticular injections of any type or arthroscopy surgery.
Recruitment/selection of patients	People were recruited from two hospitals
Age, gender and ethnicity	Age - Mean (SD): 59.4 (9.9). Gender (M:F): 99:97. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Mild to moderate Duration of symptoms: 65.3 (90.4) months
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). 3 injections in weekly intervals of 2mL 1.5% sodium hyaluronate (fermathron plus) produced from the bacterium Streptococcus equi by continuous fermentation. Molecular weight of 2.2 MDa. 15mg sodium hyaluronate, 8.5mg sodium chloride, 0.28mg disodium hydrogen orthophosphate dihydrate, 0.044mg sodium dihydrogen phosphate dihydrate and water for injection.. Duration 3 injections over 3 weeks. Concurrent medication/care: Rescue medication in the form of paracetamol only. Indirectness: No indirectness

	(n=97) Intervention 2: Placebo. 3 injections over 3 weeks of 2mL placebo - 8.5mg sodium chloride, 0.28mg disodium hydrogen orthophosphate dihydrate, 0.044mg sodium dihydrogen phosphate dihydrate and water for injection.. Duration 3 injections over 3 weeks. Concurrent medication/care: Rescue medication in the form of paracetamol only. Indirectness: No indirectness
Funding	Study funded by industry (States that multiple authors were in receipt of payment (direct or indirect) from institutes in the biomedical field)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: WOMAC pain at 3 months; Group 1: mean 4.7 (SD 4.9); n=99, Group 2: mean 5.1 (SD 4.9); n=97; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Reports means and p values. Reported HA: 4.7. Reported placebo: 5.1. P value: 0.57. Baseline values not reported.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, symptom duration, baseline WOMAC score (aggregate only - does not report baseline values for the subscales), VAS pain at rest and walking, knee flexion, KL score ; Group 1 Number missing: 3, Reason: All counted for in the analysis. 2 lost to follow up (without reason), 1 discontinued (for unforseen work committment.; Group 2 Number missing: 1, Reason: All counted for the in analysis. 1 lost to follow up (without reason).
- Actual outcome for Knee: WOMAC pain at 6 months; Group 1: mean 2.6 (SD 2); n=99, Group 2: mean 2.8 (SD 2); n=97; WOMAC pain subscale 0-20 Top=High is poor outcome; Comments: Reports means and p values. Reported HA: 2.6. Reported placebo: 2.8. P value: 0.49. Baseline values not reported.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, symptom duration, baseline WOMAC score (aggregate only - does not report baseline values for the subscales), VAS pain at rest and walking, knee flexion, KL score ; Group 1 Number missing: 3, Reason: All counted for in the analysis. 2 lost to follow up (without reason), 1 discontinued (for unforseen work committment.; Group 2 Number missing: 1, Reason: All counted for the in analysis. 1 lost to follow up (without reason).

Protocol outcome 2: Physical function at ≤3- or >3- months
- Actual outcome for Knee: WOMAC physical function at 3 months; Group 1: mean 15.6 (SD 15); n=99, Group 2: mean 16.2 (SD 15); n=97; WOMAC physical function subscale 0-68 Top=High is poor outcome; Comments: Reports means and p values. Reported HA: 15.6. Reported placebo: 16.2. P value: 0.78. Baseline values not reported.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, symptom duration, baseline WOMAC score (aggregate only - does not report baseline values for the subscales), VAS pain at rest and walking, knee flexion, KL score ; Group 1 Number missing: 3, Reason: All counted for in the analysis. 2 lost to follow up (without reason), 1 discontinued (for unforseen work committment.; Group 2 Number missing: 1, Reason: All counted for the in analysis. 1 lost to follow up (without reason).
- Actual outcome for Knee: WOMAC physical function at 6 months; Group 1: mean 20.3 (SD 18.5); n=99, Group 2: mean 19.9 (SD 18.5); n=97; WOMAC

physical function subscale 0-68 Top=High is poor outcome; Comments: Reports means and p values. Reported HA: 20.3. Reported placebo: 19.9. P value: 0.88. Baseline values not reported. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Does not report baseline values for outcomes. Therefore, even though the baselines appear comparable, the risk of domain bias for selection has been set to high.; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, symptom duration, baseline WOMAC score (aggregate only - does not report baseline values for the subscales), VAS pain at rest and walking, knee flexion, KL score ; Group 1 Number missing: 3, Reason: All counted for in the analysis. 2 lost to follow up (without reason), 1 discontinued (for unforseen work committment.; Group 2 Number missing: 1, Reason: All counted for the in analysis. 1 lost to follow up (without reason). Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 6 months; Group 1: 0/99, Group 2: 0/97 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Reports gender, age, BMI, symptom duration, baseline WOMAC score (aggregate only - does not report baseline values for the subscales), VAS pain at rest and walking, knee flexion, KL score ; Group 1 Number missing: 3, Reason: All counted for in the analysis. 2 lost to follow up (without reason), 1 discontinued (for unforseen work committment.; Group 2 Number missing: 1, Reason: All counted for the in analysis. 1 lost to follow up (without reason).	
Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Vega 2015[503]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Kellgren Lawrence grade 2-4 chronic knee osteoarthritis that was unresponsive to conventional treatments
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	Grade 2-4 osteoarthritis, identified by two different observers, according to the Kellgren-Lawrence grading scale; chronic knee pain of mechanical origin; absence of local or general infection; haematological and biochemical analyses with no significant alterations that contraindicate intervention; the person is able to understand the nature of the study; informed written consent provided by the person
Exclusion criteria	Age >75 or <18 years, or legally dependent; signs of infection or positive serology for HIV, hepatitis, or syphilis; congenital or acquired diseases leading to significant knee deformities that may interfere with cell application or the interpretation of results; obesity with a body mass index >30 (calculated as mass in kg/height in m^2); pregnancy or breast-feeding; neoplasia; immunosuppression; intraarticular injection of any drug during the previous 3 months; participation in another clinical trial or treatment with another investigational product within 30 days prior to inclusion in the study; other conditions that may, according to medical criteria, discourage participation in the study
Recruitment/selection of patients	People were recruited from either Valladolid University Hospital or at Barcelona Teknon Medical Center
Age, gender and ethnicity	Age - Mean (range): 57.0 (36-73). Gender (M:F): 11:19. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren Lawrence grade 2-4. Duration of symptoms: Not stated
Indirectness of population	No indirectness

Interventions	(n=15) Intervention 1: Intra-articular stem cell therapy - Intra-articular stem cell therapy (non-image guided). Bone marrow mesenchymal stem cells (40 x10^6 cells/knee from a 5 x10^5 cell/mL suspension by medial parapatellar injection). Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=15) Intervention 2: Intra-articular hyaluronic acid - Intra-articular hyaluronic acid (non-image guided). Hyaluronic acid (60mg in 3mL, Durolane). Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Academic or government funding (Financial support was provided by the Program for Support of Independent Clinical Research of the Spanish Ministerio de Sanidad (EC11-309), Red de Terapia Celular (RD06/0010/0000 and RD12/0019/0036) of the Instituto de Salud Carlos III, Ministerio de Economia y Competitividad, and the Centro en Red de Medicina Regenerativa de Castilla y León)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR STEM CELL THERAPY (NON-IMAGE GUIDED) versus INTRA-ARTICULAR HYALURONIC ACID (NON-IMAGE GUIDED)

Protocol outcome 1: Quality of life at ≤3- or >3- months
- Actual outcome for Knee: SF-12 physical component summary at 3 months; Group 1: mean 43 (SD 11); n=15, Group 2: mean 39 (SD 8); n=15; SF-12 physical component 0-100 Top=High is good outcome; Comments: Baseline value not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports, age, sex, side of osteoarthritis, and osteoarthritis grade; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Knee: SF-12 physical component summary at 12 months; Group 1: mean 45 (SD 11); n=15, Group 2: mean 40 (SD 8); n=15; SF-12 physical component summary 0-100 Top=High is good outcome; Comments: Baseline value not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports, age, sex, side of osteoarthritis, and osteoarthritis grade; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Knee: SF-12 mental component summary at 3 months; Group 1: mean 47 (SD 10); n=15, Group 2: mean 50 (SD 10); n=15; SF-12 mental component summary 0-100 Top=High is good outcome; Comments: Baseline value not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports, age, sex, side of osteoarthritis, and osteoarthritis grade; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Knee: SF-12 mental component summary at 12 months; Group 1: mean 40 (SD 8); n=15, Group 2: mean 45 (SD 11); n=15; SF-12 mental component summary 0-100 Top=High is good outcome; Comments: Baseline value not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports, age, sex, side of osteoarthritis, and osteoarthritis grade; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain reduction at ≤3- or >3- months - Actual outcome for Knee: WOMAC pain subscale at 12 months; Group 1: mean 30 (SD 15.5); n=15, Group 2: mean 44 (SD 23.2); n=15; WOMAC pain subscale 0-100 Top=High is poor outcome; Comments: Reports mean (SE), calculated SE from this. Reported stem cells: 30 (4). Reported HA: 44 (6). Baseline stem cells: 46 (4). Baseline HA: 50 (4). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports, age, sex, side of osteoarthritis, and osteoarthritis grade; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Serious adverse events at ≤3- or >3- months - Actual outcome for Knee: Serious adverse events at 12 months; Group 1: 0/15, Group 2: 0/15; Comments: No definition of serious adverse events Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports, age, sex, side of osteoarthritis, and osteoarthritis grade; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Study	Yavuz 2012[529]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with knee pain who met the American College of Rheumatology criteria with radiological grade 2 or other changed by the Kellgren and Lawrence classification
Stratum	Knee
Subgroup analysis within study	Not applicable
Inclusion criteria	People (55-75 years old) presenting with complaints of knee pain who met the American College of Rheumatology criteria for knee osteoarthritis, with pain severity of ≤5 by 0-10 visual analogue scale, and radiological grade 2 and over by Kellgren-Lawrence classification
Exclusion criteria	People who were administered intraarticular steroid in the last 3 months; people with serious concomitant medical diseases (uncontrolled DM, uncontrolled hypertension, previous SVO, chronic renal failure); people with secondary arthritis; people who were planned to undergo knee surgery in the next 3 months; people with contraindications to intraarticular corticosteroids (infection, anticoagulant treatment, hypersensitivity to lidocaine); people who use systemic steroids.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 60.3 (6.2). Gender (M:F): 44:76. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Diagnostic method: Diagnosed with imaging 3. Multimorbidities: Not stated / Unclear
Extra comments	Severity: Not explicitly stated. Kellgren-Lawrence grade 2-4. Duration of symptoms: Not stated
Indirectness of population	No indirectness
Interventions	(n=90) Intervention 1: Intra-articular corticosteroids - Intra-articular corticosteroids (non-image guided). Three groups received corticosteroids - these were pooled for this analysis. Group 1 received 3mg of betamethasone disodium phosphate/1mL; group 2 received 40mg of triamcinolone acetonide/1mL; group 3 received 40mg of methylprednisolone acetate in 1mL. 30 people were in each group (total = 90)..

	Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness (n=30) Intervention 2: Placebo. Intraarticular physiological 0.09% serum/1mL. Duration 1 injection. Concurrent medication/care: No additional information. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTICULAR CORTICOSTEROIDS (NON-IMAGE GUIDED) versus PLACEBO

Protocol outcome 1: Pain reduction at ≤3- or >3- months
- Actual outcome for Knee: Visual analogue scale (pain) at 12 weeks; Group 1: mean 5.4 (SD 1.4); n=90, Group 2: mean 7.4 (SD 1.7); n=30; Visual analogue scale 0-10 Top=High is poor outcome; Comments: Reported triamcinolone: 5.7 (1.5). Reported betamethasone: 5.6 (1.2). Reported methylprednisolone: 5.0 (1.3). Baseline triamcinolone: 7.5 (1.5). Baseline betamethasone: 7.6 (1.6). Baseline methylprednisolone: 7.7 (1.6). Baseline placebo: 7.6 (1.6).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex and Kellgren-Lawrence grade; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Serious adverse events at ≤3- or >3- months
- Actual outcome for Knee: Local or systemic complications associated with injections at 12 weeks; Group 1: 0/90, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex and Kellgren-Lawrence grade; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at ≤3- or >3- months; Physical function at ≤3- or >3- months; Psychological distress at ≤3- or >3- months; Osteoarthritis flares at ≤3- or >3- months

Appendix E – Forest plots

E.1 Hip osteoarthritis

E.1.1 Intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)

Figure 2: Pain (VAS, 0-100, high is poor, change score) at ≤3 months

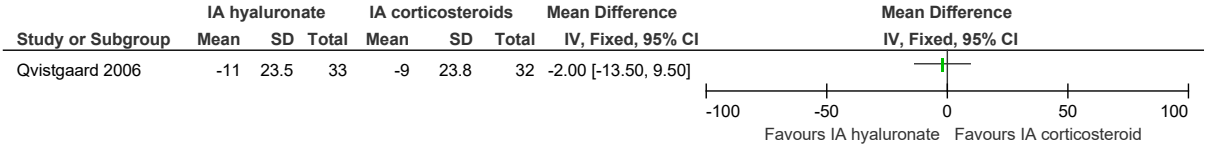


Figure 3: Pain (WOMAC, 0-100, high is poor, change score) at >3 months

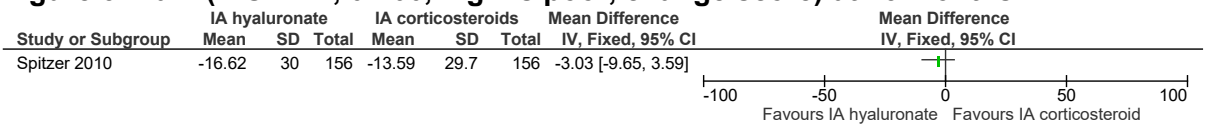


Figure 4: Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months

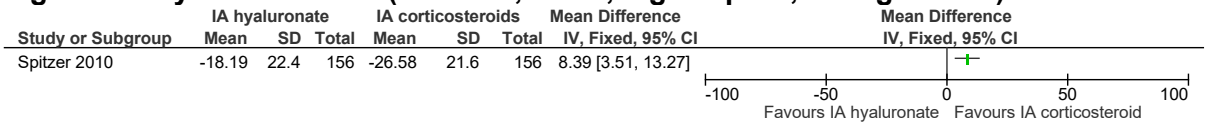


Figure 5: Physical function (WOMAC, 0-100, high is poor, change score) at >3 months

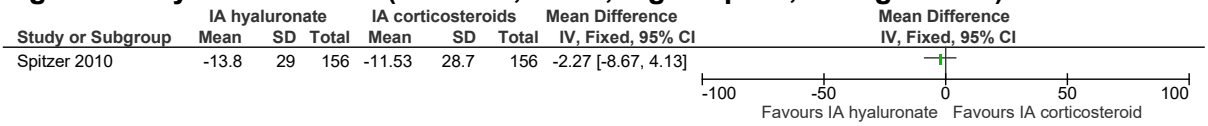


Figure 6: Osteoarthritis flares at ≤3 months

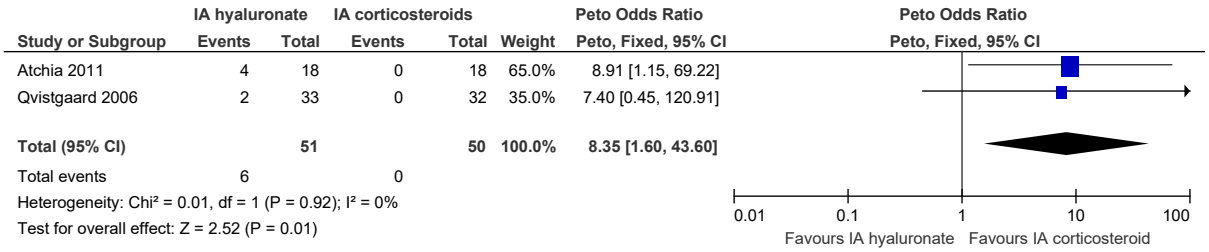


Figure 7: Serious adverse events at ≤3 months

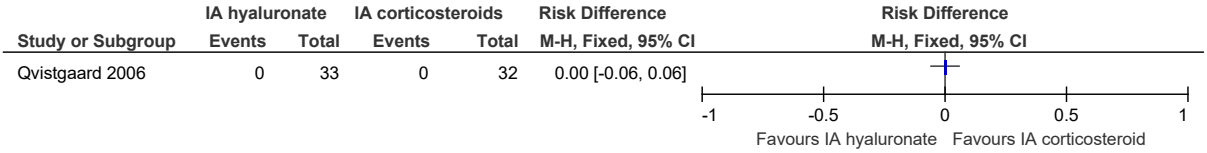
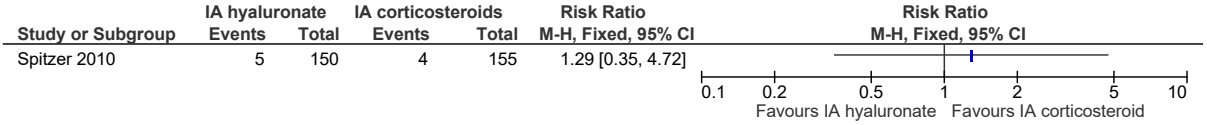


Figure 8: Serious adverse events at >3 months



E.1.2 Intra-articular hyaluronic acid (image guided) compared to placebo

Figure 9: Pain (VAS, 0-10, high is poor, final value) at ≤3 months

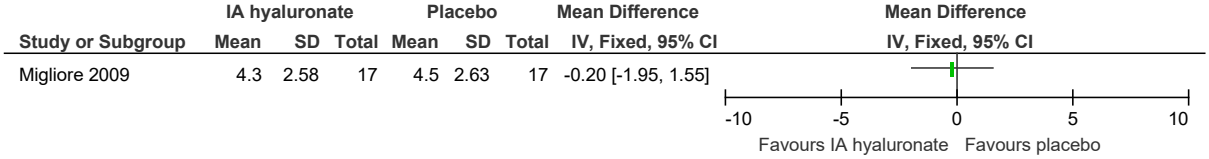


Figure 10: Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months

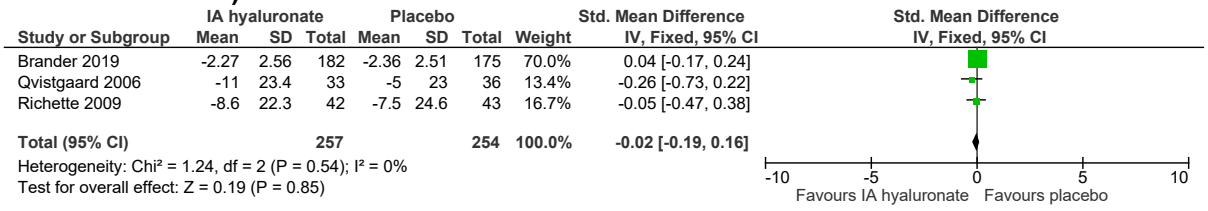


Figure 11: Pain (VAS, 0-10, high is poor, final value) at >3 months

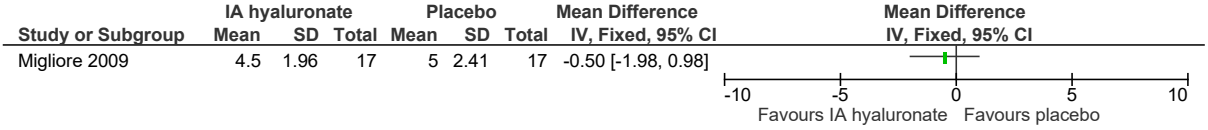


Figure 12: Pain (WOMAC, 0-11, high is poor, change score) at >3 months

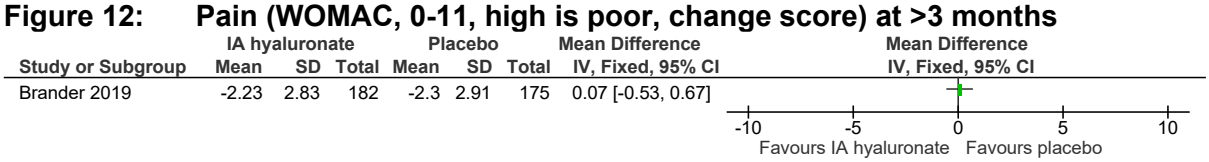


Figure 13: Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months

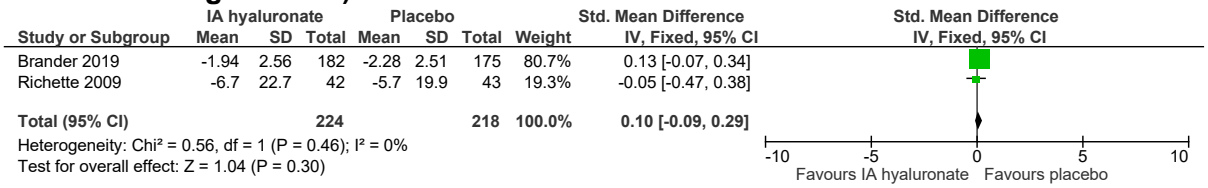


Figure 14: Physical function (WOMAC, 0-11, high is poor, change score) at >3 months

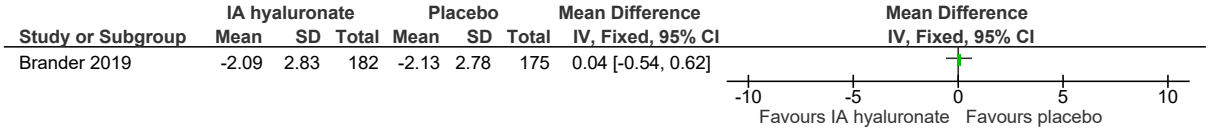


Figure 15: Osteoarthritis flares at ≤3 months

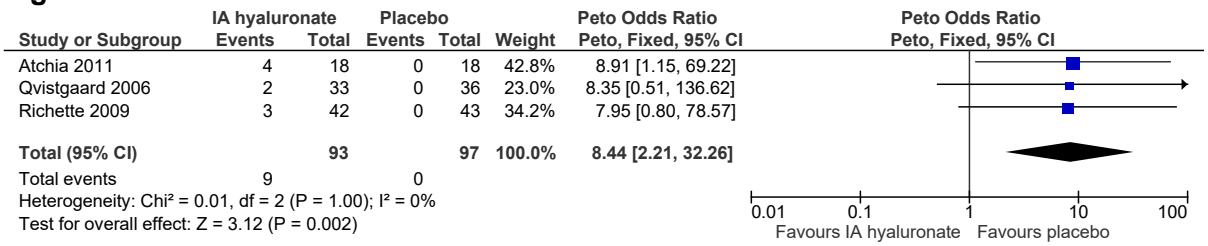


Figure 16: Serious adverse events at ≤3 months

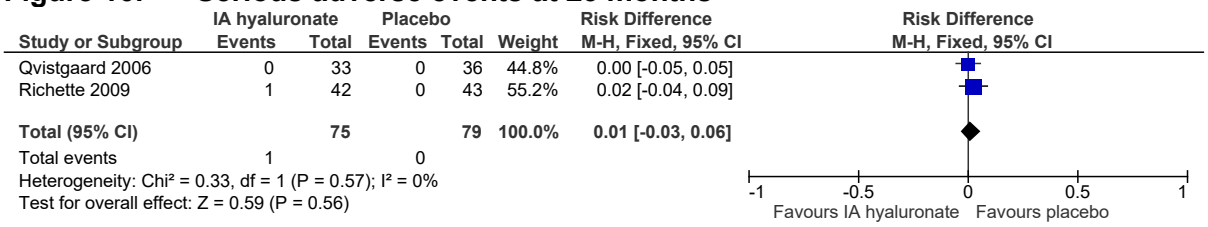
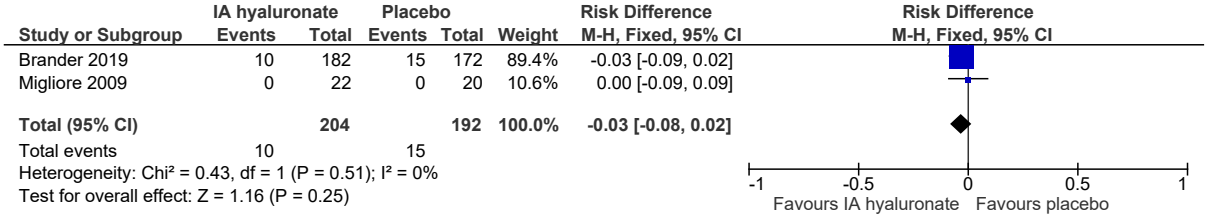


Figure 17: Serious adverse events at >3 months



E.1.3 Intra-articular corticosteroids (image guided) compared to placebo

Figure 18: Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months

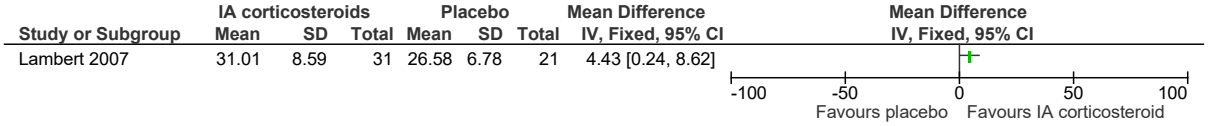


Figure 19: Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months

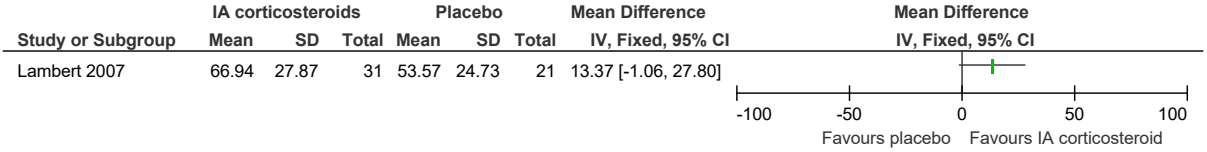


Figure 20: Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months

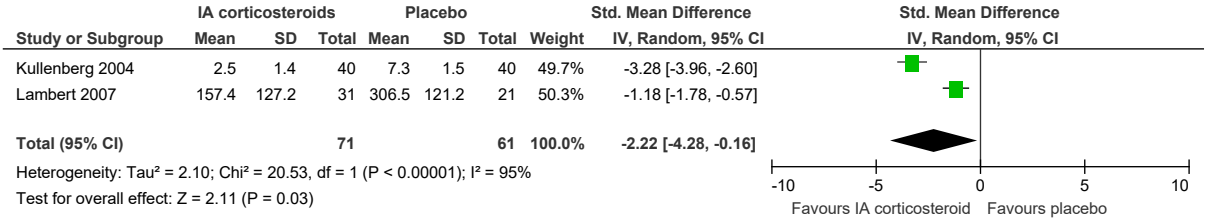


Figure 21: Pain (VAS, 0-100, high is poor, change score) at ≤3 months

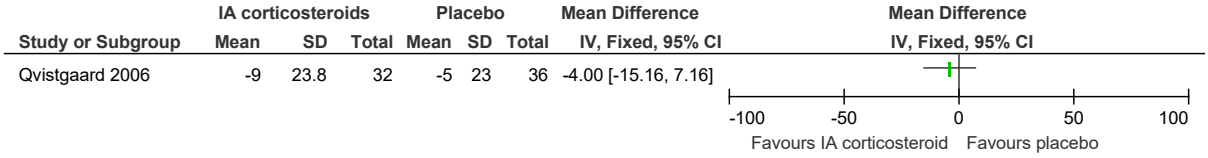


Figure 22: Physical function (WOMAC, Katz and Akpom functional ability [different scale ranges], high is poor, final values) at ≤3 months

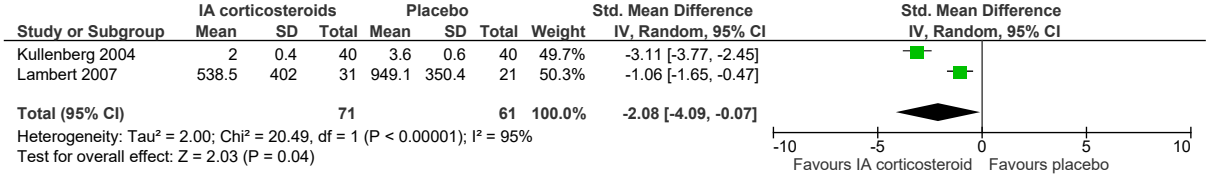


Figure 23: Osteoarthritis flares at ≤3 months

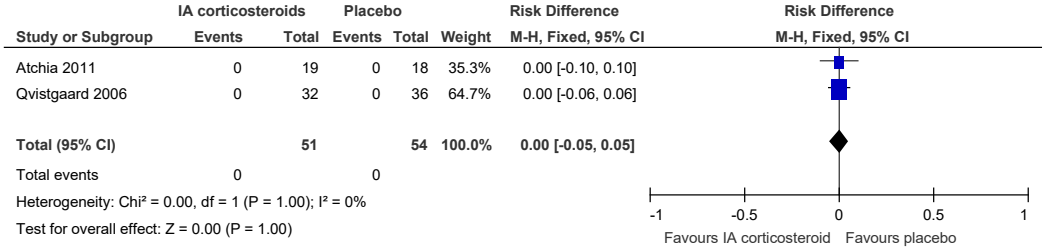
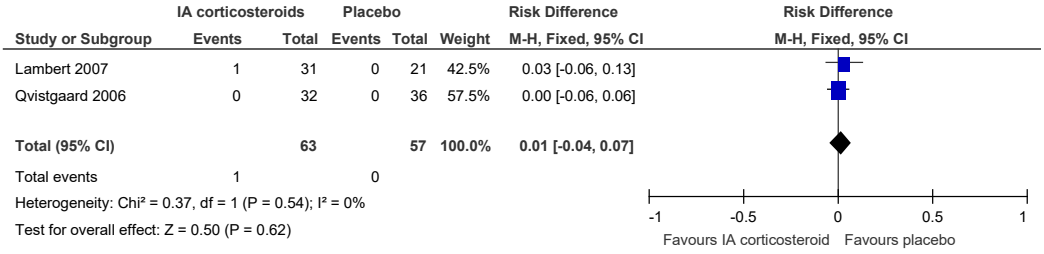


Figure 24: Serious adverse events at ≤3 months



E.2 Knee osteoarthritis

E.2.1 Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Figure 25: Quality of life (SF-36, 0-100, high is good, final values) at ≤3 months

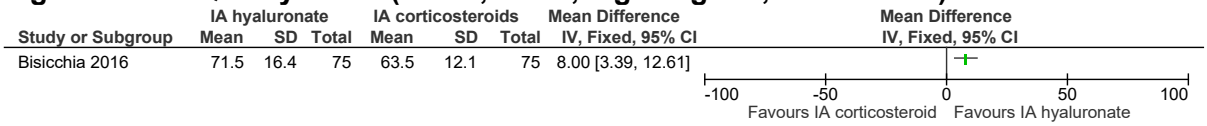


Figure 26: Quality of life (SF-36, 0-100, high is good, final values) at >3 months

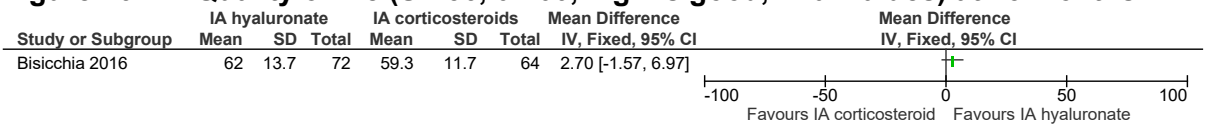


Figure 27: Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months

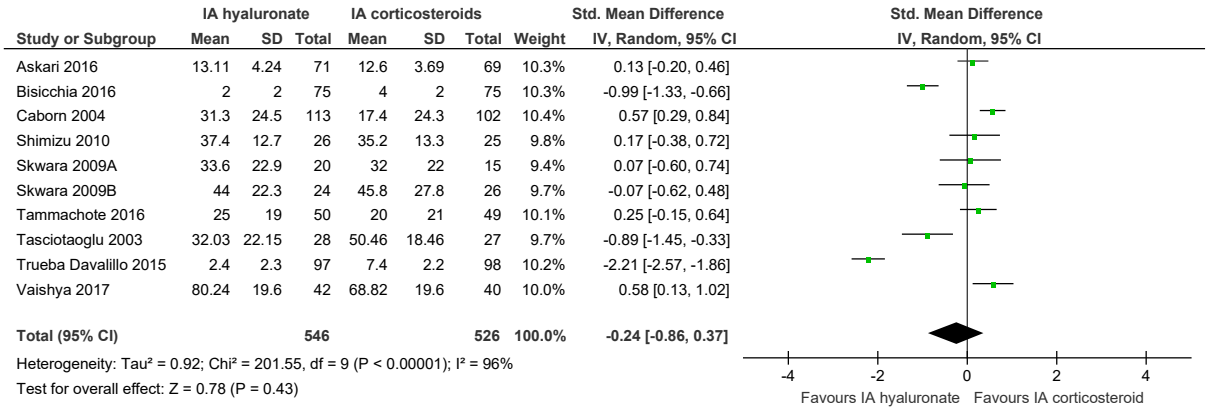


Figure 28: Pain (KSS pain, VAS, 0-100, high is poor, final values) at >3 months

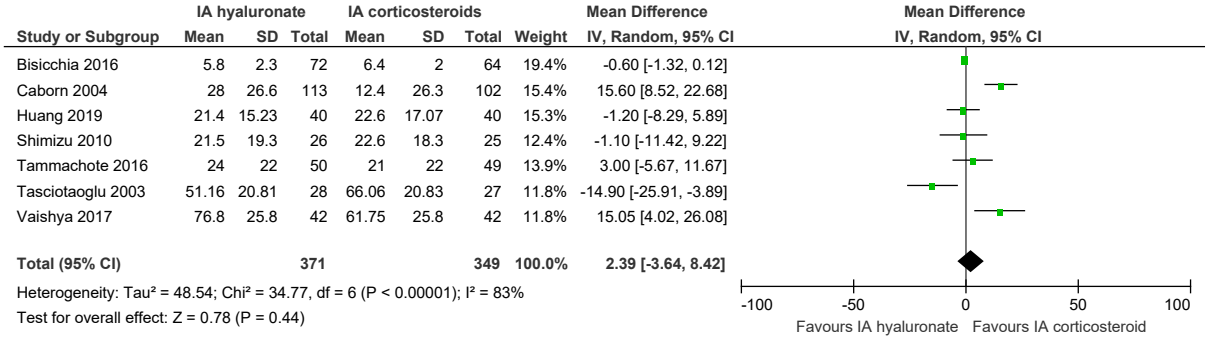


Figure 29: Pain (WOMAC, 0-20, high is poor, final values and change scores) at >3 months

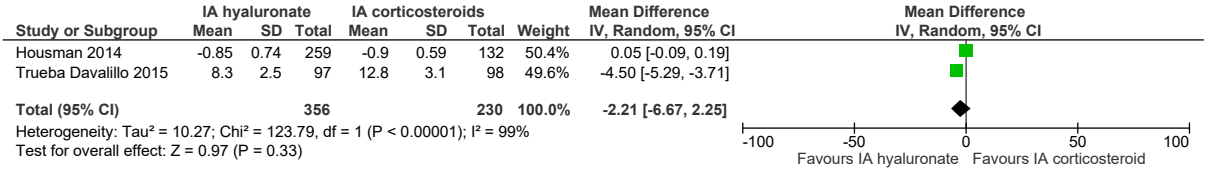


Figure 30: Physical function (WOMAC physical function, Knee society score function subscale [different scale ranges], high is poor, final values) at ≤3 months

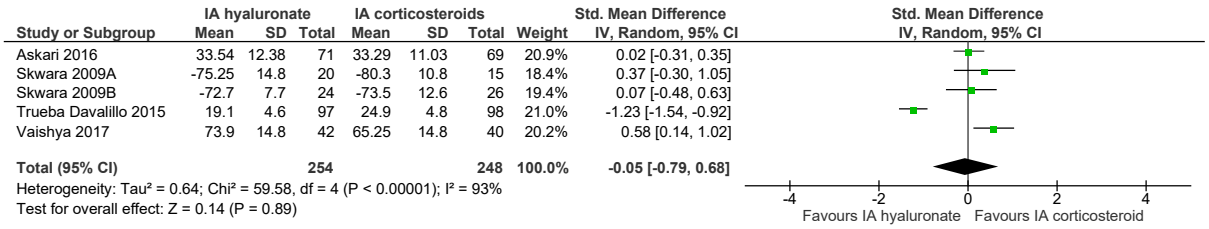


Figure 31: Physical function (WOMAC physical function, KSS function subscale [different scale ranges], high is poor, final values) at >3 months

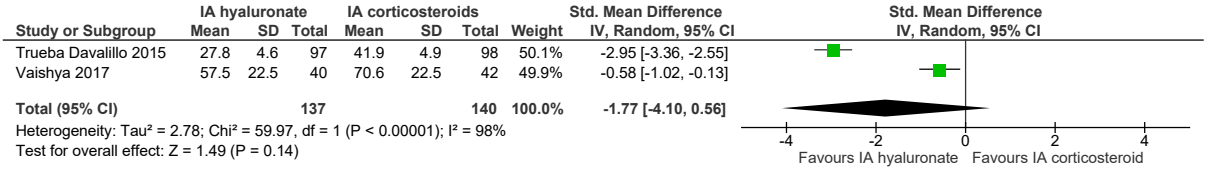


Figure 32: Serious adverse events at ≤3 months

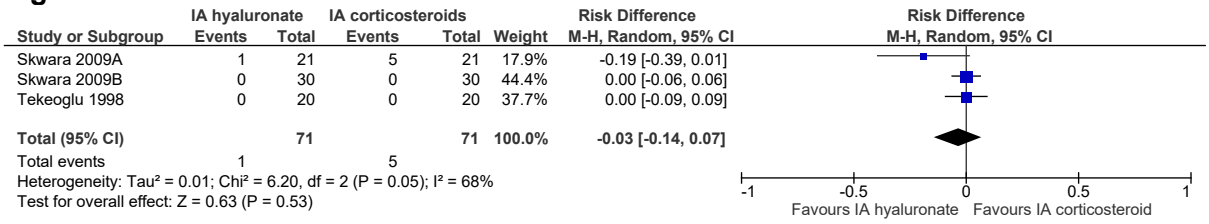
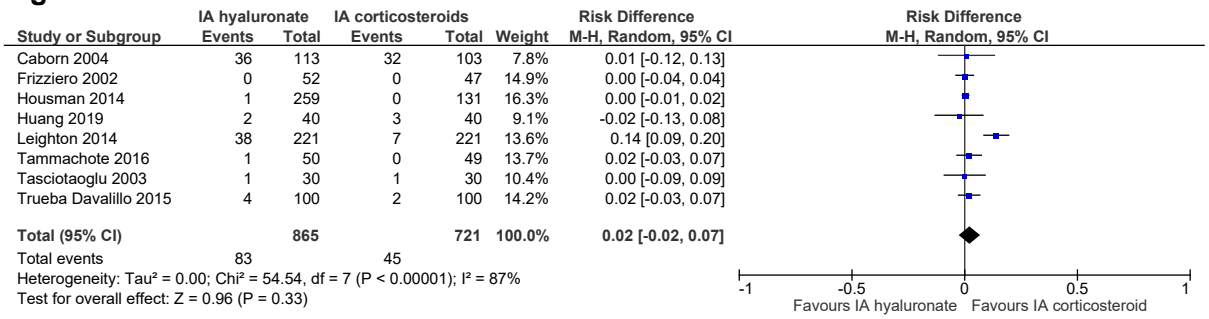


Figure 33: Serious adverse events at >3 months



E.2.2 Intra-articular hyaluronic acid (non-image guided) compared to placebo

Figure 34: Quality of life (KOOS, 0-100, high is poor) at >3 months

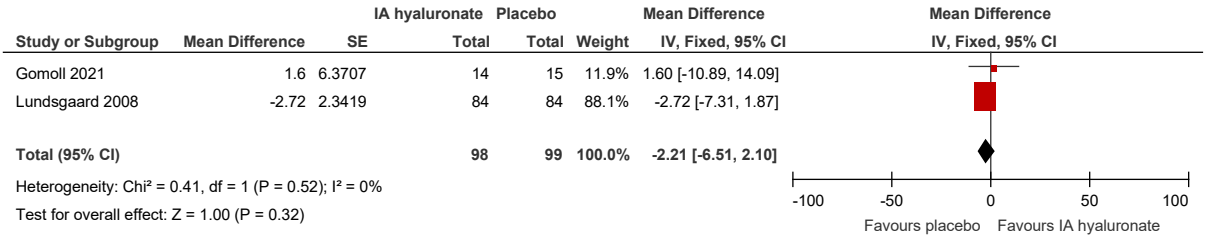


Figure 35: Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months

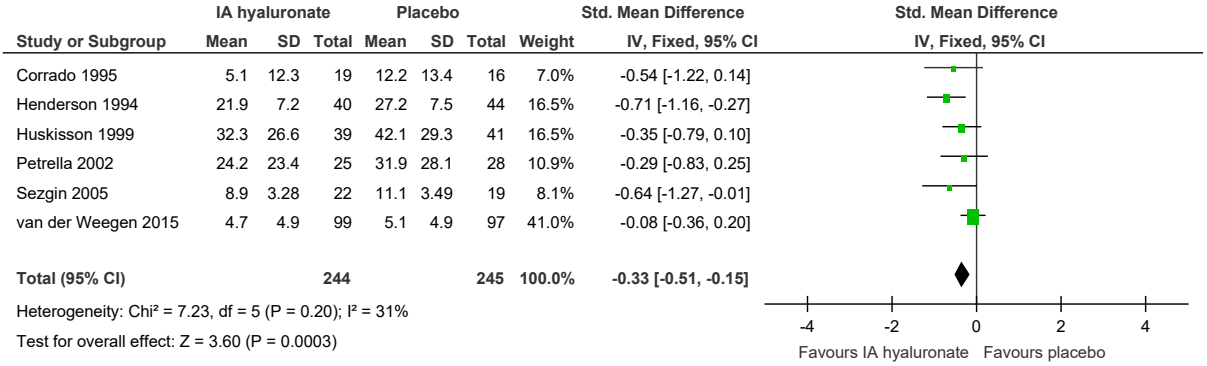


Figure 36: Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months

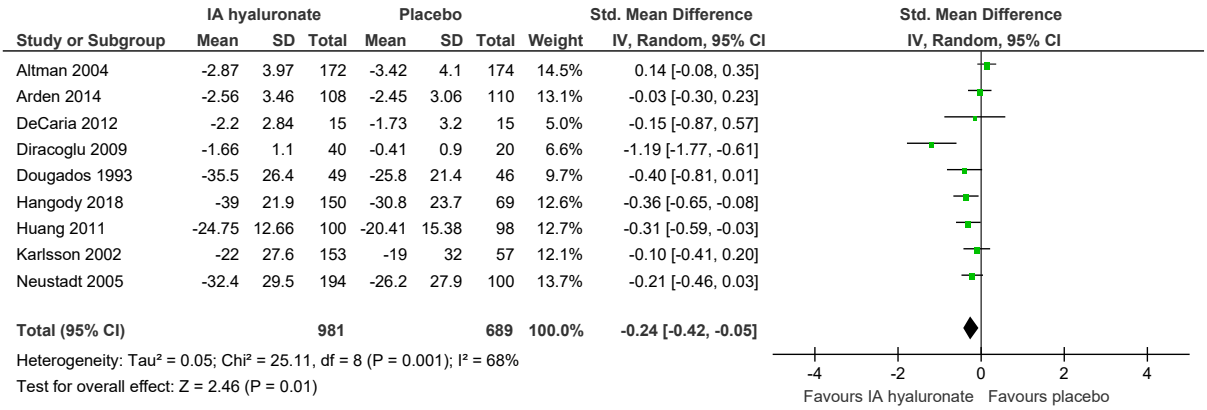


Figure 37: Pain (VAS [different scale ranges], high is poor, final values) at ≤3 months

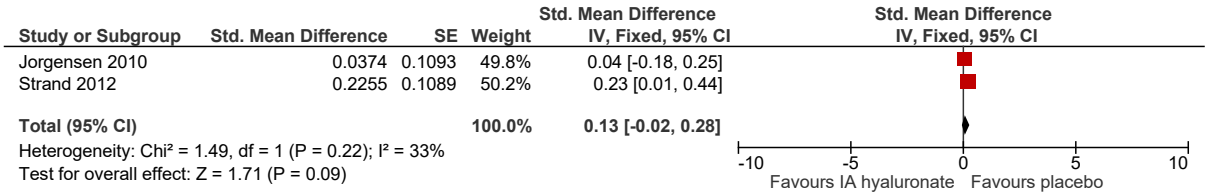


Figure 38: Pain (VAS, 0-100, high is poor, final values and change scores) at >3 months

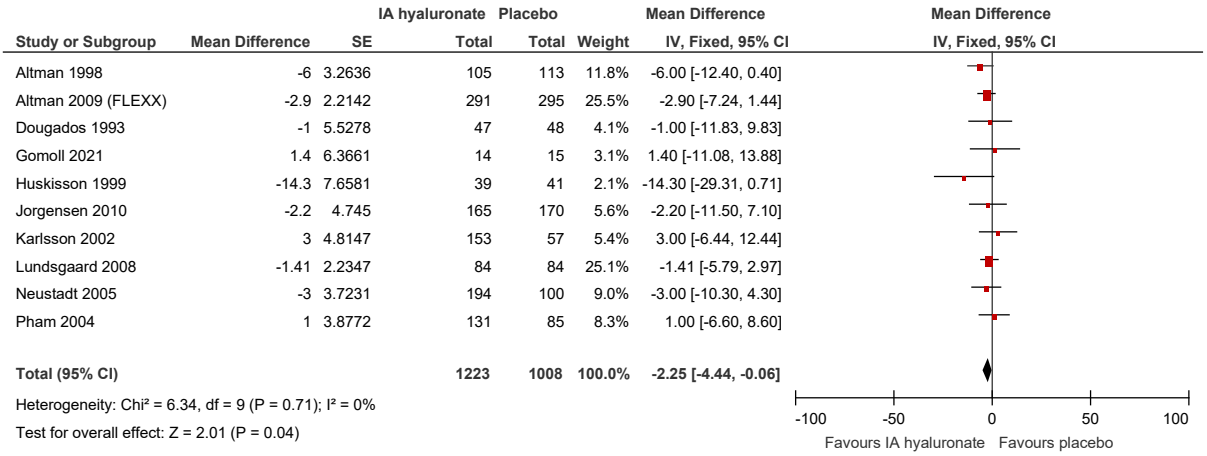


Figure 39: Pain (WOMAC, 0-20, high is poor, final values) at >3 months

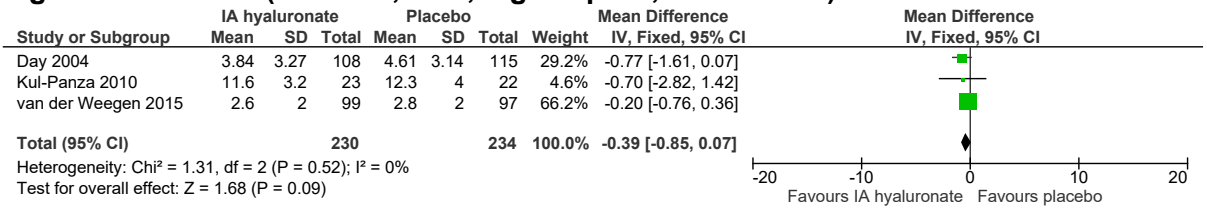


Figure 40: Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months

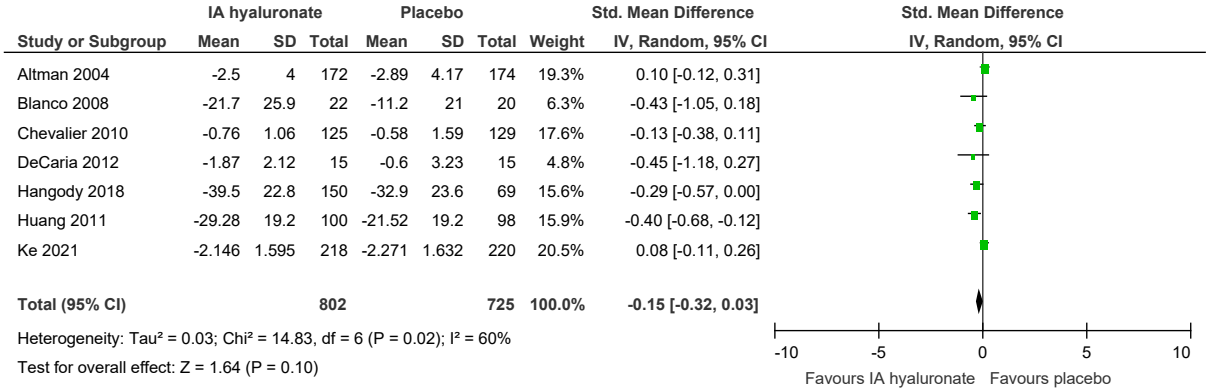


Figure 41: Physical function (WOMAC-VAS disability and physical function subscale, 0-10, high is poor, final values) at ≤3 months

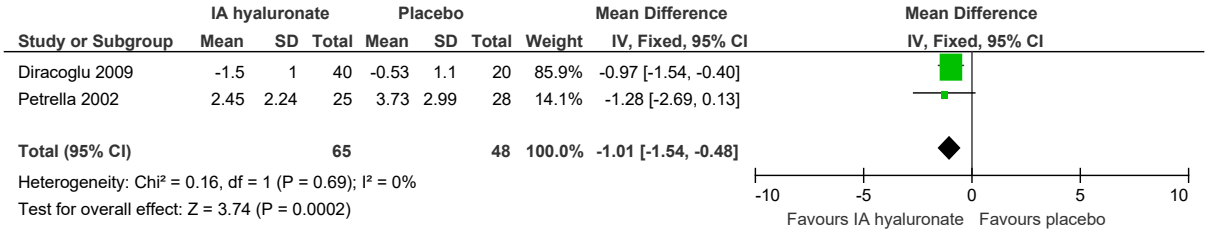


Figure 42: Physical function (WOMAC, 0-68, high is poor, change scores and final values) at ≤3 months

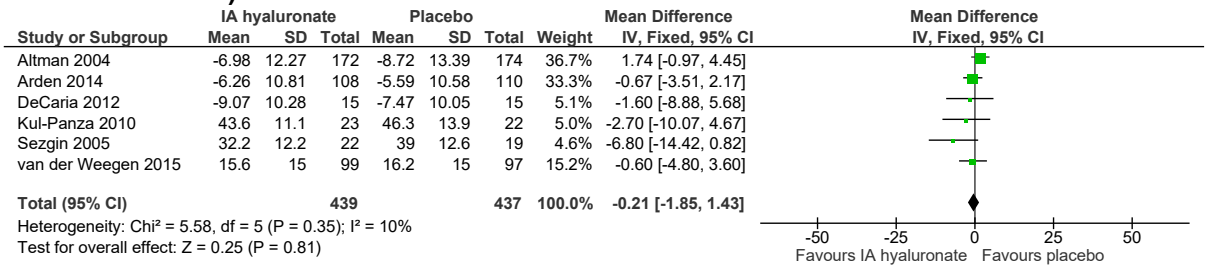


Figure 43: Physical function (WOMAC, 0-100, high is poor, final values) at ≤3 months

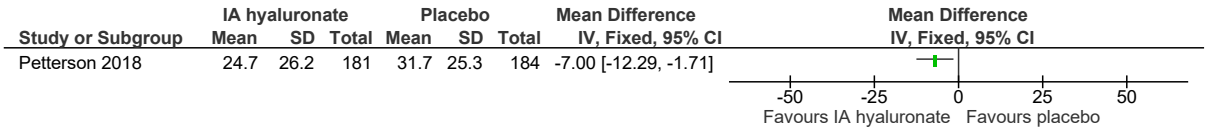


Figure 44: Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months

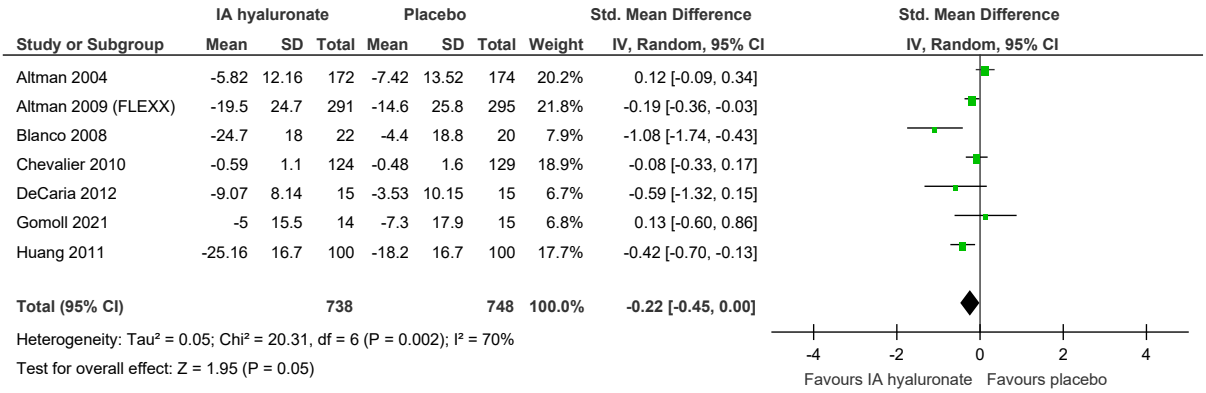


Figure 45: Physical function (WOMAC, 0-68, high is poor, final values) at >3 months

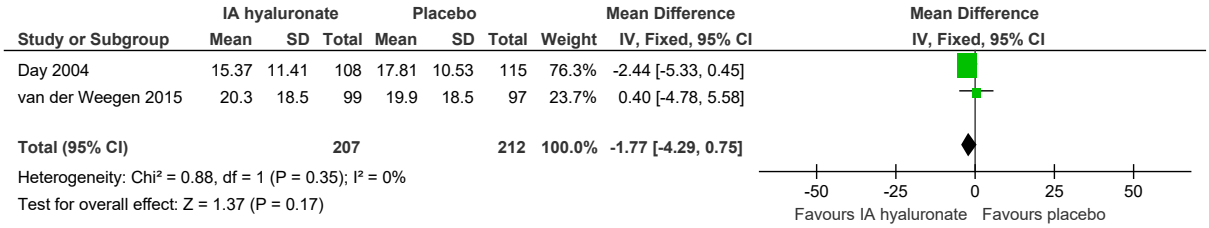


Figure 46: Physical function (KOOS activities subscale, WOMAC, 0-100, high is poor) at >3 months

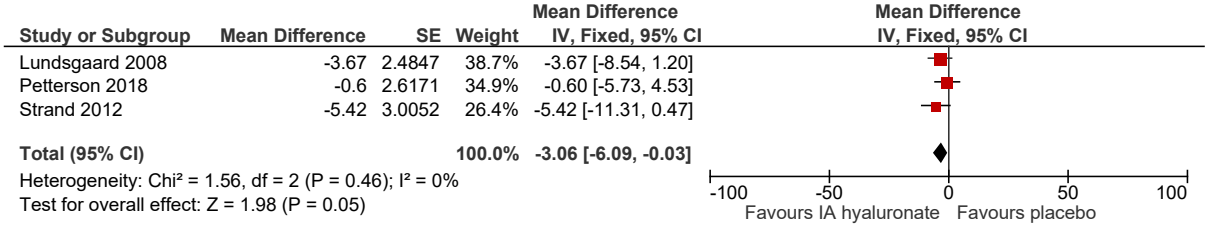


Figure 47: Osteoarthritis flare-up at >3 months

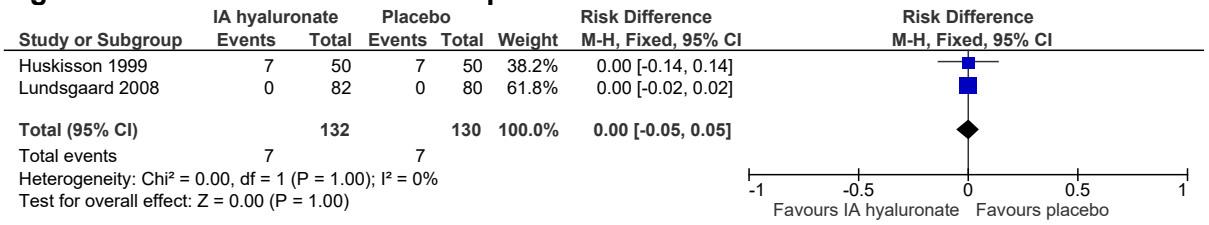
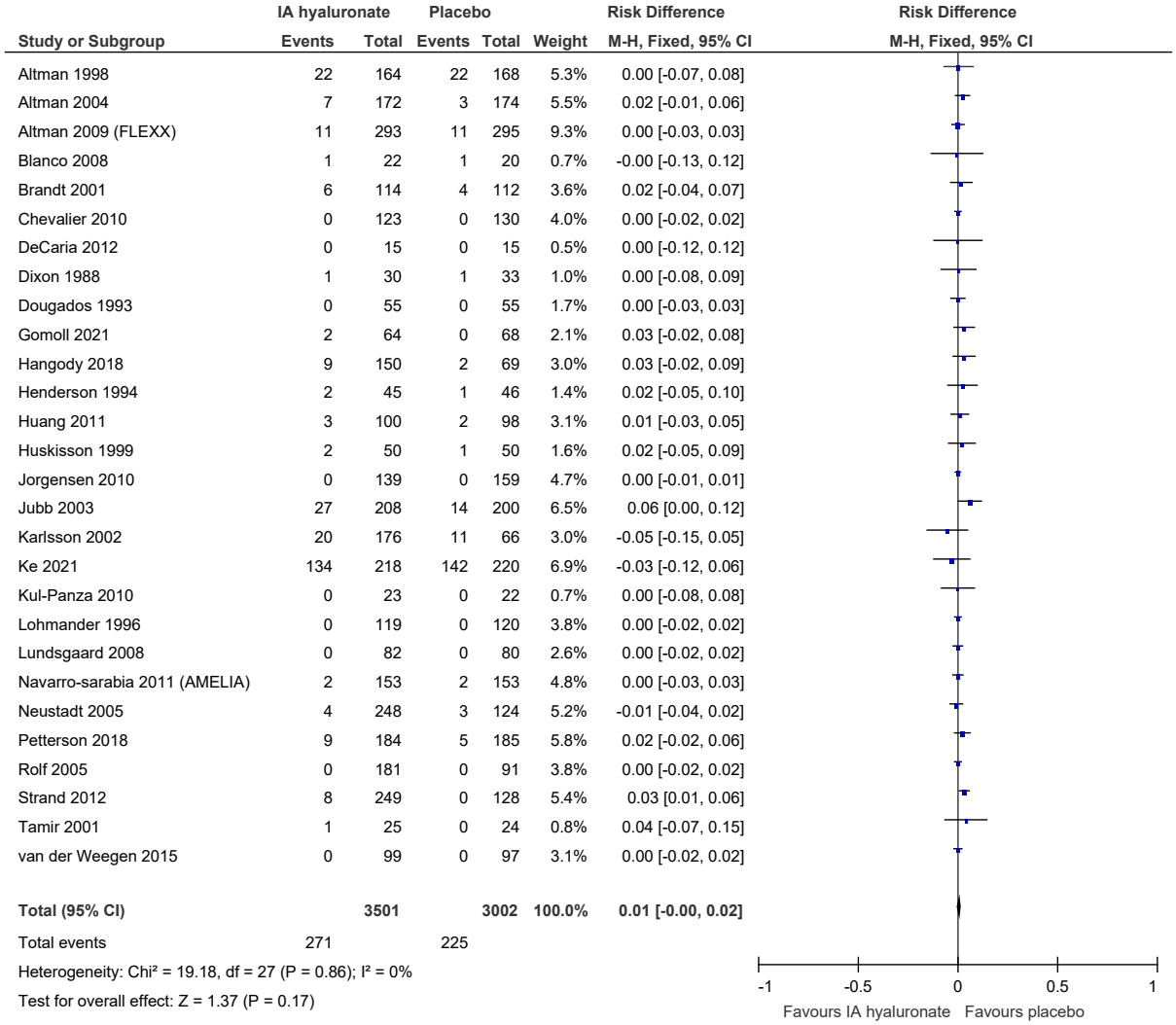


Figure 48: Serious adverse events at ≤3 months

Figure 49: Serious adverse events at >3 months



E.2.3 Intra-articular corticosteroids (non-image guided) compared to placebo

Figure 50: Quality of life (KOOS, 0-100, high is good, final values) at ≤3 months

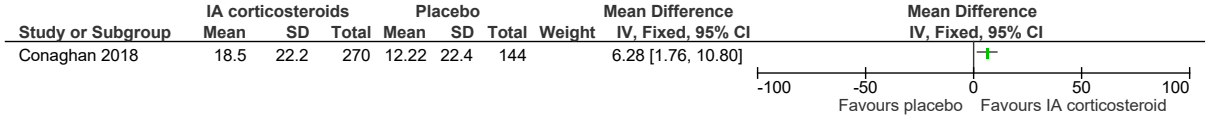


Figure 51: Quality of life (KOOS, 0-100, high is good, final values) at >3 months

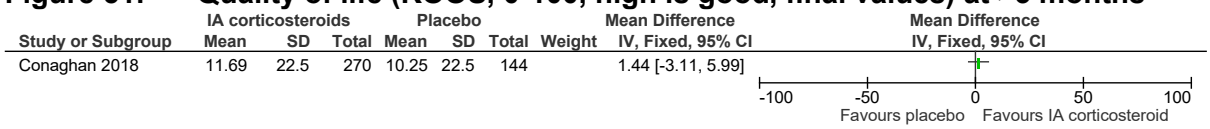


Figure 52: Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months

Study or Subgroup	IA corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gaffney 1995	35.8	26.8	42	42.9	26	42	25.0%	-0.27 [-0.70, 0.16]
Mendes 2019	5.3	4.2	35	7.4	5.1	35	24.2%	-0.44 [-0.92, 0.03]
Shrestha 2018	68	12	57	69	11	60	26.2%	-0.09 [-0.45, 0.28]
Yavus 2012	54	14	90	74	17	30	24.7%	-1.34 [-1.79, -0.90]
Total (95% CI)			**224**			**167**	**100.0%**	**-0.53 [-1.07, 0.02]**

Heterogeneity: Tau² = 0.26; Chi² = 19.77, df = 3 (P = 0.0002); I² = 85%
Test for overall effect: Z = 1.89 (P = 0.06)

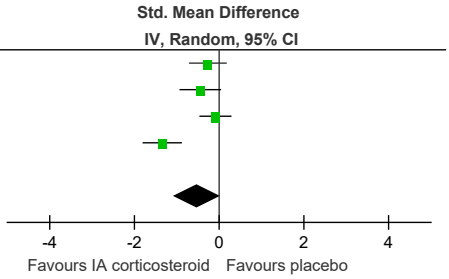


Figure 53: Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	IA corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chao 2010	-1	2.8	30	-0.2	2.2	29	34.6%	-0.31 [-0.83, 0.20]
Conaghan 2018	-0.791	0.89	314	-0.5	0.88	154	48.8%	-0.33 [-0.52, -0.13]
Lyons 2005	-53.9	26.7	10	-7	26.7	10	16.6%	-1.68 [-2.73, -0.63]
Total (95% CI)			**354**			**193**	**100.0%**	**-0.55 [-1.07, -0.03]**

Heterogeneity: Tau² = 0.13; Chi² = 6.21, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 2.07 (P = 0.04)

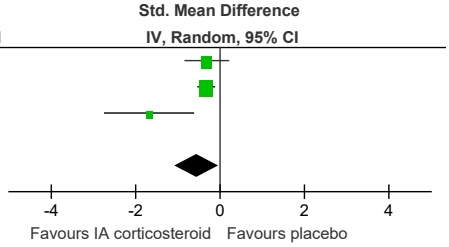


Figure 54: Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months

Study or Subgroup	IA corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Conaghan 2018	-0.59	0.59	299	-0.49	0.07	149	43.1%	-0.21 [-0.40, -0.01]
McAlindon 2017	-1.2	2.8	70	-1.9	2.8	70	33.1%	0.25 [-0.08, 0.58]
Raynauld 2003	-11.4	19.2	33	-13.8	21.5	33	23.8%	0.12 [-0.37, 0.60]
Total (95% CI)			**402**			**252**	**100.0%**	**0.02 [-0.30, 0.34]**

Heterogeneity: Tau² = 0.05; Chi² = 5.93, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 0.13 (P = 0.90)

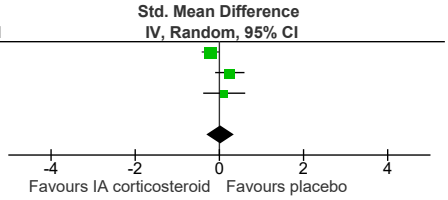


Figure 55: Physical function (Health assessment questionnaire for lower limb function, WOMAC [different scale ranges], high is poor, final values) at ≤3 months

Study or Subgroup	IA corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gaffney 1995	4.5	2.3	42	4.2	2	40	32.8%	0.14 [-0.30, 0.57]
Mendes 2019	17	12.4	35	23.3	15.1	35	30.6%	-0.45 [-0.93, 0.02]
Shrestha 2018	47.1	11.3	57	53.2	12.5	60	36.6%	-0.51 [-0.88, -0.14]
Total (95% CI)			**134**			**135**	**100.0%**	**-0.28 [-0.69, 0.13]**

Heterogeneity: Tau² = 0.08; Chi² = 5.52, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 1.34 (P = 0.18)

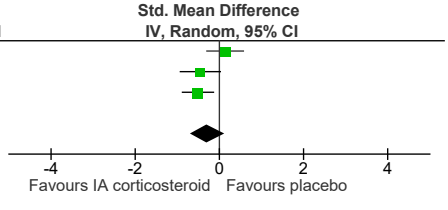


Figure 56: Physical function (WOMAC, 0-4, high is poor, change scores) at ≤3 months

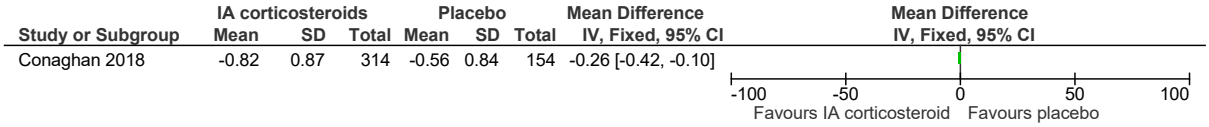


Figure 57: Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months

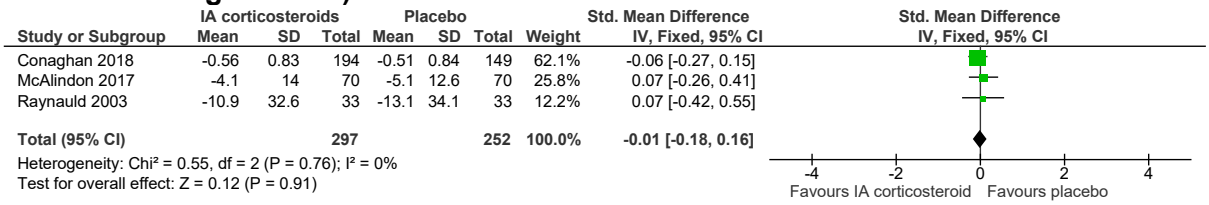
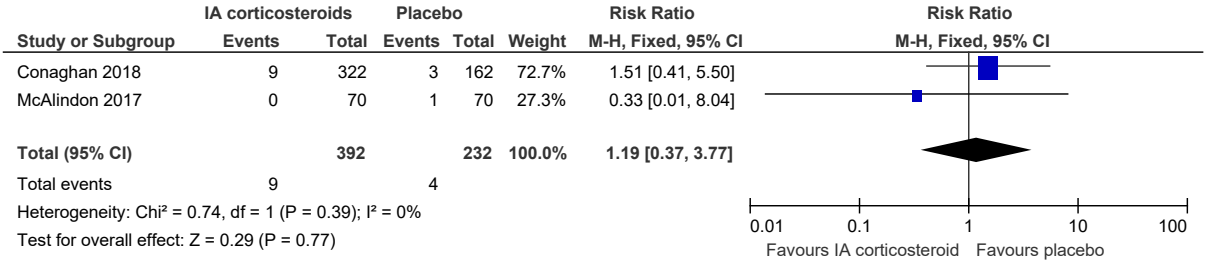


Figure 58: Serious adverse events at ≤3 months

Figure 59: Serious adverse events at >3 months



E.2.4 Intra-articular stem cell therapy (image guided) compared to placebo

Figure 60: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

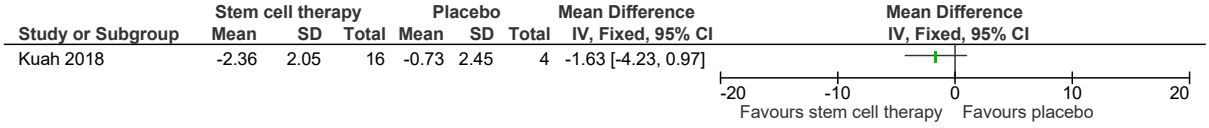
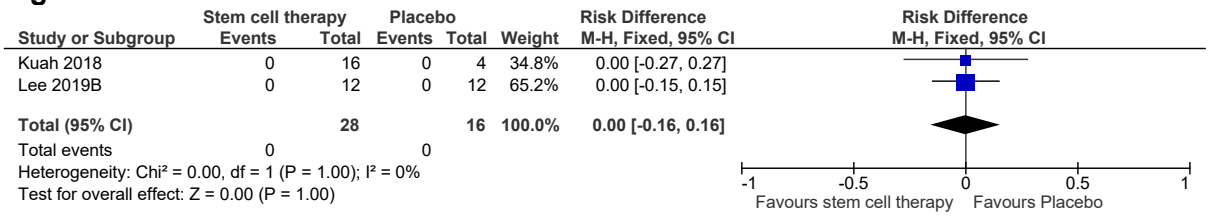


Figure 61: Serious adverse events at >3 months



E.2.5 Intra-articular stem cell therapy (non-image guided) compared to intra-articular hyaluronic acid (non-image guided)

Figure 62: Quality of life (SF-12 physical component, 0-100, high is good, final value) at ≤3 months

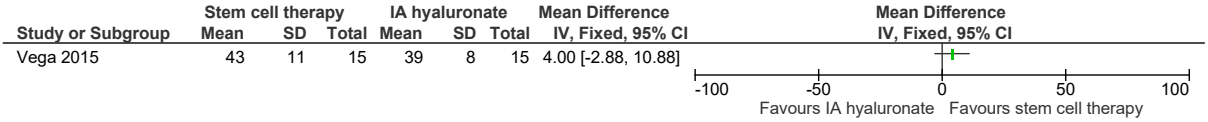


Figure 63: Quality of life (SF-12 mental component, 0-100, high is good, final value) at ≤3 months

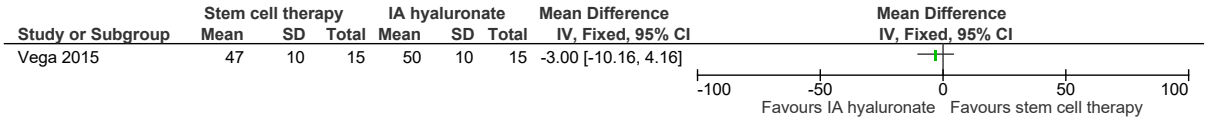


Figure 64: Quality of life (SF-12 physical component, 0-100, high is good, final value) at >3 months

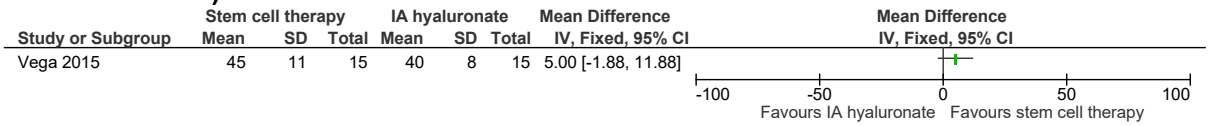


Figure 65: Quality of life (SF-12 mental component, 0-100, high is good, final value) at >3 months

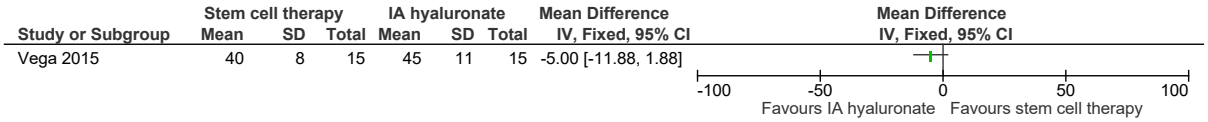


Figure 66: Pain (WOMAC [different scale ranges], high is poor, final values) at >3 months

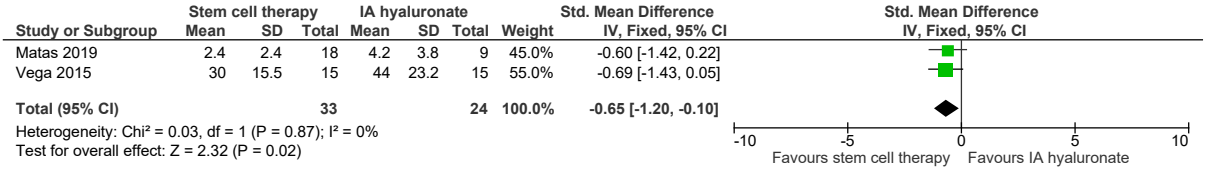


Figure 67: Physical function (WOMAC, 0-68, high is poor, final value) at >3 months

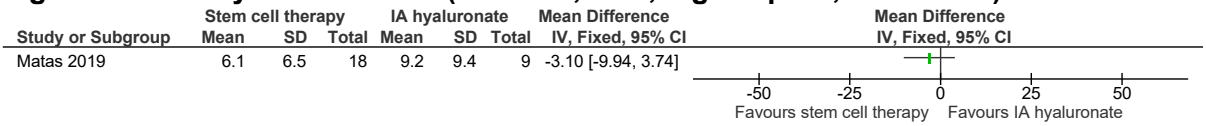
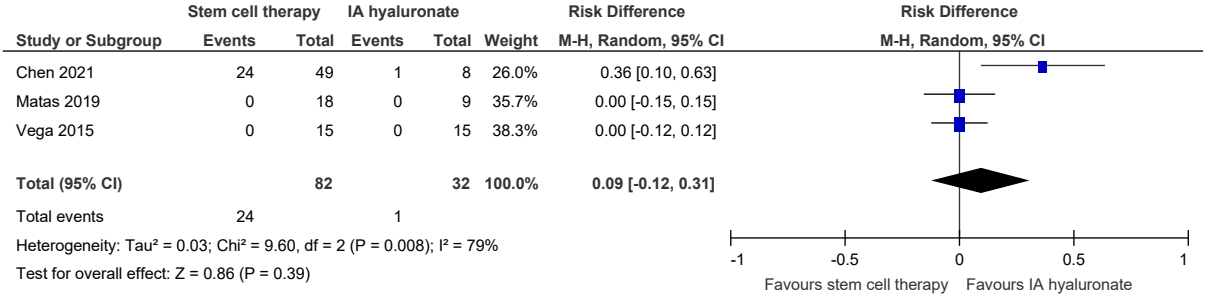


Figure 68: Serious adverse events at >3 months



E.2.6 Intra-articular stem cell therapy (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Figure 69: Quality of Life (KOOS quality of life, 0-100, high is good, change score) >3 months

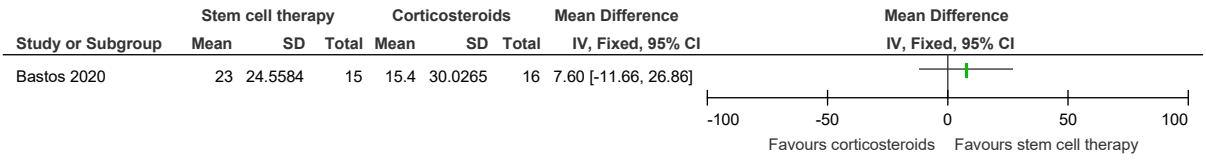


Figure 70: Pain (KOOS pain, 0-100, high is good, change score) at >3 months

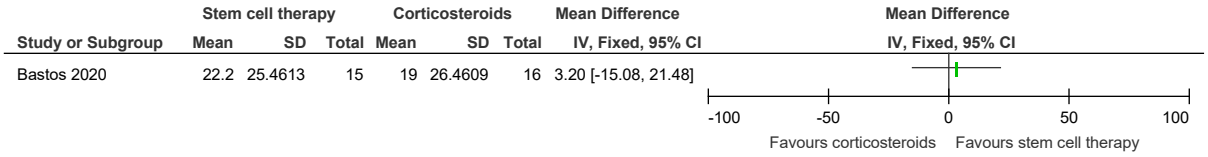
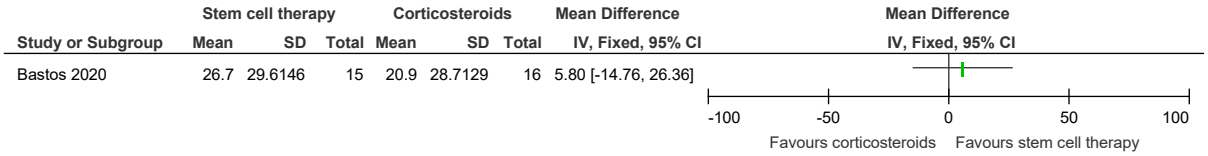


Figure 71: Physical function (KOOS function/daily living, 0-100, high is good, change score) >3 months



E.2.7 Intra-articular stem cell therapy (non-image guided) compared to placebo

Figure 72: Pain (WOMAC, VAS, 0-100, high is poor, change score) at ≤3 months

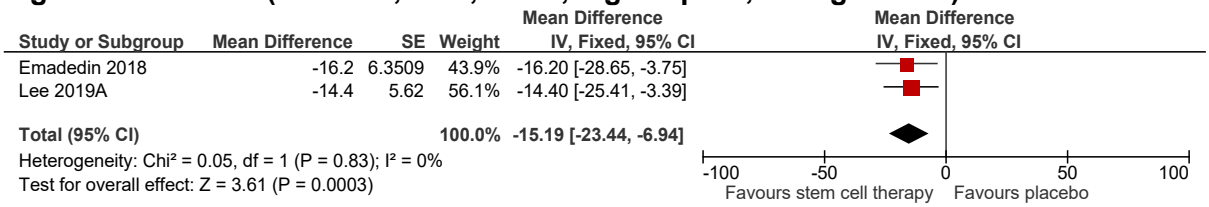


Figure 73: Pain (WOMAC, VAS, 0-100, high is poor, change score) at >3 months

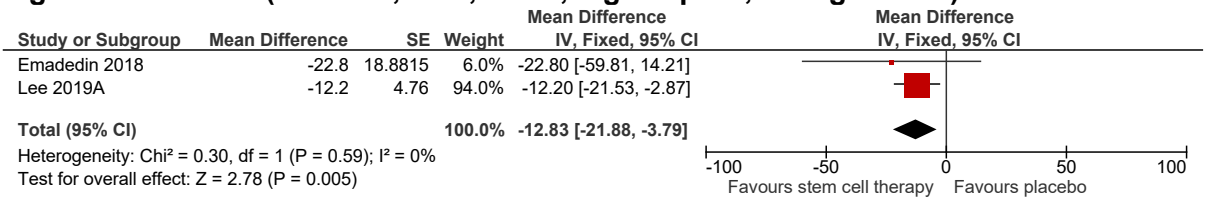


Figure 74: Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months

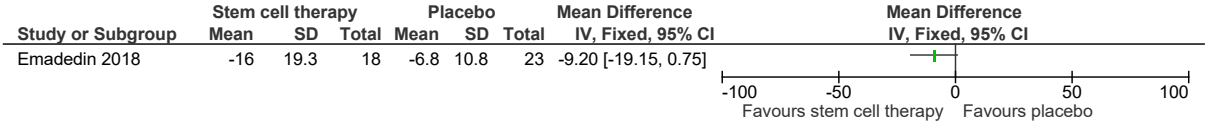


Figure 75: Physical function (WOMAC, 0-100, high is poor, change score) at >3 months

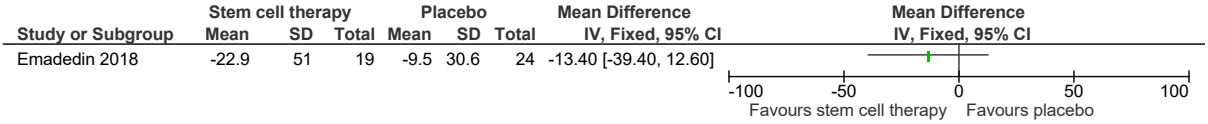
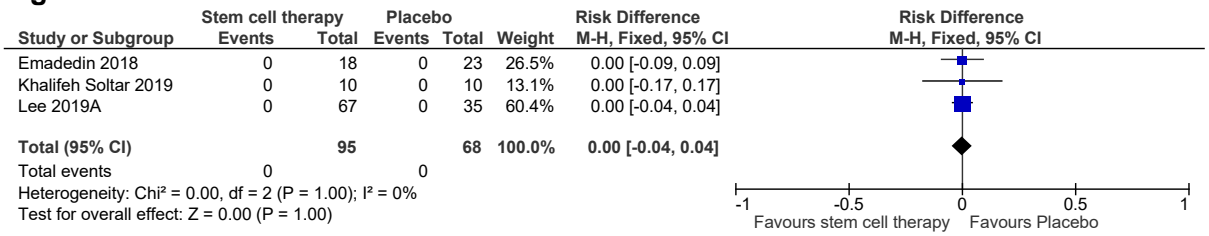


Figure 76: Serious adverse events at >3 months



E.3 Ankle osteoarthritis

E.3.1 Intra-articular hyaluronic acid (non-image guided) compared to placebo

Figure 77: Pain (ankle osteoarthritis scale pain subscale, VAS, 0-100, high is poor, change score and final value) at ≤3 months

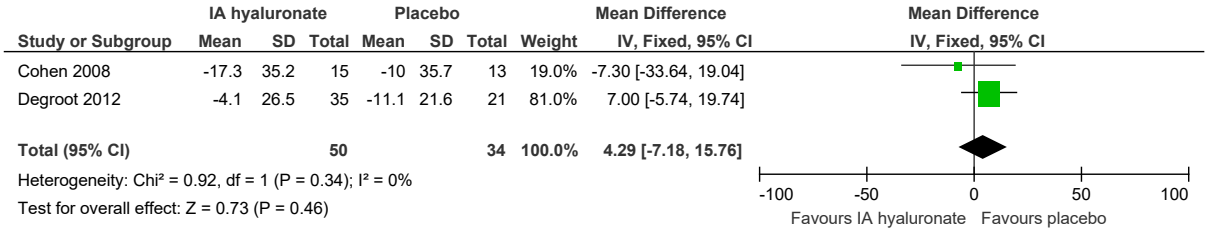


Figure 78: Pain (ankle osteoarthritis scale pain subscale, 0-100, high is poor, change score) at >3 months

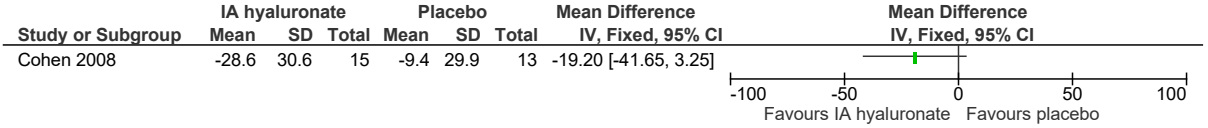


Figure 79: Physical function (ankle osteoarthritis scale disability subscale, 0-100, high is poor, change score) at ≤3 months

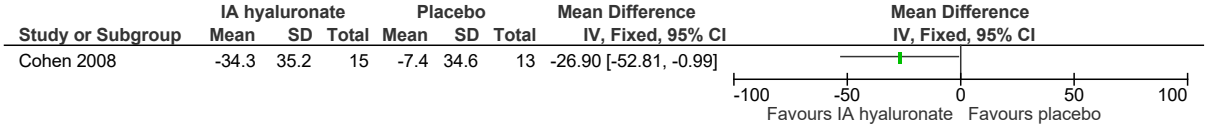


Figure 80: Physical function (ankle osteoarthritis scale disability subscale, 0-100, high is poor, change score) at >3 months

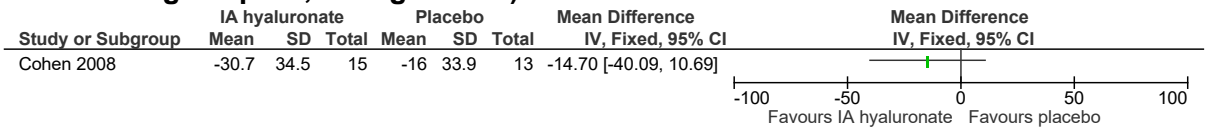


Figure 81: Osteoarthritis flares at >3 months

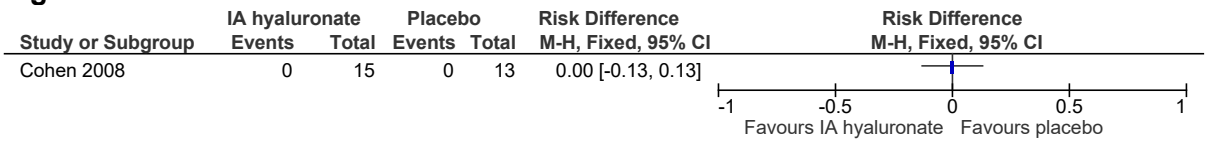


Figure 82: Serious adverse events at ≤3 months

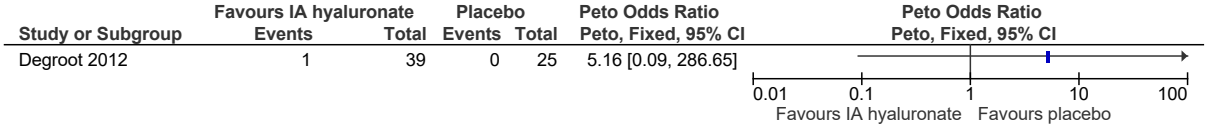
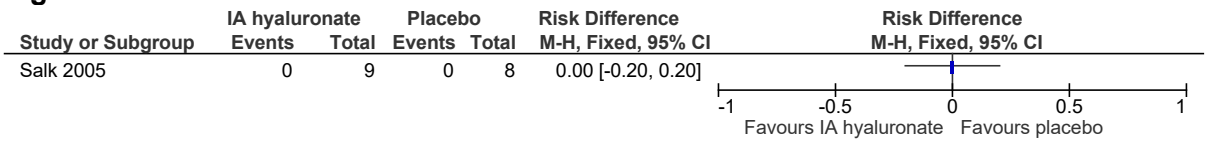


Figure 83: Serious adverse events at >3 months



E.4 Toe osteoarthritis

E.4.1 Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Figure 84: Pain (VAS, 0-100, high is poor, final value) at ≤3 months

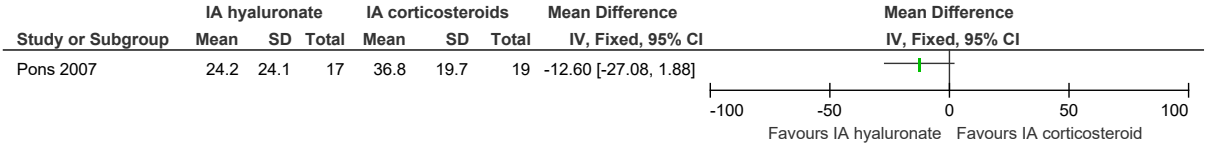
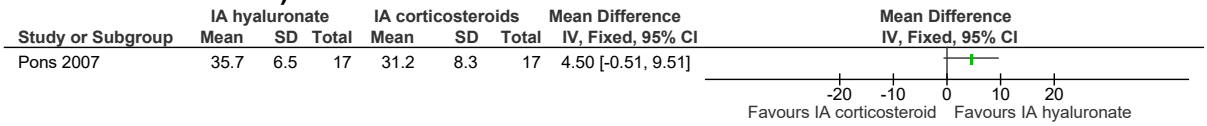


Figure 85: Physical function (AOFAS-hallux function subscale, 0-45, high is good, final value) at ≤3 months



E.4.2 Intra-articular hyaluronic acid (image guided) compared to placebo

Figure 86: Quality of life (SF-36 bodily pain subscale, 0-100, high is good, final value) at ≤3 months

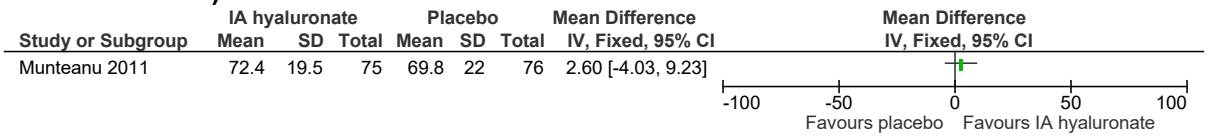


Figure 87: Quality of life (SF-36 general health subscale, 0-100, high is good, final value) at ≤3 months

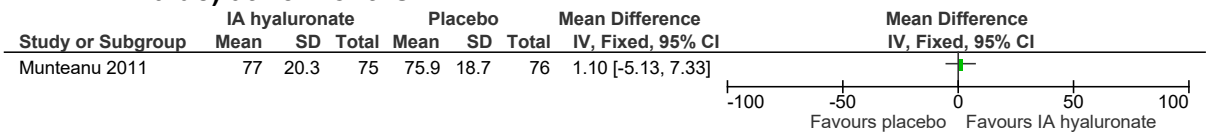


Figure 88: Quality of life (SF-36 mental health subscale, 0-100, high is good, final value) at ≤3 months

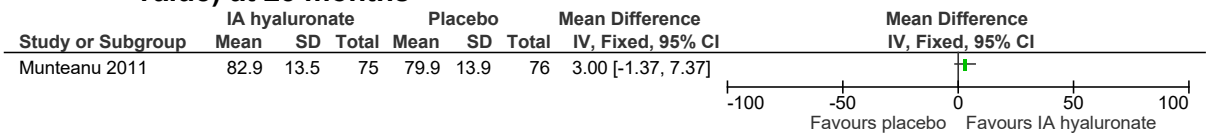


Figure 89: Quality of life (SF-36 physical function subscale, 0-100, high is good, final value) at ≤3 months

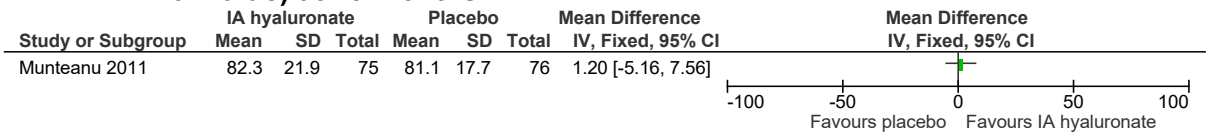


Figure 90: Quality of life (SF-36 role emotional subscale, 0-100, high is good, final value) at ≤3 months

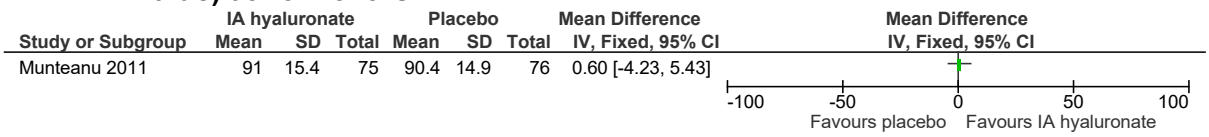


Figure 91: Quality of life (SF-36 role physical subscale, 0-100, high is good, final value) at ≤3 months

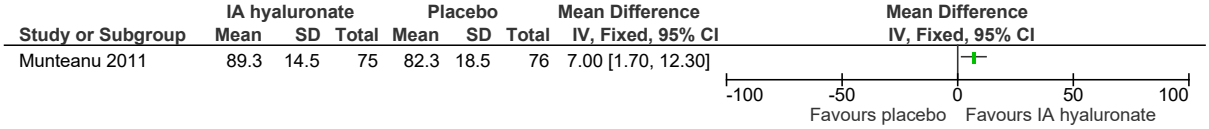


Figure 92: Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months

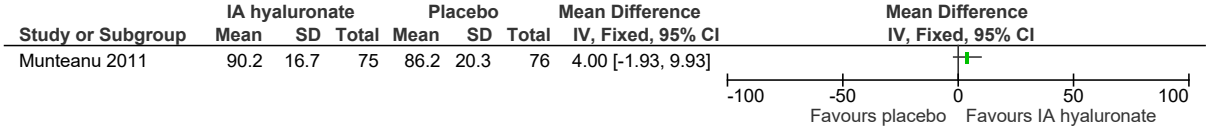


Figure 93: Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at ≤3 months

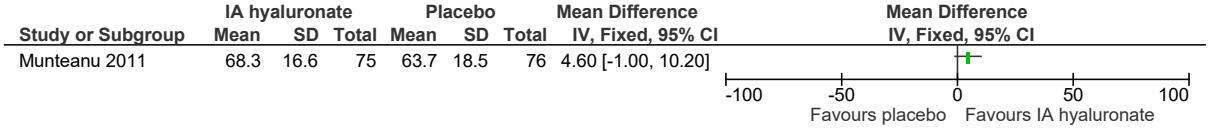


Figure 94: Quality of life (SF-36 bodily pain subscale, 0-100, high is good, final value) at >3 months

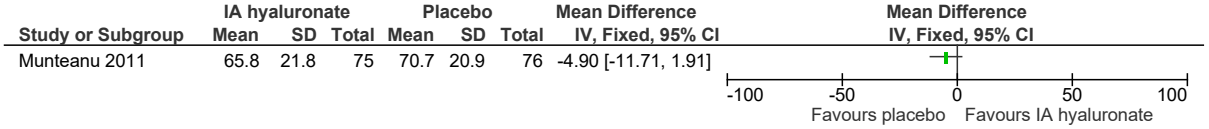


Figure 95: Quality of life (SF-36 general health subscale, 0-100, high is good, final value) at >3 months

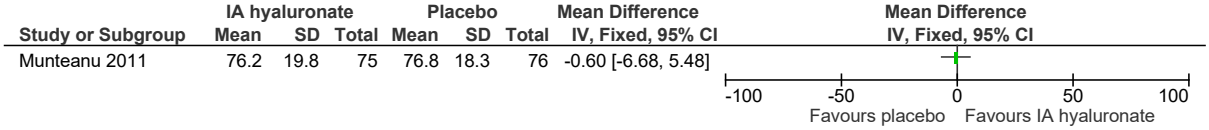


Figure 96: Quality of life (SF-36 mental health subscale, 0-100, high is good, final value) at >3 months

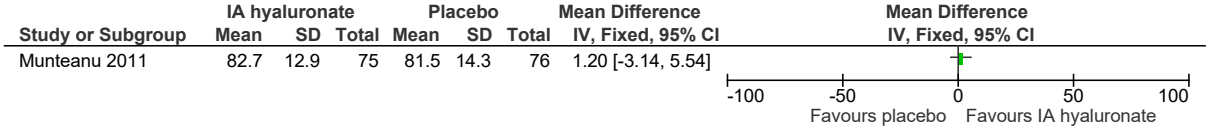


Figure 97: Quality of life (SF-36 physical function subscale, 0-100, high is good, final value) at >3 months

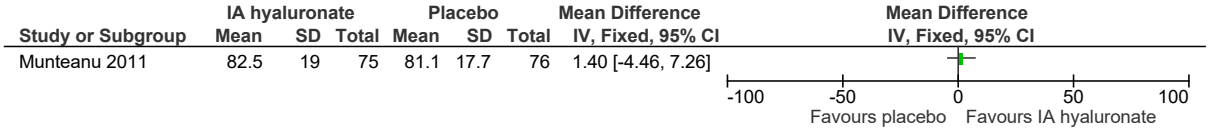


Figure 98: Quality of life (SF-36 role emotional subscale, 0-100, high is good, final value) at >3 months

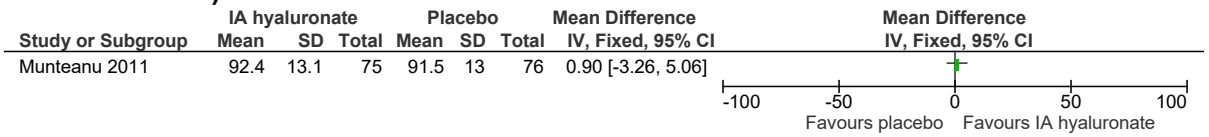


Figure 99: Quality of life (SF-36 role physical subscale, 0-100, high is good, final value) at >3 months

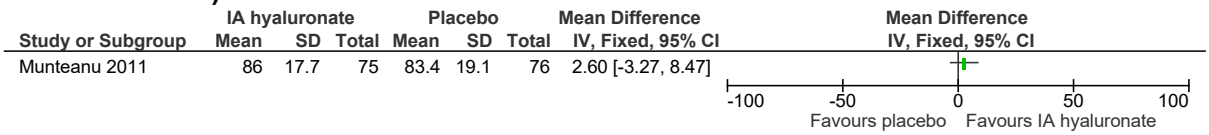


Figure 100: Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at >3 months

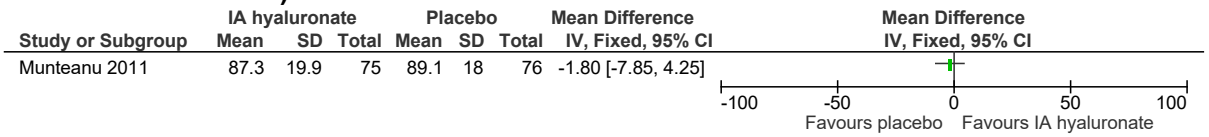


Figure 101: Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at >3 months

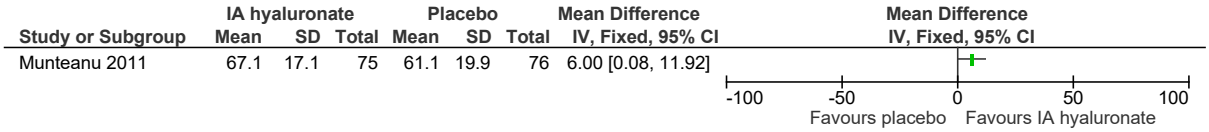


Figure 102: Pain (foot health status questionnaire pain dimension, 0-100, high is good, final value) at ≤3 months

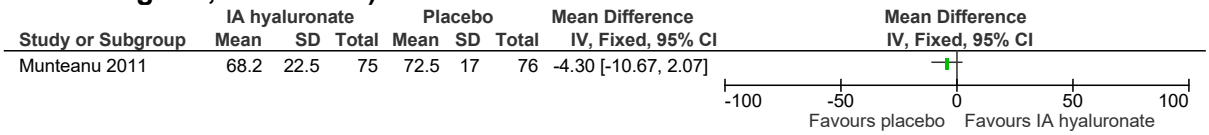


Figure 103: Pain (foot health status questionnaire pain dimension, 0-100, high is good, final value) at >3 months

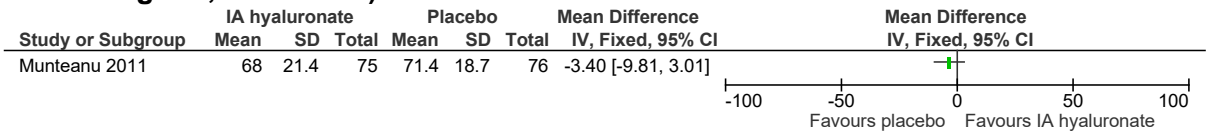


Figure 104: Physical function (foot health status questionnaire foot function, 0-100, high is good, final value) at ≤3 months

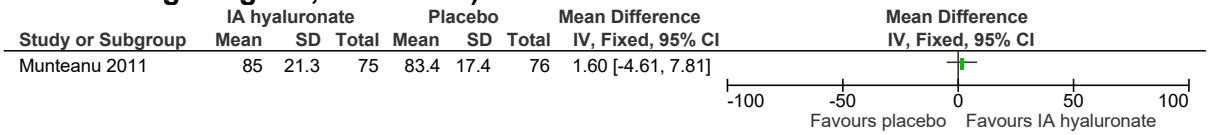


Figure 105: Physical function (foot health status questionnaire foot function, 0-100, high is good, final value) at >3 months

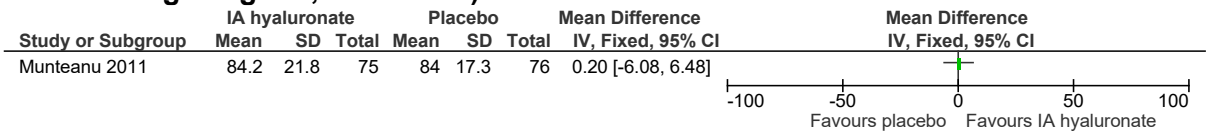
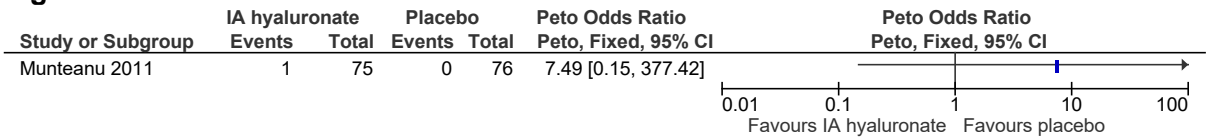


Figure 106: Serious adverse events at >3 months



E.5 Shoulder osteoarthritis

E.5.1 Intra-articular hyaluronic acid (non-image guided) compared to placebo

Figure 107: Pain (VAS, 0-100, high is poor, mean difference) at >3 months

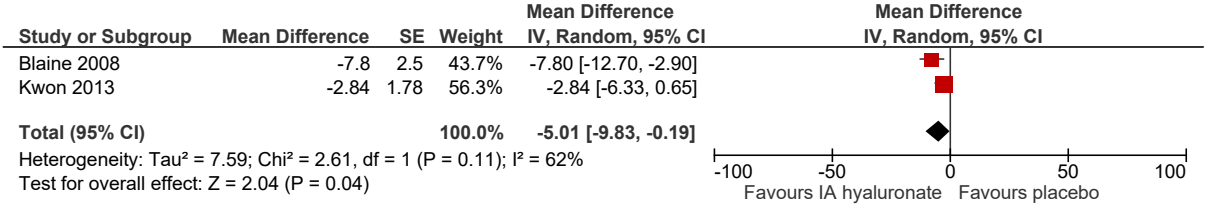
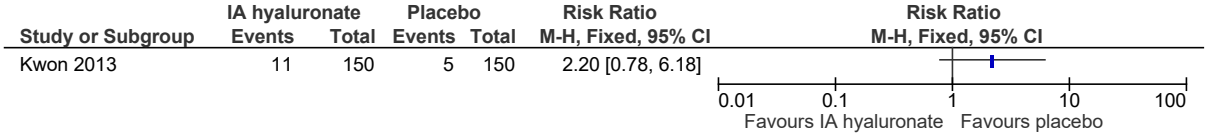


Figure 108: Serious adverse events at >3 months



E.6 Thumb osteoarthritis

E.6.1 Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided

Figure 109: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months

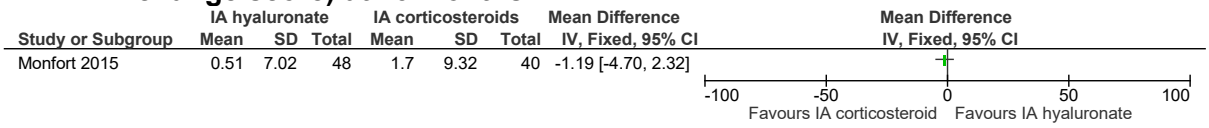


Figure 110: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months

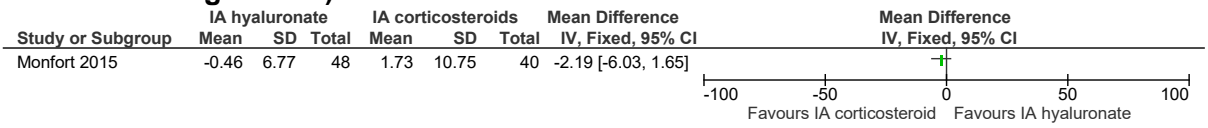


Figure 111: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >3 months

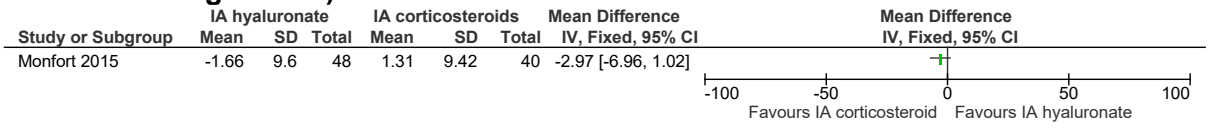


Figure 112: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >3 months

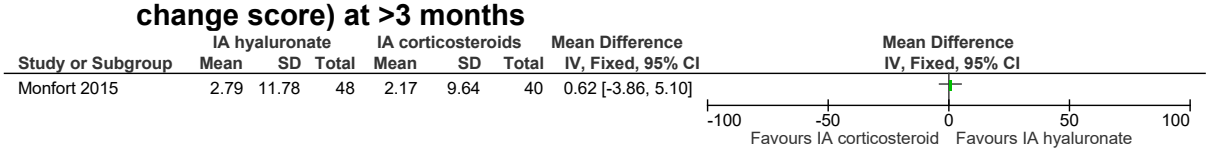


Figure 113: Pain (VAS, 0-10, high is poor, change score) at ≤3 months

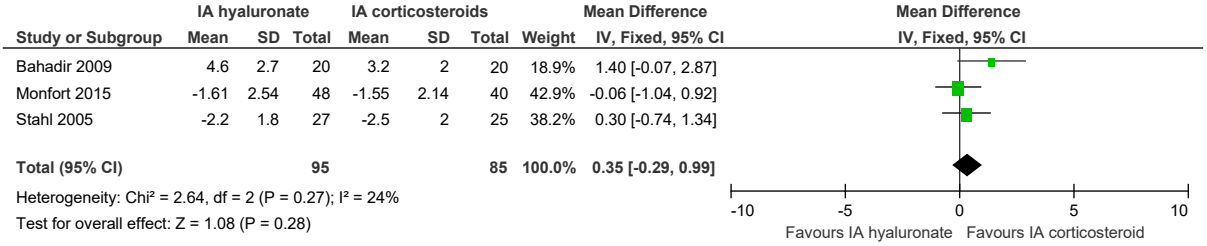


Figure 114: Pain (VAS, 0-10, high is poor, change score) at >3 months

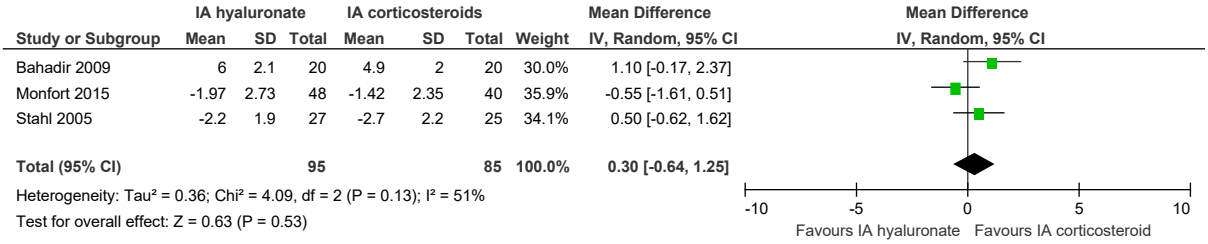


Figure 115: Physical function (Duruöz hand index, 0-90, high is poor, final value) at ≤3 months

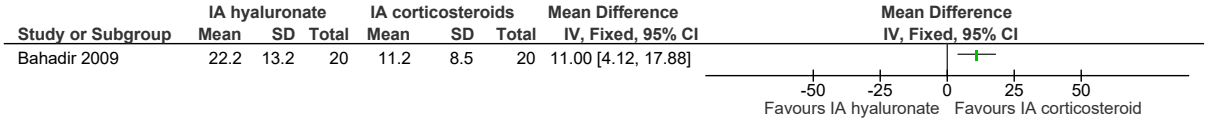


Figure 116: Physical function (Duruöz hand index, 0-90, high is poor, final value) at >3 months

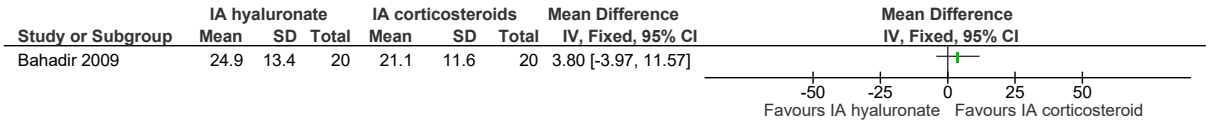
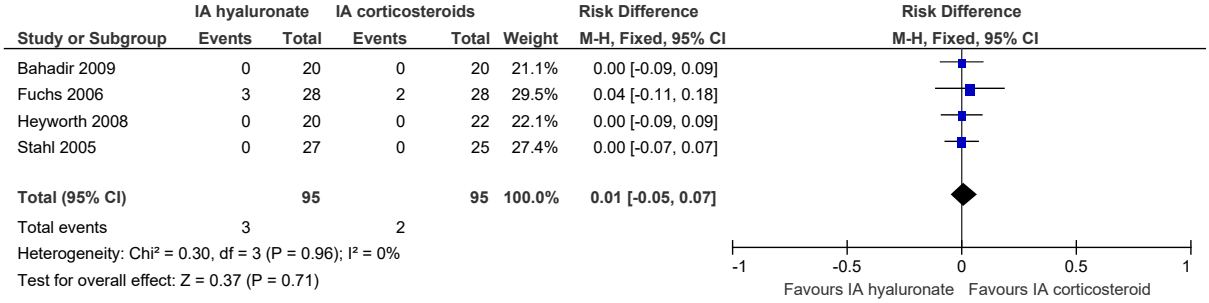


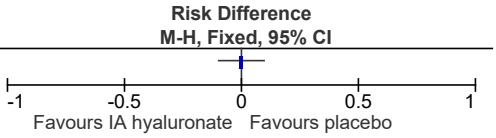
Figure 117: Serious adverse events at >3 months



E.6.2 Intra-articular hyaluronic acid (non-image guided) compared to placebo

Figure 118: Serious adverse events at >3 months

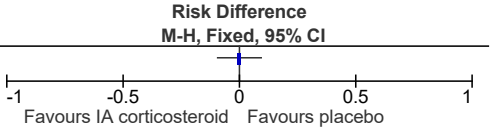
Study or Subgroup	IA hyaluronate Events	Total	Placebo Events	Total	Risk Difference M-H, Fixed, 95% CI
Heyworth 2008	0	20	0	18	0.00 [-0.10, 0.10]



E.6.3 Intra-articular corticosteroid (non-image guided) compared to placebo

Figure 119: Serious adverse events at >3 months

Study or Subgroup	IA corticosteroids Events	Total	Placebo Events	Total	Risk Difference M-H, Fixed, 95% CI
Heyworth 2008	0	22	0	18	0.00 [-0.09, 0.09]



E.7 Finger osteoarthritis

E.7.1 Intra-articular corticosteroids (non-image guided) compared to placebo

Figure 120: Pain (AUSCAN pain subscale, 0-20, high is poor, final value) at ≤3 months

Study or Subgroup	IA corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Spolidoro paschoal nde 2015	5.3	4.7	30	7	4.8	30	-1.70 [-4.10, 0.70]

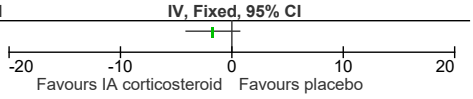
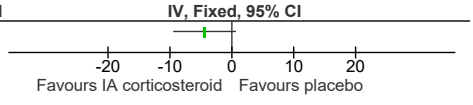


Figure 121: Physical function (AUSCAN function subscale, 0-36, high is poor, final value) at ≤3 months

Study or Subgroup	IA corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Spolidoro paschoal nde 2015	12.3	9.8	30	16.7	9.8	30	-4.40 [-9.36, 0.56]

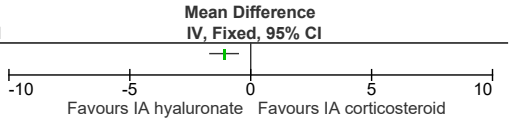


E.8 Temporomandibular joint osteoarthritis

E.8.1 Intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)

Figure 122: Pain (VAS, 0-10, high is poor, final value) at ≤3 months

Study or Subgroup	IA hyaluronate Mean	SD	Total	IA corticosteroids Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Gencer 2014	3.41	0.9	25	4.51	1.2	25	-1.10 [-1.69, -0.51]



E.8.2 Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Figure 123: Pain (VAS, 0-100, high is poor, final value) at ≤3 months

Study or Subgroup	IA hyaluronate Mean	SD	Total	IA corticosteroids Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Bjornland 2007	32	25.6	20	42	27.8	20	-10.00 [-26.56, 6.56]

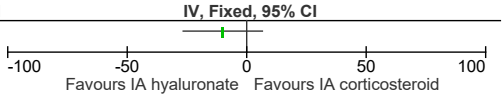
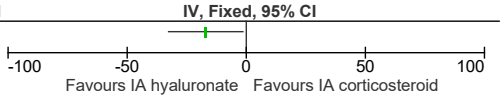


Figure 124: Pain (VAS, 0-100, high is poor, final value) at >3 months

Study or Subgroup	IA hyaluronate Mean	SD	Total	IA corticosteroids Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Bjornland 2007	14	16.2	20	31	31.7	20	-17.00 [-32.60, -1.40]



Appendix F – GRADE tables

F.1 Hip osteoarthritis

Table 57: Clinical evidence profile: intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	intra-articular corticosteroids (image guided)	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-100, high is poor, change score) at ≤3 months (follow up: 12 weeks; assessed with: VAS; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	33	32	-	MD **2 lower** (13.5 lower to 9.5 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, 0-100, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	156	156	-	MD **3.03 lower** (9.65 lower to 3.59 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months (follow up: 4 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	156	156	-	MD **8.39 higher** (3.51 higher to 13.27 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-100, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	intra-articular corticosteroids (image guided)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	156	156	-	MD **2.27 lower** (8.67 lower to 4.13 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Osteoarthritis flares at ≤3 months (follow up: mean 10 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	6/51 (11.8%)	0/50 (0.0%)	**OR 8.53** (1.60 to 43.60)	**120 fewer per 1,000** (from 220 fewer to 20 fewer) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at ≤3 months (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	0/33 (0.0%)	0/32 (0.0%)	**RD 0.00** (-0.06 to 0.06)	**0 fewer per 1,000** (from 60 fewer to 60 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at >3 months (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	5/150 (3.3%)	4/155 (2.6%)	**RR 1.29** (0.35 to 4.72)	**7 fewer per 1,000** (from 17 fewer to 96 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

d. Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 58: Clinical evidence profile: intra-articular hyaluronic acid (image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-10, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: VAS; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	17	17	-	MD **0.2 lower** (1.95 lower to 1.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 12 weeks; assessed with: WOMAC, VAS)												
3	randomised trials	very serious [a]	not serious	not serious	not serious	none	257	254	-	SMD **0.02 lower** (0.19 lower to 0.16 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (VAS, 0-10, high is poor, final value) at >3 months (follow up: 24 weeks; assessed with: VAS; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	17	17	-	MD **0.5 lower** (1.98 lower to 0.98 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, 0-11, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	182	175	-	MD **0.07 higher** (0.53 lower to 0.67 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 12 weeks; assessed with: WOMAC)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	224	218	-	SMD **0.1 higher** (0.09 lower to 0.29 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Physical function (WOMAC, 0-11, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	182	175	-	MD **0.04 higher** (0.54 lower to 0.62 higher)	⨁⨁◯◯ LOW	CRITICAL
Osteoarthritis flares at ≤3 months (follow up: mean 11 weeks)												
3	randomised trials	very serious [a]	not serious	not serious	not serious	none	9/93 (9.7%)	0/97 (0.0%)	**OR 8.44** (2.21 to 32.26)	**100 fewer per 1,000** (from 160 fewer to 30 fewer) [c]	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events at ≤3 months (follow up: mean 12 weeks)												
2	randomised trials	serious [a]	serious [d]	not serious	very serious [e]	none	1/75 (1.3%)	0/79 (0.0%)	**RD 0.00** (-0.03 to 0.06)	**10 fewer per 1,000** (from 60 fewer to 30 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at >3 months (follow up: mean 25 weeks)												
2	randomised trials	very serious [a]	serious [d]	not serious	very serious [e]	none	10/204 (4.9%)	15/192 (7.8%)	**RD -0.03** (-0.08 to 0.02)	**30 fewer per 1,000** (from 20 fewer to 80 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **OR:** Odds ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one study arm

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Table 59: Clinical evidence profile: intra-articular corticosteroids (image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months (follow up: 8 weeks; assessed with: SF-36 physical component; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	31	21	-	MD **4.43 higher** (0.24 higher to 8.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months (follow up: 8 weeks; assessed with: SF-36 social functioning subscale; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	31	21	-	MD **13.37 higher** (1.06 lower to 27.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 6 weeks; assessed with: WOMAC, VAS)												
2	randomised trials	serious [a]	very serious [c]	not serious	serious [b]	none	71	61	-	SMD **2.09 lower** (3.88 lower to 0.29 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-100, high is poor, change score) at ≤3 months (follow up: 12 weeks; assessed with: VAS; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	32	36	-	MD **4 lower** (15.16 lower to 7.16 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, Katz and Akpom function ability [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 6 weeks; assessed with: WOMAC, Katz and Akpom functional ability)												
2	randomised trials	serious [a]	very serious [c]	not serious	serious [b]	none	71	61	-	SMD **2.08 lower** (4.09 lower to 0.07 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Osteoarthritis flares at ≤3 months (follow up: mean 10 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	very serious [d]	none	0/51 (0.0%)	0/54 (0.0%)	**RD 0.00** (-0.05 to 0.05)	**0 fewer per 1,000** (from 50 fewer to 50 more) [f]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at ≤3 months (follow up: mean 10 weeks)												
2	randomised trials	serious [a]	serious [e]	not serious	very serious [d]	none	1/63 (1.6%)	0/57 (0.0%)	**RD 0.01** (-0.04 to 0.07)	**10 fewer per 1,000** (from 70 fewer to 40 more) [f]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)

f. Absolute effect calculated by risk difference due to zero events in at least one study arm

F.2 Knee osteoarthritis

Table 60: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36, 0-100, high is good, final values) at ≤3 months (follow up: 12 weeks; assessed with: SF-36; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	75	75	-	MD **8 higher** (3.39 higher to 12.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36, 0-100, high is good, final values) at >3 months (follow up: 12 months; assessed with: SF-36; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	62	64	-	MD **2.7 higher** (1.57 lower to 6.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 11 weeks; assessed with: WOMAC, VAS)												
10	randomised trials	very serious [a]	very serious [c]	not serious	serious [b]	none	564	526	-	SMD **0.24 lower** (0.86 lower to 0.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (KSS pain, VAS, 0-100, high is poor, final values) at >3 months (follow up: mean 33 weeks; assessed with: KSS pain, VAS; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	very serious [a]	very serious [c]	not serious	serious [b]	none	371	349	-	MD **2.39 higher** (3.64 lower to 8.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, 0-20, high is poor, final values and change scores) at >3 months (follow up: mean 38 weeks; assessed with: WOMAC pain; Scale from: 0 to 20)												
2	randomised trials	serious [a]	very serious [c]	not serious	very serious [b]	none	356	230	-	MD **2.21 lower** (6.67 lower to 2.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, KSS function [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 12 weeks; assessed with: WOMAC, KSS function)												
5	randomised trials	very serious [a]	very serious [c]	not serious	very serious [b]	none	254	248	-	SMD **0.05 lower** (0.79 lower to 0.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, KSS function [different scale ranges], high is poor, final values) at >3 months (follow up: mean 38 weeks; assessed with: WOMAC, KSS function)												
2	randomised trials	very serious [a]	very serious [c]	not serious	very serious [b]	none	137	140	-	SMD **1.77 lower** (4.1 lower to 0.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events at ≤3 months (follow up: mean 12 weeks)												
3	randomised trials	very serious [a]	serious [c]	not serious	very serious [d]	none	1/71 (1.4%)	5/71 (7.0%)	**RR 0.20** (-0.85 to 1.28)	**30 fewer per 1,000** (from 70 fewer to 140 more) [e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at >3 months (follow up: mean 32 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
8	randomised trials	serious [a]	very serious [c]	not serious	serious [d]	none	83/865 (9.6%)	45/721 (6.2%)	**RR 1.72** (1.32 to 2.12)	**20 fewer per 1,000** (from 70 fewer to 20 more) [e]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

e. Absolute effect calculated from risk difference due to zero events in at least one study arm

Table 61: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (KOOS, 0-100, high is poor, mean difference) at >3 months (follow up: 26 weeks; assessed with: KOOS; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	98	99	-	MD **2.21 lower** (6.51 lower to 2.10 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 7 weeks; assessed with: WOMAC, VAS)												
6	randomised trials	very serious [a]	not serious	not serious	not serious	none	244	245	-	SMD **0.3 lower** (0.47 lower to 0.12 lower)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: WOMAC, VAS)												
9	randomised trials	serious [a]	serious [b]	not serious	not serious	none	981	689	-	SMD **0.24 lower** (0.42 lower to 0.05 lower)	⨁⨁◯◯ LOW	CRITICAL
Pain (VAS [difference scale ranges], high is poor, final values) at ≤3 months (follow up: mean 12 weeks; assessed with: VAS)												
2	randomised trials	not serious	serious [b]	not serious	not serious	none	416	298	-	SMD **0.13 higher** (0.02 lower to 0.28 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (VAS, KOOS score, 0-100, high is poor, final values and change scores) at >3 months (follow up: mean 33 weeks; assessed with: VAS; Scale from: 0 to 100)												
10	randomised trials	serious [a]	not serious	not serious	not serious	none	1223	1008	-	MD **2.25 lower** (4.44 lower to 0.06lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (WOMAC, 0-20, high is poor, final values) at >3 months (follow up: mean 19 months; assessed with: WOMAC; Scale from: 0 to 20)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	230	234	-	MD **0.39 lower** (0.85 lower to 0.07 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow up: mean 25 weeks; assessed with: WOMAC)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	serious [a]	serious [b]	not serious	not serious	none	802	725	-	SMD **0.15 lower** (0.32 lower to 0.03 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC-VAS disability and physical function subscale, 0-10, high is poor, final values) at ≤3 months (follow up: 4 weeks; assessed with: WOMAC-VAS disability; Scale from: 0 to 10)												
2	randomised trials	serious [a]	not serious	not serious	serious [c]	none	65	48	-	MD **1.01 lower** (1.54 lower to 0.48 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change scores and final values) at ≤3 months (follow up: mean 10 weeks; assessed with: WOMAC; Scale from: 0 to 68)												
6	randomised trials	serious [a]	not serious	not serious	not serious	none	439	437	-	MD **0.21 lower** (1.85 lower to 1.43 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Physical function (WOMAC, 0-100, high is poor, final values) at ≤3 months (follow up: 12 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	181	184	-	MD **7 lower** (12.29 lower to 1.71 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow up: mean 26 weeks; assessed with: WOMAC)												
7	randomised trials	serious [a]	very serious [a]	not serious	not serious	none	738	748	-	SMD **0.22 lower** (0.45 lower to 0.00 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, final values) at >3 months (follow up: mean 22 weeks; assessed with: WOMAC; Scale from: 0 to 68)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	207	212	-	MD **1.77 lower** (4.29 lower to 0.75 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Physical function (KOOS activities subscale, WOMAC, 0-100, high is poor) at >3 months (follow up: mean 22 weeks; assessed with: KOOS activities subscale, WOMAC; Scale from: 0 to 100)												
3	randomised trials	not serious	not serious	not serious	not serious	none	516	396	-	MD **3.06 lower** (6.09 lower to 0.03 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Osteoarthritis flare-up at >3 months (follow up: mean 26 weeks)												
2	randomised trials	very serious [a]	serious [d]	not serious	very serious [e]	none	7/132 (5.3%)	7/130 (5.4%)	**RR 1.00** (0.07 to 1.93)	**0 fewer per 1,000** (from 50 fewer to 50 fewer) [f]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at ≤3 months (follow up: mean 5 weeks)												
2	randomised trials	very serious [a]	serious [d]	not serious	very serious [e]	none	1/133 (0.8%)	0/138 (0.0%)	**RD 0.01** (-0.02 to 0.03)	**10 fewer per 1,000** (from 30 fewer to 20 more) [f]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at >3 months (follow up: mean 34 weeks)												
28	randomised trials	very serious [a]	serious [d]	not serious	very serious [e]	none	271/3501 (7.7%)	225/3002 (7.5%)	**RD 0.01** (-0.00 to 0.02)	**10 more per 1,000** (from 0 fewer to 20 more) [f]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 62: Clinical evidence profile: intra-articular corticosteroids (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (KOOS, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	270	144	-	MD **6.28 higher** (1.76 higher to 10.8 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (KOOS, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	270	144	-	MD **1.44 higher** (3.11 lower to 5.99 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 11 weeks; assessed with: WOMAC, VAS)												
4	randomised trials	serious [a]	very serious [b]	not serious	serious [c]	none	224	167	-	SMD **0.53 lower** (1.07 lower to 0.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 11 weeks; assessed with: WOMAC, VAS)												
3	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	354	193	-	SMD **0.55 lower** (1.07 lower to 0.03 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow up: mean 1.5 years; assessed with: WOMAC)												
3	randomised trials	serious [a]	serious [b]	not serious	not serious	none	402	252	-	SMD **0.02 higher** (0.3 lower to 0.34 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (Health assessment questionnaire for lower limb function, WOMAC [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 10 weeks; assessed with: Health assessment questionnaire for lower limb function, WOMAC)												
3	randomised trials	very serious [a]	serious [b]	serious [d]	serious [c]	none	134	135	-	SMD **0.28 lower** (0.69 lower to 0.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-4, high is poor, change scores) at ≤3 months (follow up: 12 weeks; assessed with: WOMAC; Scale from: 0 to 4)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	314	154	-	MD **0.26 lower** (0.42 lower to 0.1 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow up: mean 1.5 years; assessed with: WOMAC)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	297	252	-	SMD **0.01 lower** (0.18 lower to 0.16 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events at ≤3 months (follow up: mean 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	serious [e]	none	0/125 (0.0%)	0/65 (0.0%)	**RD 0.00** (0.00 to 0.04)	**0 fewer per 1,000** (from 40 fewer to 40 more) [g]	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events at >3 months (follow up: mean 16 months)												
2	randomised trials	serious [a]	serious [f]	not serious	serious [c]	none	7/392 (1.8%)	4/232 (1.7%)	**RR 1.19** (-0.37 to 3.77)	**0 fewer per 1,000** (from 30 fewer to 20 more) [g]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 or 2 increments because of outcome indirectness

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)

g. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 63: Clinical evidence profile: intra-articular stem cell therapy (image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 52 weeks; assessed with: WOMAC; Scale from: 0 to 20)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	16	4	-	MD **1.63 lower** (4.23 lower to 0.97 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events at >3 months (follow up: mean 39 weeks)												
2	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	0/28 (0.0%)	0/16 (0.0%)	**RD 0.00** (-0.16 to 0.16)	**0 fewer per 1,000** (from 160 fewer to 160 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

c. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

d. Absolute effect calculated from risk difference due to zero events in at least one study arm

Table 64: Clinical evidence profile: intra-articular stem cell therapy (non-image guided) compared to intra-articular hyaluronic acid (non-image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (non-image guided)	intra-articular hyaluronic acid (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-12 physical component, 0-100, high is good, final value) at <3 months (follow-up: 12 weeks; assessed with: SF-12 physical component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15	15	-	MD **4 higher** (2.88 lower to 10.88 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-12 mental component, 0-100, high is good, final value) at <3 months (follow-up: 12 weeks; assessed with: SF-12 mental component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15	15	-	MD **3 lower** (10.16 lower to 4.16 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-12 physical component, 0-100, high is good, final value) at >3 months (follow-up: 12 months; assessed with: SF-12 physical component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15	15	-	MD **5 higher** (1.88 lower to 11.88 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-12 mental component, 0-100, high is good, final value) at >3 months (follow-up: 12 months; assessed with: SF-12 mental component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15	15	-	MD **5 lower** (11.88 lower to 1.88 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (WOMAC [different scale ranges], high is poor, final values) at >3 months (follow-up: mean 12 months; assessed with: WOMAC)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	33	24	-	SMD **0.65 lower** (1.2 lower to 0.1 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (non-image guided)	intra-articular hyaluronic acid (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months (follow-up: 12 months; assessed with: WOMAC; Scale from: 0 to 68)												
1	randomised trials	serious[b]	not serious	not serious	serious[a]	none	18	9	-	MD **3.1 lower** (9.94 lower to 3.74 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events at >3 months (follow-up: mean 10 months)												
3	randomised trials	serious[b]	very serious[c]	not serious	not serious	none	24/82 (29.3%)	1/32 (3.1%)	**RD 0.09** (-0.12 to 0.31)	**90 more per 1,000** (from 120 fewer to 310 more)[d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Absolute effect calculated from risk difference due to zero events in at least one study arm

Table 65: Clinical evidence profile: intra-articular stem cell therapy (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (non-image guided)	corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Quality of life (KOOS quality of life, 0-100, high is good, change score) >3 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (non-image guided)	corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15	16	-	MD **7.6 higher** (11.66 lower to 26.86 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (KOOS pain, 0-100, high is good, change score) at >3 months												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	15	16	-	MD **3.2 higher** (15.08 lower to 21.48 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (KOOS function/daily living, 0-100, high is good, change score) >3 months												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	15	16	-	MD **5.8 higher** (14.76 lower to 26.36 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 66: Clinical evidence profile: intra-articular stem cell therapy (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, VAS, 0-100, high is poor, change score) at ≤3 months (follow up: mean 12 weeks; assessed with: WOMAC, VAS; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular stem cell therapy (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	91	60	-	MD **15.19 lower** (23.44 lower to 6.94 lower)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, VAS, 0-100, high is poor, change score) at >3 months (follow up: mean 16 months; assessed with: WOMAC, VAS; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	91	60	-	MD **12.83 lower** (21.88 lower to 3.79 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months (follow up: 12 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	18	23	-	MD **9.2 lower** (19.15 lower to 0.75 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-100, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	19	24	-	MD **13.4 lower** (39.4 lower to 12.6 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events at >3 months (follow up: mean 51 weeks)												
3	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	0/95 (0.0%)	0/68 (0.0%)	**RD 0.00** (-0.04 to 0.04)	**0 fewer per 1,000** (from 40 fewer to 40 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

d. Absolute effect calculated from risk difference due to zero events in at least one study arm

F.3 Ankle osteoarthritis

Table 67: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (ankle osteoarthritis scale pain subscale, VAS, 0-100, high is poor, final value and change score) at ≤3 months (follow up: mean 12 weeks; assessed with: ankle osteoarthritis scale pain subscale, VAS; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	50	34	-	MD **4.29 higher** (7.18 lower to 15.76 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (ankle osteoarthritis scale pain subscale, 0-100, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: ankle osteoarthritis scale pain subscale; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	15	13	-	MD **19.2 lower** (41.65 lower to 3.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (ankle osteoarthritis scale disability subscale, 0-100, high is poor, change score) at ≤3 months (follow up: 12 weeks; assessed with: ankle osteoarthritis scale disability subscale; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	15	13	-	MD **26.9 lower** (52.81 lower to 0.99 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Physical function (ankle osteoarthritis scale disability subscale, 0-100, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: ankle osteoarthritis scale disability subscale; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	15	13	-	MD **14.7 lower** (40.09 lower to 10.69 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Osteoarthritis flares at >3 months (follow up: 26 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	0/15 (0.0%)	0/13 (0.0%)	**RD 0.00** (-0.13 to 0.13)	**0 fewer per 1,000** (from 130 fewer to 130 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events at ≤3 months (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	1/39 (2.6%)	0/25 (0.0%)	**OR 5.16** (0.09 to 286.65)	**30 fewer per 1,000** (from 100 fewer to 50 more) [d]	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	0/9 (0.0%)	0/8 (0.0%)	**RD 0.0** (-0.2 to 0.2)	**0 fewer per 1,000** (from 200 fewer to 200 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

d. Absolute effect calculated by risk difference due to zero events in at least one study arm

F.4 Toe osteoarthritis

Table 68: Clinical evidence profile: intra-articular hyaluronic acid (image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 bodily pain subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **2.6 higher** (4.03 lower to 9.23 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 general health subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 general health subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **1.1 higher** (5.13 lower to 7.33 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 mental health subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 mental health subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **3 higher** (1.37 lower to 7.37 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 physical function subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 physical function subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **1.2 higher** (5.16 lower to 7.56 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 role emotional subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 role emotional subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **0.6 higher** (4.23 lower to 5.43 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 role physical subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 role physical subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **7 higher** (1.7 higher to 12.3 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 social functioning subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **4 higher** (1.93 lower to 9.93 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 vitality subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **4.6 higher** (1 lower to 10.2 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 bodily pain subscale; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **4.9 lower** (11.71 lower to 1.91 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 general health subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 general health subscale; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **0.6 lower** (6.68 lower to 5.48 higher)	⨁⨁◯◯ LOW	CRITICAL

Quality of life (SF-36 mental health subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 mental health subscale; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **1.2 higher** (3.14 lower to 5.54 higher)	⨁⨁◯◯ LOW	CRITICAL

Quality of life (SF-36 physical function subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 physical function subscale; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **1.4 higher** (4.46 lower to 7.26 higher)	⨁⨁◯◯ LOW	CRITICAL

Quality of life (SF-36 role emotional subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 role emotional subscale; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **0.9 higher** (3.26 lower to 5.06 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality of life (SF-36 role physical subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 role physical subscale; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **2.6 higher** (3.27 lower to 8.47 higher)	⨁⨁◯◯ LOW	CRITICAL

Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 social functioning subscale; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	75	76	-	MD **1.8 lower** (7.85 lower to 4.25 higher)	⨁⨁◯◯ LOW	CRITICAL

Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: SF-36 vitality subscale; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **6 higher** (0.08 higher to 11.92 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (foot health status questionnaire pain dimension, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: foot health status questionnaire pain dimension; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	75	76	-	MD **4.3 lower** (10.67 lower to 2.07 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (foot health status questionnaire pain dimension, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: foot health status questionnaire pain dimension; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	75	76	-	MD **3.4 lower** (9.81 lower to 3.01 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Physical function (foot health status questionnaire foot function, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: foot health status questionnaire foot function; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	75	76	-	MD **1.6 higher** (4.61 lower to 7.81 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Physical function (foot health status questionnaire foot function, 0-100, high is good, final value) at >3 months (follow up: 26 weeks; assessed with: foot health status questionnaire foot function; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	75	76	-	MD **0.2 higher** (6.08 lower to 6.48 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Serious adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	1/75 (1.3%)	0/76 (0.0%)	**OR 7.49** (0.15 to 377.42)	**10 fewer per 1,000** (from 50 fewer to 20 more) [b]	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 69: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-100, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: VAS; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	17	19	-	MD **12.6 higher** (27.08 lower to 1.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (AOFAS-hallux function subscale, 0-45, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: AOFAS-hallux function subscale; Scale from: 0 to 45)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	17	17	-	MD **4.5 higher** (0.51 lower to 9.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.5 Shoulder osteoarthritis

Table 70: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-100, high is poor, mean difference) at >3 months (follow up: mean 26 weeks; assessed with: VAS; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	279	283	-	MD **5.01 lower** (9.83 lower to 0.19 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	11/150 (7.3%)	5/150 (3.3%)	**RR 2.20** (0.78 to 6.18)	**40 more per 1,000** (from 7 fewer to 173 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.6 Thumb osteoarthritis

Table 71: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	48	40	-	MD **1.19 lower** (4.7 lower to 2.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	48	40	-	MD **2.19 lower** (6.03 lower to 1.65 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >3 months (follow up: 26 weeks; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	48	40	-	MD **2.97 lower** (6.96 lower to 1.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >3 months (follow up: 26 weeks; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	48	40	-	MD **0.62 higher** (3.86 lower to 5.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (visual analogue scale, 0-10, high is poor, final value and change scores) at ≤3 months (follow up: mean 12 weeks; assessed with: visual analogue scale; Scale from: 0 to 10)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	95	85	-	MD **0.35 higher** (0.29 lower to 0.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (visual analogue scale, 0-10, high is poor, final value and change scores) at >3 months (follow up: mean 35 weeks; assessed with: visual analogue scale; Scale from: 0 to 10)												
3	randomised trials	very serious [a]	serious [c]	not serious	serious [b]	none	95	85	-	MD **0.3 higher** (0.64 lower to 1.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (Duruöz hand index, 0-90, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: Duruöz hand index; Scale from: 0 to 90)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	20	20	-	MD **11 higher** (4.12 higher to 17.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (Duruöz hand index, 0-90, high is poor, final value) at >3 months (follow up: 12 months; assessed with: Duruöz hand index; Scale from: 0 to 90)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	20	20	-	MD **3.8 higher** (3.97 lower to 11.57 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events at >3 months (follow up: mean 33 weeks)												
4	randomised trials	serious [a]	serious [d]	not serious	serious [e]	none	3/95 (3.2%)	2/95 (2.1%)	**RD 0.01** (-0.05 to 0.07)	**10 more per 1,000** (from 50 fewer to 70 more) [f]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in both arms of one study)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 72: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/20 (0.0%)	0/18 (0.0%)	**RD 0.0** (-0.1 to 0.1)	**0 fewer per 1,000** (from 100 fewer to 100 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

c. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

Table 73: Clinical evidence profile: intra-articular corticosteroids (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/22 (0.0%)	0/18 (0.0%)	**RD 0.00** (-0.09 to 0.09)	**0 fewer per 1,000** (from 90 fewer to 90 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

c. Absolute effect calculated from risk difference due to zero events in at least 1 study arm

F.7 Finger osteoarthritis

Table 74: Clinical evidence profile: intra-articular corticosteroids (non-image guided) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (AUSCAN pain subscale, 0-20, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: AUSCAN pain subscale; Scale from: 0 to 20)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular corticosteroids (non-image guided)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **1.7 lower** (4.1 lower to 0.7 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Physical function (AUSCAN function subscale, 0-36, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: AUSCAN function subscale; Scale from: 0 to 20)

1	randomised trials	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **4.4 lower** (9.36 lower to 0.56 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.8 Temporomandibular joint osteoarthritis

Table 75: Clinical evidence profile: intra-articular hyaluronic acid (image guided) compared to intra-articular corticosteroids (image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	intra-articular corticosteroids (image guided)	Relative (95% CI)	Absolute (95% CI)		

Pain (VAS, 0-10, high is poor, final value) at ≤3 months (follow up: 6 weeks; assessed with: VAS; Scale from: 0 to 10)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (image guided)	intra-articular corticosteroids (image guided)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	25	25	-	MD **1.1 lower** (1.69 lower to 0.51 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 76: Clinical evidence profile: intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intra-articular hyaluronic acid (non-image guided)	intra-articular corticosteroids (non-image guided)	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-100, high is poor, final value) at ≤3 months (follow up: 4 weeks; assessed with: VAS; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	20	20	-	MD **10 lower** (26.56 lower to 6.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (VAS, 0-100, high is poor, final value) at >3 months (follow up: 26 weeks; assessed with: VAS; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	20	20	-	MD **17 lower** (32.6 lower to 1.4 lower)	⨁◯◯◯ VERY LOW	CRITICAL

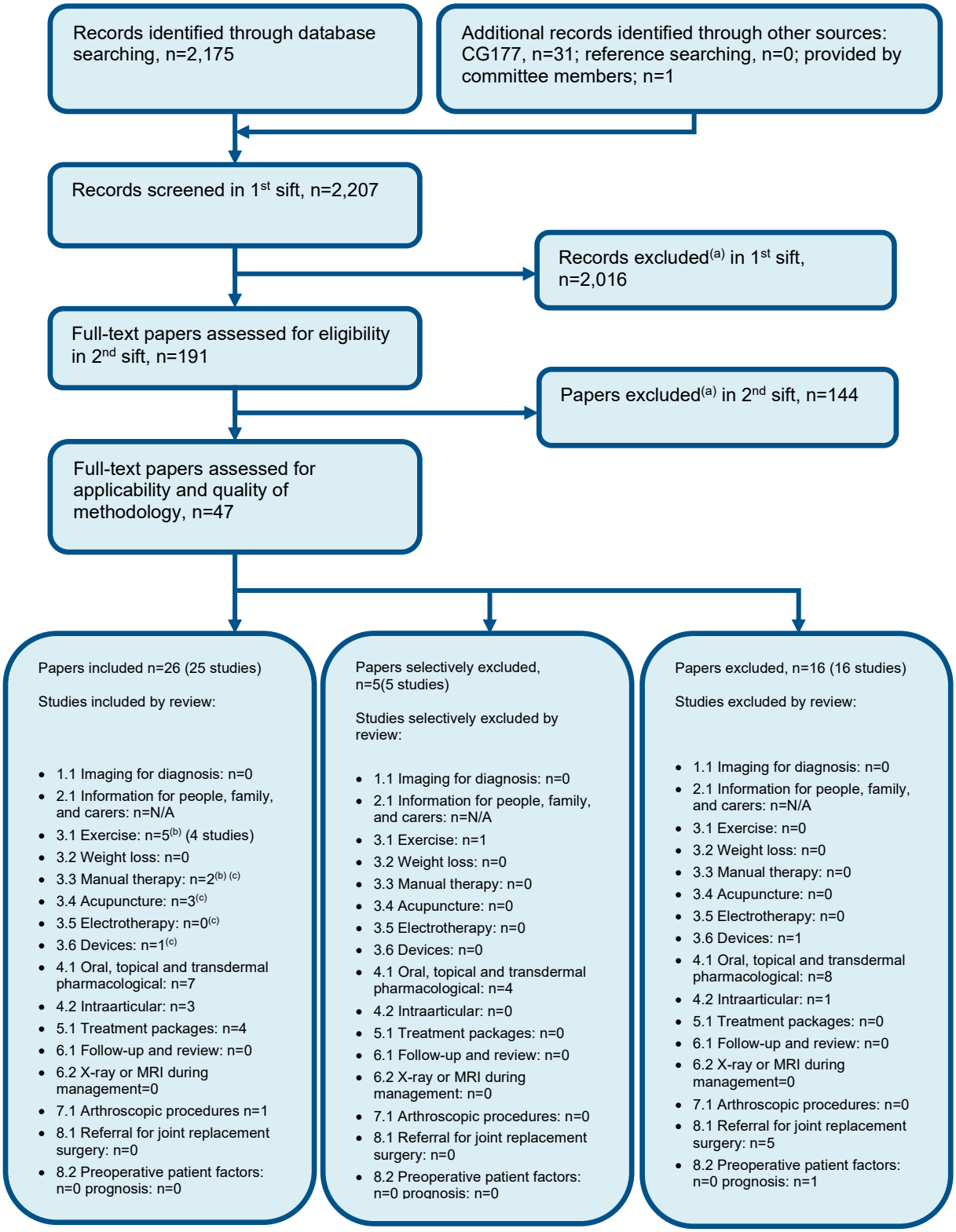
CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G – Economic evidence study selection



(a) Non-relevant population, intervention, comparison, design or setting; non-English language.
(b) Two articles identified were applicable to Q3.1 and Q3.3, for the purposes of this diagram they have been included under Q3.1 only.
(c) One article identified was applicable to Q3.3, Q3.4, Q3.5 and Q3.6, for the purposes of this diagram it has been included under Q3.3 only.

Appendix H – Economic evidence tables

Study	Hermans 2018			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Within-trial analysis of VISK RCT[188] **Approach to analysis:** Analysis of individual level data for EQ-5D and resource use. Unit costs applied. Missing data was imputed and adjustments for baseline differences were made. **Perspective:** Dutch healthcare perspective (societal also analysed but not presented here) **Follow-up:** 1 year **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** People age 18-65 with symptomatic knee osteoarthritis: pain >3 months, pain severity >2, Kellgren/Lawrence grade I to III. **Patient characteristics:** N = 156 Age: 1. 53.6 (8.6) 2. 54.8 (6.4) Male: 1. 52% 2. 49% **Intervention 1:** Usual care - pain medication (including acetaminophen or NSAIDs) when needed, physical therapy and lifestyle recommendations. **Intervention 2:** Intraarticular injection with hyaluronic acid plus usual care **–** 3 weekly intraarticular injections with HylanG-F20 performed by experienced knee pathology orthopaedic surgeons through the superlateral approach.	**Total costs (mean per patient):** Intervention 1: £929 Intervention 2: £1,304 Incremental (2−1): £375 (95% CI: -£207, £943; p=NR) **Currency & cost year:** 2010 Euros (presented here as 2010 UK pounds[(a)]) **Cost components incorporated:** Knee-related physician and paramedical therapist visits, use of aids (e.g. braces, inlay soles, home care use, knee-related surgery, and medication use. Medication costs included prescription fees pharmacists receive per prescription.	**QALYs (mean per patient):** Intervention 1: 0.727 Intervention 2: 0.779 Incremental (2−1): 0.052 (95% CI: 0.014, 0.092); p=NR)	**ICER (Intervention 2 versus Intervention 1):** £7,212 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (€20K threshold): 86% **Analysis of uncertainty:** Bootstrapping was undertaken to assess uncertainty in costs and effects. No further sensitivity analyses were undertaken.
Data sources				
Health outcomes: Within trial analysis - QALYs were calculated using patient-level utility data collected at baseline, 6, 13, 26, 39 and 52 weeks. Missing data were imputed by means of linear interpolation. Baseline adjustments made using the inverse probability of treatment weighting method. **Quality-of-life weights:** EQ-5D-3L, Dutch tariff. **Cost sources:** Primarily Dutch national tariffs. If national tariffs were unavailable, the tariff was calculated based on mean tariffs charged by different practices.				

Comments
Source of funding: Supported by ZonMW (grant), commissioned by the Dutch Ministry of Health, Welfare, and Sport and the Netherlands Organisation for Scientific Research. **Limitations:** Study does not include all comparators. Dutch resource use data (2009-2010) and unit costs (2010) may not reflect current NHS practice. Within-trial analysis and so may not reflect full body of available evidence for this comparison. **Other:** None.
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) Converted using 2019 purchasing power parities[344]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Migliore 2019[314]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Cost effectiveness analysis of Hylan G-F 20 versus pharmacological management based on data from literature. **Approach to analysis:** Markov model simulating the progression between health states for stages II-IV on the Kellgren-Lawrence scale, followed by states for either TKR or THR and post-surgery. Death is an absorbing state. (Results from a budget impact model are also presented but not reported here.) **Perspective:** Italian healthcare perspective **Time horizon:** 5 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People with knee or hip OA **Patient characteristics:** Age: NR Male: NR **Intervention 1:** Usual care (NSAIDs) **Intervention 2:** Usual care (paracetamol) **Intervention 3:** 1 x 6ml Hylan G-F 20 in knee OA **Intervention 4:** 3 x 2ml Hylan G-F 20 in knee OA **Intervention 5:** 1 x 2ml Hylan G-F 20 in hip OA	**Total costs (mean per patient):** Knee OA Intervention 1: £5,585 Intervention 2: £5,143 Intervention 3: £6,190 Intervention 4: £,6417 Incremental (3−1): £605 Incremental (3−2): £1047 Incremental (4−1): £832 Incremental (4−2): £1,273 (95% CI: NR; p=NR) Hip OA Intervention 1: £8,108 Intervention 2: £7,709 Intervention 5: £7,886 Incremental (5−1): -£221 Incremental (5−2): £177 (95% CI: NR; p=NR) **Currency & cost year:** 2013 Euros (presented here as 2013 UK pounds[(a)]) **Cost components incorporated:**	**QALYs (mean per patient):** Knee OA Intervention 1: 2.767 Intervention 2: 2.503 Intervention 3: 2.854 Intervention 4: 2.854 Incremental (3−1): 0.086 Incremental (3−2): 0.351 Incremental (4−1): 0.086 Incremental (4−2): 0.351 (95% CI: NR); p=NR) Hip OA Intervention 1: 2.856 Intervention 2: 2.654 Intervention 5: 2.922 Incremental (5−1): 0.066 Incremental (5−2): 0.268 (95% CI: NR); p=NR)	**ICER** (pa) **Knee OA** **(Intervention 3 versus Intervention 1):** £7,016 per QALY gained **(Intervention 3 versus Intervention 2):** £2,980 per QALY gained **(Intervention 4 versus Intervention 1):** £9,646 per QALY gained **(Intervention 4 versus Intervention 2):** £3,626 per QALY gained 95% CI: NR **Hip OA** **(Intervention 5 versus Intervention 1):** Intervention 5 dominates intervention 1 **(Intervention 5 versus Intervention 2):** £661 per QALY gained **Probability of cost effectiveness (£20/30K threshold)** [(a)]**:** Knee OA

		Cost of administering Hylan G-F 20. Drug costs included NSAID and paracetamol costs and subsequent serious AE costs (cardiovascular, GI or PE). TKR/THR surgery costs were also included. Productivity loss resulting from treatment failure was also included.		Intervention 3 versus Intervention 1: 54%/56% Intervention 3 versus Intervention 2: 74%/76% Intervention 4 versus Intervention 1 53%/55% Intervention 4 versus Intervention 2 73%/77% <u>Hip OA</u> Intervention 5 versus Intervention 1 59%/59% Intervention 5 versus Intervention 2 82%/82% **Analysis of uncertainty:** In one-way sensitivity analyses, the cost per QALY gained for all Hylan G-F 20 formulations remained below £16K except for three scenarios which were deemed unlikely or unrealistic by authors: - Compared to paracetamol when utility form an effective paracetamol treatment exceed utility from an effective Hylan G-F formulation (1x6ml and 3x2ml). - Compared to NSAIDs, when efficacy of Hylan G-F

				(1x6ml and 3x2ml) is less than NSAIDs. - Compared to NSAIDS, when utility assigned to treatment failure is at the upper value in the potential range.
Data sources				
Health outcomes: Treatment effectiveness was defined as reductions in knee symptoms, which were taken from clinical trials.[64, 75, 214, 231]Progression rates for the knee and hip were taken from Pavelka 2000[360] and Jordan 2011[224], respectively. TKR, revision surgery and THR incidence rates as well as AE probabilities were also taken from literature. **Quality-of-life weights:** NR. **Cost sources:** The costs of Hylan G-F 20 were provided by a pharmaceutical company. The costs of NSAIDs and paracetamol were taken from the CODIFA database. The choice of usual care drugs used in the analysis was based on the expert opinion of the study author. Costs of intraarticular administration costs, TKA, and THR procedures were all taken from the Ministry of Health. Adverse event costs were taken from the literature.				
Comments				
Source of funding: Sanofi Italia. **Limitations:** Unclear what utilities were used (e.g., EQ-5D), how they were sourced and how they were applied in the model. Effectiveness of Hylan based on one systematic review from 2010 identified during the clinical review but does not take into account the 25 studies since 2010 listed in the clinical review. Time horizon may not be sufficiently long to capture all important relevant costs and outcomes. Expert opinion regarding usual care treatment options included in the analysis and Italian unit costs (2013) may not reflect current NHS practice. Productivity loss resulting from treatment failure were included in the cost of interventions and could not be disaggregated. **Other:** None.				
Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; NSAIDs=non-steroidal anti-inflammatory drugs; OA= osteoarthritis; pa= probabilistic analysis; OA= osteoarthritis; QALYs= quality-adjusted life years; THR: total hip arthroplasty; TKR= total knee arthroplasty

(a) Converted using 2013 purchasing power parities[344]

(b) Values were read manually from a graph

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

No original economic modelling was undertaken.

Appendix J – Excluded studies

Clinical studies

Table 77: Studies excluded from the clinical review

Study	Exclusion reason
Aamir 2019[1]	Incorrect study design (non-randomised study)
Abdelsabor sabaah 2020[2]	No usable outcomes (medians plus IQR reported)
Acuna 2020[3]	Systematic review; references checked
Adams 1995[4]	Incorrect interventions (Intraarticular hyaluronic acid with oral NSAIDs, intraarticular hyaluronic acid alone, oral NSAIDs alone)
Agarwal 2021[5]	Systematic review; references checked
Alhamadani 2021[7]	Incorrect study design (other non-randomised study)
Al-omran 2014[6]	Inappropriate comparison (osteonil hyaluronic acid versus durolane and synvisc hyaluronic acid)
Altman 2015[13]	Incorrect interventions. Inappropriate comparison (assessing the clinical practice guideline methodology for treatment with intraarticular hyaluronic acid- the AGREE II instrument)
Altman 2016[10]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acid at different molecular weights)
Altman 2018[8]	Inappropriate comparison (hyaluronic acid reinjection (1-4 times) versus no reinjection)
Alvarez-camino 2013[14]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions Incorrect interventions (autologous conditioned serum)
Alvarez hernandez 2020[15]	Systematic review; references checked
Anon 2017[128] (Rodrigo Royo 2007)	Incorrect study design (non-randomised study). Inappropriate comparison (hyaluronic acid v no comparator)
Arensi 2006[17]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acid)
Arteaga-solís 2014[18]	Not in English language
Astolfi 2014[20]	Wrong study type (clinical scenario). Incorrect interventions (autologous conditioned serum). Includes animal studies
Atamaz 2006[21]	Incorrect interventions (intraarticular hyaluronic acid versus interferential therapy)
Auerbach 2002[23]	Not in English language
Ayub 2021[24]	Systematic review; references checked
Babaei-ghazani 2019[25]	Non-English language study
Baltzer 2009[27]	Incorrect unit of randomisation (knee)
Bannuru 2009[28]	Systematic review; references checked
Bannuru 2014[30]	Systematic review; references checked
Bannuru 2016[29]	Systematic review; references checked
Baron 2018[31]	Incorrect study design (non-randomised study)
Bastos 2018[33]	Inappropriate comparison (mesenchymal stem cells versus mesenchymal stem cells and PRPs)
Bayat 2018[34]	Not in English language
Bayramoglu 2003[35]	Inappropriate comparison (high molecular weight hyaluronic acid injection versus low molecular weight hyaluronic acid)
Bellamy 2005[37]	Systematic review of systematic reviews; references checked

Study	Exclusion reason
Bellamy 2006[38]	Systematic review; references checked
Bellamy 2016[36]	Incorrect interventions (intraarticular ketorolac versus intraarticular corticosteroid)
Benazzo 2016[39]	Incorrect study design (non-randomised study)
Berenbaum 2012[40]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acid)
Bergstrand 2019[41]	Incorrect interventions (arthrocentesis with hyaluronic acid injection versus arthrocentesis with joint lavage)
Bertolami 1993[42]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated) Includes people without osteoarthritis (unclear proportion)
Beyaz 2012[43]	Incorrect interventions (intraarticular steroid, intraarticular morphine)
Bingol 2013[44]	Not in English language
Bisicchia 2017[46]	Mini-review article; references checked
Bodick 2015[50]	Inappropriate comparison (extended release triamcinolone acetonide versus immediate release triamcinolone acetonide)
Borakati 2018[51]	Systematic review: study designs inappropriate (contains observational studies)
Boric 2019[52]	Incorrect study design (other non-randomised study)
Bragantini 1987[53]	No appropriate outcomes reported
Brander 2009[55]	Systematic review; references checked
Buendia-lopez 2018[57]	Incorrect interventions (intraarticular hyaluronic acid, oral NSAID administration)
Bunyaratavej 2001[58]	No appropriate outcomes reported
Campos 2011[61]	Conference abstract only
Campos 2012[63]	Incorrect interventions. Inappropriate comparison (intraarticular hyaluronic acid and corticosteroid versus intraarticular hyaluronic acid alone).. Abstract only
Campos 2014[62]	Conference abstract only
Campos 2017[60]	Wrong unit of randomisation (knee)
Carrabba 1995[65]	Not review population (Inclusion criteria included people with osteoarthritis and a joint effusion)
Cederlof 1966[66]	No usable outcomes
Cen 2018[67]	Incorrect interventions. Inappropriate comparison (intraarticular hyaluronic acid and oral glucosamine versus intraarticular hyaluronic acid alone)
Centeno 2018[68]	Incorrect interventions (autologous bone marrow concentrate and platelet products versus exercise therapy) . Protocol only
Chahla 2016[69]	Systematic review: study designs inappropriate (observational studies)
Chahla 2016[70]	Not review population (chondral defects as well as OA). Systematic review: study designs inappropriate (contains observational studies)
Chao 2009[71]	Conference abstract only
Chen 2013[74]	Incorrect interventions (Intraarticular hyaluronic acid,TENS)
Chevalier 2020[76]	Systematic review; references checked

Study	Exclusion reason
Cho 2017[77]	Inappropriate comparison(allogenic human chondrocytes modified to express transforming growth factor beta-1 versus a lower dose of the cells)
Clar 2005[78]	Unclear population cartilage defects of the knee (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (autologous chondrocyte implantation, microfracture and others.) . Systematic review: study designs inappropriate
Clarke 2005[79]	Incorrect study design (non-randomised study)
Clementi 2018[80]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acid)
Cole 2018[82]	Incorrect interventions (intraarticular low molecular weight fraction of 5% human serum albumin, intraarticular placebo)
Colen 2010[83]	Protocol only
Comert kilic 2016[84]	Incorrect interventions. Inappropriate comparison (arthrocentesis and intraarticular corticosteroid and washout versus arthrocentesis and washout)
Concoff 2017[86]	Systematic review; references checked
Conrozier 2003[88]	Incorrect study design (non-randomised study)
Conrozier 2006[87]	Incorrect study design (non-randomised study)
Conrozier 2009[89]	Inappropriate comparison (intraarticular hyaluronic acid versus different doses of hyaluronic acid)
Crawford 2012[91]	Unclear population distal femoral cartilage lesion (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (autologous cartilage tissue implant, microfracture)
Creamer 1994[93]	Incorrect unit of randomisation (knee)
Creamer 1996[92]	Inappropriate comparison (intraarticular anaesthetic versus intraarticular saline)
Cubukcu 2005[95]	Wrong unit of randomisation (knee)
Cui 2016[96]	Systematic review: study designs inappropriate (contains observational studies)
Dai 2019[98]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acid)
Dai 2021[97]	Order cancelled (multiple papers in the same journal, paper was deemed to be unlikely to provide additional useful information)
Dallari 2018[99]	Inappropriate comparison (intraarticular polynucleotides associated with hyaluronic acid versus intraarticular hyaluronic acid alone)
Davidson 2018[100]	Systematic review: study designs inappropriate (contains observational studies)
Davis 2018[101]	Incorrect interventions (cooled radiofrequency ablation, intraarticular corticosteroid)
De 2012[107]	Systematic review; references checked
De campos 2013[103]	Inappropriate comparison (intra-articular hyaluronic acid and corticosteroid versus intra-articular hyaluronic acid alone)
De caro 2015[104]	Systematic review: study designs inappropriate (includes observational studies,includes animal studies). Incorrect interventions (intraarticular stem cells versus potentially high tibial osteotomy and surgical procedures)
De oliva spolidoro 2013[105]	Abstract only

Study	Exclusion reason
De souza 2010[106]	Incorrect interventions. Inappropriate comparison (intraarticular methylprednisolone and morphine versus intraarticular methylprednisolone alone)
Delanois 2019[111]	Systematic review: study designs inappropriate (includes observational studies)
Delgado-enciso 2018[113]	Incorrect interventions (BIOF2 (corticosteroid, insulin, organic acids combination) versus NSAIDs alone, arthroplasty)
Deyle 2016[115]	Incorrect interventions (intraarticular corticosteroid versus physical therapy) . Protocol only
Deyle 2020[114]	Inappropriate comparison (intraarticular corticosteroids versus exercise)
Di giacomo 2017[116]	Incorrect interventions (intraarticular hyaluronic acid and physical therapy versus physical therapy alone)
Di sante 2012[117]	Not review population (mixed). Incorrect interventions (aspiration and corticosteroid injection versus aspiration, corticosteroid and horizontal therapy)
Dickson 2001[118]	Incorrect interventions(intraarticular hyaluronic acid Diclofenac retard 100mg capsules once daily, arthrocentesis and dummy capsules)
Dieppe 1980[119]	Wrong unit of randomisation (knee)
Dieu-donne 2016[120]	Incorrect interventions (intraarticular corticosteroids, oral NSAIDs)
Diracoglu 2016[121]	Inappropriate comparison (single dose Monovisc hyaluronic acid versus three doses of Adant hyaluronic acid)
Dorleijn 2011[124]	Incorrect interventions (intramuscular corticosteroid, intramuscular saline)
Dorleijn 2018[125]	Incorrect interventions (intramuscular glucocorticoid injection, intramuscular placebo)
Douglas 2014[127]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions. Inappropriate comparison (different angles of approach for aspiration or injection of the knee)
Egsmose 1984[129]	Incorrect interventions (intraarticular indoprofen)
Erturk 2016[131]	Inappropriate comparison (intraarticular hyaluronic acid with corticosteroid-lidocaine versus intraarticular hyaluronic acid alone)
Euppayo 2017[132]	Not review population (animal study). Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acids plus corticosteroids or NSAIDs).
Eymard 2017[133]	Incorrect study design (non-randomised study).. Inappropriate comparison (two types of intraarticular hyaluronic acid)
Faleiro 2016[134]	Systematic review; references checked
Faundez 2016[135]	Not in English language
Ferreira 2018[136]	Systematic review; references checked (includes observational studies)
Fice 2019[137]	Incorrect interventions (platelet rich plasma). Includes animal studies. Systematic review: study designs inappropriate (includes observational studies)
Figen ayhan 2009[138]	No appropriate outcomes reported (in graphical format only)
Filardo 2016[139]	Systematic review: study designs inappropriate (includes observational studies)
Flanagan 1988[140]	No relevant outcomes

Study	Exclusion reason
Formiguera sala 1995[141]	No appropriate outcomes reported
Forster 2003[142]	Incorrect interventions (intraarticular Hyalgan injection, arthroscopic washout)
Fowler 2015[143]	Systematic review: study designs inappropriate (includes observational studies). Systematic review; references checked
Frampton 2010[144]	. Wrong study type (drug profile only)
Freitag 2015[147]	Unclear population (intraarticular chondral defects) (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions. Inappropriate comparison (arthroscopic microfracture versus arthroscopic microfracture combined with postoperative mesenchymal stem cell injections)
Freitag 2016[145]	Inappropriate comparison. Systematic review: study designs inappropriate (contains observational studies)
Freitag 2019[146]	Inappropriate comparison (autologous adipose-derived mesenchymal stem cell therapy versus different doses of the same therapy, no treatment)
Frias 2004[148]	Incorrect interventions (joint lavage plus corticosteroids, joint lavage alone)
Friedman 1980[149]	No appropriate outcomes reported (reports pain score in text with a p value for both arms)
Frizziero 1998[150]	Incorrect study design (non-randomised study)
Gammer 1984[154]	Incorrect interventions (intraarticular orgotein versus methylprednisolone)
Garay-mendoza 2018[155]	Incorrect interventions (mesenchymal stem cells, paracetamol)
Garg 2014[156]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy). includes people with rheumatoid arthritis Inappropriate comparison (intraarticular corticosteroid versus other steroids)
Garza 2020[157]	No usable outcomes (medians and IQRs only reported)
Gazi 2005[158]	Not in English language
Gigis 2016[160]	Inappropriate comparison (high molecular weight hyaluronic acid injection versus low molecular weight hyaluronic acid)
Gokce kutuk 2019[161]	No usable outcomes (medians and IQRs only reported)
Gopal 2014[163]	Inappropriate comparison. Systematic review: study designs inappropriate (contains observational studies)
Graf 1993[164]	Incorrect interventions (intraarticular hyaluronic acid, intraarticular mucopolysaccharide polysulfuric acid ester)
Grecomoro 1987[165]	Wrong unit of randomisation (knee)
Grecomoro 1992[166]	No appropriate outcomes reported (outcomes only report means, no standard error/standard deviations)
Gregori 2018[167]	Systematic review; references checked (included any active pharmacological intervention)
Gu 1998[168]	No appropriate outcomes reported
Guarda-nardini 2012[169]	Inappropriate comparison (Medium molecular weight hyaluronic acid versus low molecular weight hyaluronic acid)
Gudas 2012[170]	Unclear population (osteochondral defect) (for example, the proportion of participants with an osteoarthritis diagnosis not

Study	Exclusion reason
	stated). Incorrect interventions (mosaic osteochondral autologous transplantation, microfracture)
Guidolin 2001[172]	No appropriate outcomes reported (histology)
Guidolin 2018[171]	Inappropriate comparison. Incorrect interventions (guidelines looking at hyaluronic acid injections versus other guidelines)
Gupta 2016[173]	Inappropriate comparison (allogenic mesenchymal stromal cells with hyaluronic acid versus different doses and placebo (PLASMA-LYTE) with hyaluronic acid))
Ha 2017[174]	Inappropriate comparison (single injection of cross-linked sodium hyaluronate versus three injections of high molecular weight sodium hyaluronate)
Ha 2019[175]	Systematic review: study designs inappropriate (contains observational studies)
Haien 2018[176]	Unclear population (osteochondral defect)(for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (osteochondral autologous transplantation,microfracture)
Han 2020[178]	Systematic review; references checked
Han 2021[177]	Systematic review; references checked
Harrison-brown 2019[180]	Protocol only
He 2017[181]	Systematic review; references checked
Hempfling 2007[182]	Incorrect interventions (arthroscopy plus intra-articular corticosteroids, arthroscopy only)
Henricsdotter 2016[184]	No appropriate outcomes reported
Henriksen 2015[185]	Inappropriate comparison (intraarticular corticosteroid injection before exercise therapy versus intraarticular placebo injection before exercise therapy)
Henrotin 2017[186]	Incorrect interventions (intraarticular hyaluronic acid and mannitol, intraarticular saline)
Hepper 2009[187]	Systematic review; references checked
Hermans 2018[189]	Incorrect interventions (high molecular weight hyaluronic acid plus usual care v usual care)
Hernigou 2018[190]	Incorrect interventions. Wrong unit of randomisation (knee)
Heybeli 2008[191]	Incorrect interventions (arthroscopic debridement and intra-articular hyaluronic acid versus arthroscopic debridement only)
Hong 2019[193]	Wrong unit of randomisation (knee)
Honvo 2019[194]	Systematic review; references checked
Howard 2013[196]	Systematic review: study designs inappropriate (contains observational studies)
Huang 2005[197]	Incorrect interventions (isokinetic exercises versus isokinetic exercise plus pulse ultrasound, isokinetic exercise plus pulse ultrasound plus intraarticular hyaluronic acid)
Hurley 2018[200]	Systematic review: study designs inappropriate (contains observational studies)
Huskisson 1981[202]	Incorrect interventions (intraarticular orgotein (superoxide dismutase) versus intraarticular saline)
Iannitti 2012[203]	Inappropriate comparison(intraarticular hyaluronic acid versus intraarticular hyaluronic acid).. Wrong unit of randomisation (knee)
Iijima 2018[204]	Systematic review: study designs inappropriate (contains observational studies)

Study	Exclusion reason
Im 2016[205]	Systematic review: study designs inappropriate (contains observational studies). Includes animal studies
Im 2018[206]	Systematic review: study designs inappropriate (contains observational studies).
Ishijima 2012[207]	Abstract only
Ishijima 2014[208]	Incorrect interventions (Intraarticular hyaluronic acid, oral NSAIDs)
Iturriaga 2017[210]	Systematic review; references checked
Iturriaga 2018[209]	Systematic review: study designs inappropriate (contains observational studies).
Jacer 2018[211]	Animal study
Jahangiri 2014[212]	Incorrect interventions (Intraarticular corticosteroid, Intraarticular hypertonic dextrose- being used as prolotherapy rather than placebo)
Jameel 2018[213]	Inappropriate comparison (methylprednisolone injection in one knee versus triamcinolone injection in one knee)
Jarner 1992[215]	Incorrect interventions (triamcinolone hexacetonide injection, indomethacin injection) . Abstract only
Jevotovsky 2018[216]	Systematic review: study designs inappropriate (contains observational studies).
Jevsevar 2015[217]	Systematic review; references checked
Jo 2017[218]	Incorrect study design(non-randomised study). Inappropriate comparison (mesenchymal stem cells, different doses)
Johansen 2016[219]	Systematic review; references checked
Jones 1995[221]	Wrong unit of randomisation (knee)
Jones 1996[220]	Cross over study - sufficient evidence is present for this stratum
Jones 2018[223]	Protocol only
Jones 2019[222]	Systematic review: study designs inappropriate (methodology unclear)
Juni 2007[228]	Inappropriate comparison (high molecular weight hyaluronic acid versus medium molecular weight and low molecular weight hyaluronic acid)
Jüni 2015[227]	Cochrane review; references checked
Kahan 2002[229]	Not in English language
Kahan 2003[230]	Incorrect interventions (hyaluronic acid injection versus conventional treatment (medications and exercise - but not well defined))
Karatay 2004[232]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular cross-linked hyaluronic acid)
Karatay 2005[233]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular cross-linked hyaluronic acid)
Karatosun 2005[234]	Inappropriate comparison (high molecular weight hyaluronic acid injection versus low molecular weight hyaluronic acid)
Karatosun 2006[235]	Incorrect interventions (intraarticular hyaluronic acid versus progressive knee exercises for six weeks)
Karatosun 2008[236]	Incorrect interventions (intraarticular hyaluronic acid, exercise therapy)
Kawabata 1993[238]	Not in English language
Kawasaki 2009[239]	Incorrect interventions (intraarticular hyaluronic acid, therapeutic home exercise)

Study	Exclusion reason
Kearey 2017[241]	Incorrect study design (observational study. Incorrect comparison (intraarticular hyaluronic acid (synvisc) versus no comparison)
Khanasuk 2012[243]	Inappropriate comparison (Hylan G-F 20 (Synvisc) versusHA (Hyalgan))
Kim 2019[244]	Systematic review; references checked
Kirchner 2006[245]	Inappropriate comparison (Hyaluronic acid injection - Bio-HA versus hyaluronic acid injection - CL-HA)
Kivitz 2019[246]	Pooled analysis including studies already included in the analysis
Knutsen 2004[249] Knutsen 2004[249] Knutsen 2016[248] Knutsen 2007[247]	Unclear population Single symptomatic cartilage defect, none with generalized osteoarthritis (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (autologous chondrocyte implantation, microfracture)
Koh 2016[250]	Not guideline condition. Inappropriate comparison. Incorrect interventions (mesenchymal stem cells and microfracture, microfracture alone)
Kon 2018[251]	Incorrect interventions (autologous protein solution, placebo)
Kopp 1985[252]	No appropriate outcomes reported
Kotevoglu 2006[253]	No appropriate outcomes reported (graphical format only)
Kraeutler 2018[254]	Incorrect interventions (autologous chondrocyte implantation, microfracture)
Kroon 2016[255]	Systematic review; references checked
Kroon 2018[256]	Systematic review; references checked
Kubosch 2018[258]	Includes animal studies. Systematic review: study designs inappropriate (includes observational studies)
Lamo-espinosa 2016[264]	Inappropriate comparison (autologous bone marrow mesenchymal stem cells and hyaluronic acid versus hyaluronic acid alone)
Lamo-espinosa 2018[263]	Inappropriate comparison
Leardini 1987[266]	Wrong unit of randomisation (knee)
Leardini 1991[267]	No appropriate outcomes reported
Lee 2006[271]	Inappropriate comparison (high molecular weight hyaluronic acid injection versus low molecular weight hyaluronic acid)
Lee 2011[272]	Incorrect interventions(Intraarticular ketorolac, intraarticular hyaluronic acid)
Lee 2014[274]	Incorrect interventions (microfracture, unclear comparison)
Lee 2017[270]	Incorrect interventions (extracorporeal shockwave therapy, intraarticular hyaluronic acid)
Lee 2020[269]	Incorrect interventions (bone marrow aspirate and PRP, hyaluronic acid)
Lei 2020[275]	Not review population (hip arthroplasty)
Leighton 2018[277]	Systematic review; references checked
Leopold 2002[279]	Incorrect study design (non-randomised study)
Leopold 2003[278]	No appropriate outcomes reported (medians only reported)
Lertwanich 2016[280]	Inappropriate comparison (intraarticular sodium hyaluronate 2% and 0.5% mannitol)
Lieberman 2015[281]	Systematic review: study designs inappropriate (contains observational studies). Systematic review; references checked
Likar 1997[282]	Incorrect interventions (intraarticular morphine versus intraarticular saline)

Study	Exclusion reason
Lin 2019[283]	Wrong unit of randomisation (knee)
List 2001[284]	Incorrect interventions (intraarticular morphine versus intraarticular saline)
Listrat 1997[285]	Incorrect interventions (hyaluronic acid injection versus standard care (no injections, otherwise same as intervention group))
Liu 2018[286]	Systematic review; references checked
Lomonte 2015[288]	Inappropriate comparison (triamcinolone hexacetonide injection versus methylprednisolone acetate injection)
Lozada 2017[289]	Incorrect interventions (intraarticular homeopathy (Tr14 and Ze14) versus intraarticular saline)
Lue 2017[290]	Systematic review; references checked
Ma 2020[293]	Systematic review; references checked
Machold 2010[294]	Not guideline condition. Not review population (rheumatoid arthritis. Incorrect interventions (intramuscular corticosteroid versus intramuscular saline)
Maheu 2002[295]	Systematic review; references checked
Maheu 2011[297]	Inappropriate comparison(medium molecular weight hyaluronic acid versus high molecular weight hyaluronic acid)
Maheu 2019[296]	Systematic review; references checked
Mandl 2009[298]	Incorrect study design (non-randomised study)
Mandl 2012[299]	Abstract only
Martin martin 2016[300]	Incorrect interventions (MD-knee - Collagen device, hyaluronic acid injection)
Mautner 2018[302]	Systematic review: study designs inappropriate (includes observational studies).. Inappropriate comparison (allogenic mesenchymal stem cells versus autologous mesenchymal stem cells)
Mcalindon 2018[304]	Incorrect interventions (intraarticular botulinum toxin A versus intraarticular placebo)
Mcarthur 2012[305]	Inappropriate comparison (intraarticular hyaluronic acid versus no specific comparator)
Mccabe 2016[306]	Systematic review; references checked
Mcdonald 2000[307]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular hyaluronic acid)
Mcintyre 2018[308]	Systematic review: study designs inappropriate (contains observational studies)
Medical advisory 2005[309]	Systematic review; references checked
Merolla 2011[312]	Incorrect study design (non-randomised study)
Migliore 2011[313]	Incorrect study design (non-randomised study)
Migliorini 2020[317]	Systematic review; references checked
Migliorini 2021[316]	Systematic review; references checked
Miller 1958[318]	No usable outcomes
Miller 2021[319]	Systematic review; references checked
Miltner 2002[320]	Incorrect study design. Inappropriate comparison (comparison of hyaluronic acid in left versus right knee)
Mistry 2017[321]	Unclear population (chondral defects of the knee)(for example, the proportion of participants with an osteoarthritis diagnosis not stated)
Moldez 2018[322]	Systematic review; references checked

Study	Exclusion reason
Monticone 2016[324]	Systematic review; references checked
Moystad 2008[326]	No appropriate outcomes reported
Møystad 2008[325]	No usable outcomes
Muhammad 2019[327]	Not guideline condition. Not review population (articular cartilage defect). Inappropriate comparison (stem cells v secretome). Includes animal studies
Mullaji 2010[328]	Incorrect interventions (total knee arthroplasty with periarticular injection of bupivacaine, total knee arthroplasty with periarticular injection of fentanyl and methylprednisolone)
Najm 2021[331]	Systematic review; references checked
Nancarrow-lei 2017[332]	Systematic review is not relevant to review question or unclear PICO. Inappropriate comparison (adult mesenchymal stem cell sources versus unclear comparison group)
Nazempour 2016[337]	Systematic review is not relevant to review question or unclear PICO Unclear methodology
Nguyen 2017[339]	Incorrect interventions. Inappropriate comparison (arthroscopic microfracture with stromal vascular fraction injection, arthroscopic microfracture alone)
Nielsen 2018[341]	Inappropriate comparison (intraarticular glucocorticosteroids prior to exercise therapy versus intraarticular saline prior to exercise therapy)
Noh 2004[342]	Not in English language
O'hanlon 2016[343]	Systematic review; references checked. Systematic review: study designs inappropriate Includes observational studies
Ozturk 2006[345]	Inappropriate comparison (Intraarticular hyaluronic acid with steroid versus intraarticular hyaluronic acid alone)
Pai 2014[346]	Systematic review; references checked
Paik 2019[347]	Systematic review; references checked
Pak 2016[348]	Systematic review: study designs inappropriate Includes observational studies
Pak 2018[349]	Systematic review: study designs inappropriate Includes observational studies
Paker 2006[350]	Incorrect interventions (TENS, intra-articular hyaluronic acid injection)
Papalia 2017[353]	Loan not available
Papalia 2017[352]	Loan not available
Papalia 2017[351]	Loan not available
Paresce 1990[354]	Incorrect interventions (Intraarticular hyaluronic acid, intraarticular orgotein (superoxide dismutase))
Parker 2020[355]	Inappropriate comparison (glucocorticoid injection versus exercise)
Parmigiani 2010[356]	Incorrect interventions (joint lavage plus triamcinolone hexacetonide injection versus triamcinolone hexacetonide alone)
Pas 2017[357]	Systematic review: study designs inappropriate contains observational trials
Paskins 2018[358]	Protocol only
Pastinen 1988[359]	Incorrect interventions (intraarticular glycosaminoglycan polysulphate injection, intraarticular saline)
Pavelka 1995[361]	Incorrect interventions (intraarticular glycosaminoglycan polysulfuric acid, intraarticular placebo)

Study	Exclusion reason
Pavelka 2011[362]	Inappropriate comparison (intraarticular hyaluronic acid (Sinovial) versus intraarticular hyaluronic acid (hylan G-F20)
Payne 2000[363]	No appropriate outcomes reported
Pereira 2018[364]	Not guideline condition. Not review population (not OA). Inappropriate comparison(hyaluronic acid versus no comparator)
Peretti 2018[365]	Not ordered - loan not available
Pérez-serna 2011[366]	Not in English language
Petrella 2006[372]	Inappropriate comparison (intraarticular hyaluronic acid for 3 weeks, followed by intraarticular hyaluronic acid for 3 weeks versus intraarticular saline for 3 weeks, followed by intraarticular hyaluronic acid for 3 weeks)
Petrella 2008[367]	Inappropriate comparison (combined lower and higher molecular weight hyaluronic acid injection versus high molecular weight hyaluronic acid, low molecular weight hyaluronic acid)
Petrella 2011[368]	Inappropriate comparison (intraarticular low molecular weight hyaluronic acid versus intraarticular high molecular weight hyaluronic acid)
Petrella 2012[370]	Inappropriate comparison (intra-articular hyaluronic acid v intra-articular hyaluronic acid plus corticosteroid). Abstract only
Petrella 2015[371]	Inappropriate comparison (intraarticular hyaluronic acid (hydros) versus intraarticular hyaluronic acid and steroid, intraarticular hyaluronic acid (synvisc))
Petterson 2019[373]	Duplicate reference (Petterson, 2019 #722)
Pietrogrande 1991[375]	No appropriate outcomes reported
Polacco 2013[376]	Incorrect study design (non-randomised study)
Popma 2015[378]	Inappropriate comparison (intrarticular triamcinolone acetonide 40mg versus intraarticular triamcinolone acetonide 80mg)
Popov 1989[379]	Not in English language
Puhl 1993[380]	Inappropriate comparison (intraarticular hyaluronic acid versus intraarticular very low dose of hyaluronic acid)
Pyne 2004[382]	Inappropriate comparison (intraarticular triamcinolone hexacetonide versus intraarticular methylprednisolone acetate)
Raeissadat 2021[384]	Inappropriate comparison (platelet rich plasma versus plasma rich in growth factor, hyaluronic acid, ozone)
Raman 2008[385]	Inappropriate comparison (hylan G-F20 injection versus sodium hyaluronate injection)
Ran 2018[386]	Systematic review; references checked
Randsborg 2016[387]	Unclear population Focal cartilage defect (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (autologous chondrocyte implantation, arthroscopic debridement)
Ranmuthu 2018[388]	Systematic review: study designs inappropriate (observational studies only). Inappropriate comparison (adipose-derived stem cells versus no control, different doses, surgical interventions)
Ravaud 1999[389]	Incorrect interventions (joint lavage plus corticosteroids versus joint lavage, corticosteroids, placebo)
Raynauld 1999[390]	Letter only
Raynauld 2002[393]	Incorrect interventions (intraarticular hyaluronic acid and standard care versus standard care alone)

Study	Exclusion reason
Raynauld 2005[392]	Incorrect interventions (intraarticular hyaluronic acid (including single course and multiple courses) and standard care versus standard care without hyaluronic acid)
Reichenbach 2007[394]	Inappropriate comparison (high molecular weight hyaluronic acid versus low molecular weight hyaluronic acid)
Reissis 2016[395]	Systematic review: study designs inappropriate (includes observational studies)
Richards 2016[396]	Systematic review: study designs inappropriate (methodology unclear, probably includes observational studies)
Richette 2015[397]	Systematic review; references checked
Riis 2017[399]	Incorrect interventions (intraarticular glucocorticoids and exercise versus intraarticular saline and exercise)
Rivera 2016[401]	Incorrect study design(non-randomised study). . Incorrect interventions (intraarticular hyaluronic acid and chondroitin sulfate versus no comparator)
Rivera 2016[400]	Incorrect study design (non-randomised study).
Rocchi 2017[402]	Incorrect interventions (intraarticular corticosteroid versus physiotherapy)
Rodriguez-merchan 2014[405]	Incorrect interventions (mesenchymal stem cells versus various, comparators, including high tibial osteotomy and arthroscopy)
Rodriguez-merchan 2016[403]	Systematic review; references checked Methodology unclear, no relevant studies included
Rodriguez-merchan 2018[404]	Systematic review: study designs inappropriate. Includes animal studies and observational studies
Roffi 2018[406]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions (looking at types of injectable systems)
Roman 2000[408]	Inappropriate comparison (intraarticular hyaluronic acid (Adant)versus intraarticular hyaluronic acid (Hyalgan))
Rosen 2016[409]	Inappropriate comparison (intraarticular hyaluronic acid versus different types of hyaluronic acid. Economic information only)
Rossini 2015[410]	Incorrect interventions (intraarticular clodronate versus intraarticular placebo)
Ruane 2021[411]	Incorrect interventions (mesenchymal stem cell therapy followed by PRP versus hyaluronic acid)
Russell 2018[412]	Inappropriate comparison (intraarticular extended release corticosteroid versus intraarticular standard release corticosteroid)
Saccomanno 2016[413]	Incorrect interventions (Intraarticular hyaluronic acid, exercise programme, combined intraarticular hyaluronic acid and exercise programme)
Sadoni 2017[414]	Incorrect interventions (intraarticular methylprednisolone alone, intraarticular methylprednisolone and ketamine)
Saeed 2015[415]	Incorrect interventions(intraarticular hyaluronic acid,,arthroscopic debridement)
Salmon 2018[418]	Systematic review; references checked
Saltychev 2020[419]	Systematic review; references checked
Saltzman 2017[420]	Inappropriate comparison (intraarticular saline post-injection, intraarticular saline at 3 months)
Sari 2018[421]	Incorrect interventions (radiofrequency neurotomy of the genicular nerves, intraarticular bupivacaine, morphine and betamethasone)

Study	Exclusion reason
Saris 2008[423]	Unclear population (cartilage defects of the knee. Excludes patients with osteoarthritis grade 2 or above) (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (characterised chondrocyte implantation, microfracture)
Saris 2014[422]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions(matrix-applied characterised autologous cultured chondrocytes, microfracture). Wrong population (symptomatic focal cartilage defect).
Sarumathy 2015[424]	Incorrect study design (non-randomised study)
Scale 1994[425]	No appropriate outcomes reported
Schrock 2017[426]	Systematic review: study designs inappropriate (.includes observational studies) Unclear population (chondral lesion of the knee)(for example, the proportion of participants with an osteoarthritis diagnosis not stated)
Schue 2011[427]	Conference abstract only
Schuette 2017[428]	Incorrect interventions (microfracture, unclear). Systematic review: study designs inappropriate (Includes observational studies)
Seo 2005[429]	Not in English language
Shah 2019[431]	Commentary only
Shanmugaraj 2019[432]	Systematic review: study designs inappropriate
Shanmugasundaram 2021[433]	Systematic review; references checked
Sheth 2021[434]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy) >20% had rheumatoid arthritis or crystal arthritis
Shewale 2017[435]	Incorrect study design (non-randomised study)
Shi 2002[437]	Not in English Language
Shi 2017[436]	Systematic review: study designs inappropriate (Includes observational studies)
Shimozono 2018[439]	Systematic review: study designs inappropriate (Includes observational studies)
Shin 2018[440]	Systematic review: study designs inappropriate (Includes observational studies)
Sibbitt 2009[443]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy) Included people with rheumatoid arthritis
Sibbitt 2011[442]	Wrong intervention – image-guided injection gives an additional 3mL of lidocaine, while non-image guided injection does not contain lidocaine.
Siddharth 2017[444]	No appropriate outcomes reported (No standard deviation/Cis/standard error. Just raw median outcome value.)
Smith 2003[448]	Incorrect interventions (arthroscopic lavage, arthroscopic lavage plus intra-articular corticosteroids)
Smith 2019[447]	Inappropriate comparison (combined intraarticular hyaluronic acid and corticosteroid versus intraarticular hyaluronic acid alone)

Study	Exclusion reason
Soler 2016[449]	Incorrect study design (non-randomised study)
Soriano-maldonado 2016[450]	No appropriate outcomes reported
Spaans 2015[451]	Systematic review; references checked
Spolidoro 2013[453]	Conference abstract only
Stein 1996[456]	Not in English language
Stein 1999[457]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritisOsteoarthritis and inflammatory arthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy). Incorrect interventions (intraarticular morphine, intraarticular dexamethasone, intraarticular saline)
Stitik 2007[458]	Incorrect interventions (intraarticular hyaluronic acid, intraarticular hyaluronic acid (a different type)
Stitik 2017[459]	Inappropriate comparison (3 weekly injections of hyaluronic acid versus 5 weekly injections of hyaluronic acid)
Strand 2006[461]	Systematic review; references checked
Strand 2015[463]	Systematic review; references checked
Sun 2017[464]	Inappropriate comparison (Intraarticular HYA-JOINT versus intraarticular Synvisc-One)
Suppan 2017[465]	Inappropriate comparison (One large dose of intraarticular hyaluronic acid versus three conventional doses of intraarticular hyaluronic acid)
Tamaddon 2018[468]	Article only
Tan 2021[471]	Systematic review; references checked
Tang 2010[472]	No usable outcomes
Tashiro 2012[474]	Incorrect interventions (oral hyaluronic acid, oral placebo)
Tetik 2003[476]	Incorrect interventions (intraarticular hyaluronic acid and physical therapy versus physical therapy alone)
Thein 2010[477]	People with meniscal injury without osteoarthritis. Incorrect interventions (arthroscopic partial meniscectomy and intra-articular hyaluronic acid, arthroscopic partial meniscectomy only)
Tian 2018[478]	Systematic review: study designs inappropriate. Retracted by editors as two studies included did not fit their protocol
Tikiz 2005[479]	Inappropriate comparison (high molecular weight hyaluronic acid injection versus low molecular weight hyaluronic acid)
Torrance 2002[480]	Incorrect interventions (intraarticular hyaluronic acid and standard care versus standard care alone)
Tran 2019[481]	Incorrect study design (non-randomised study).. Incorrect interventions. Inappropriate comparison (microfracture with stromal vascular fraction versus microfracture alone)
Trellu 2015[482]	Systematic review; references checked
Triantaffilidou 2013[483]	Incorrect study design (non-randomised study).
Trigkilidas 2013[484]	Systematic review; references checked
Turajane 2017[486]	Inappropriate comparison (autologous activated peripheral blood stem cells and hyaluronic acid versus hyaluronic acid)
Ucar 2013[487]	Inappropriate comparison (older cohort versus younger cohort)
Ulstein 2014[488]	Incorrect interventions (microfracture, osteochondral autologous transplantation mosaicplasty.) Unclear population (for example, the

Study	Exclusion reason
	proportion of participants with an osteoarthritis diagnosis not stated) Articular chondral lesions of the knee
Uluçay 2007[489]	Incorrect interventions (Na-hyaluronate after arthroscopic management, streptococcal HA and Hylan G-F 20 after arthroscopic management)
Unlu 2006[491]	Incorrect interventions (intraarticular tenoxicam, oral tenoxicam)
Unlu 2006[490]	Incorrect interventions (intraarticular tenoxicam and exercise, exercise alone (also a nonrandomised flare group))
Unsal 2008[492]	Not available from any UK/NLM source
Vadala 2016[493]	Systematic review: study designs inappropriate (observational studies only) . Incorrect interventions (bone marrow concentrated cells and stromal vascular fraction cell injections)
Vajaradul 1981[495]	Incorrect interventions (Intraarticular glucosamine,intraarticular saline)
Van middelkoop 2013[498]	Protocol only
Van middelkoop 2016[497]	Incorrect interventions (Intraarticular corticosteroid, placebo, intraarticular hyaluronic acid, tidal irrigation)
Vangsness 2014[499]	Inappropriate comparison (partial medial meniscectomy and allogenic mesenchymal stem cells versus partial medial meiscectomy and hyaluronic acid)
Vanlauwe 2011[500]	Incorrect interventions (Characterised chondrocyte implantation, microfracture). Unclear population (cartilage defects of the knee) (for example, the proportion of participants with an osteoarthritis diagnosis not stated)
Vannabouathong 2018[501]	Systematic review: study designs inappropriate (Includes observational studies.)
Vasiliadis 2010[502]	Unclear population (articular cartilage defects of the knee) (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Incorrect interventions (Autologous chondrocyte implantation, mosaicplasty, microfracture)
Volz 2017[504]	Incorrect interventions (autologous matrix-induced chondrogenesis, microfracture). Incorrect population (Medium sized cartilage defect)
Wang 2011[509]	No appropriate outcomes reported
Wang 2014[508]	Systematic review: study designs inappropriate (contains observational studies)
Wang 2015[505]	Systematic review; references checked
Wang 2016[510]	Not available in English Language
Wang 2017[511]	Unclear population (post- anterior cruciate reconstruction) (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Inappropriate comparison (injection of mesenchymal precursor cells plus hyaluronan v hyaluronan alone)
Wang 2018[507]	Inappropriate comparison (intraarticular combined corticosteroid and hyaluronic acid versus intraarticular hyaluronic acid)
Wang 2021[506]	Non-English language study
Wasiak 2006[512]	Incorrect interventions (autologous chondrocyte implantation, another intervention including mosaicplasty, periosteal grafting and tibial/femoral osteotomies). Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated)
Weil 2011[513]	Incorrect study design (non-randomised study)
Wheeler 2020[514]	Correspondence only

Study	Exclusion reason
Witteveen 2010[516]	Inappropriate comparison (Different doses of hyaluronic acid)
Witteveen 2015[515]	Cochrane systematic review; references checked
Wobig 1998[518]	Incorrect unit of randomisation (knee)
Wobig 1999[517]	Inappropriate comparison (high molecular weight hyaluronic acid injection versus low molecular weight hyaluronic acid)
Wu 1997[521]	No appropriate outcomes reported (reports results in graphical format only)
Wu 2004[520]	Not in English language
Wu 2017[519]	Systematic review; references checked
Xia 2015[522]	Systematic review: study designs inappropriate (includes observational studies)
Xin 2016[523]	Inappropriate comparison (Intraarticular hyaluronic acid injection (Adant) versus intraarticular hyaluronic acid injection (Artz))
Xing 2017[524]	Systematic review is not relevant to review question or unclear PICO (evaluating risk of bias in SRs for managing OA with hyaluronic acid)
Xing 2018[525]	Systematic review: study designs inappropriate (contains observational studies)
Xu 2015[526]	Not review population. Systematic review: study designs inappropriate (includes observational studies)
Yamamoto 1994[527]	Not in English language
Yang 2018[528]	Incorrect interventions. Inappropriate comparison (hyaluronic acid injection and oral glucosamine versus hyaluronic acid injection and placebo)
Yentur 2003[530]	Incorrect interventions. Inappropriate comparison (Intraarticular hyaluronic acid and trigger point therapy versus intraarticular hyaluronic acid alone)
Young 2001[531]	No appropriate outcomes reported (graphical format only)
Yuan 2016[532]	Incorrect interventions (Intraarticular betamethasone,intraarticular pulsed radiofrequency)
Yubo 2017[533]	Systematic review; references checked
Zhang 2015[535]	Inappropriate comparison (Durolane hyaluronic acid and sham skin punctures versus Artz hyaluronic acid)
Zhang 2016[536]	Inappropriate comparison (Intraarticular hyaluronic acid after arthrocentesis versus Intraarticular hyaluronic acid with no arthrocentesis
Zhang 2019[534]	Systematic review: study designs inappropriate (included observational studies)
Zhao 2016[537]	Systematic review is not relevant to review question or unclear PICO. Inappropriate comparison (High molecular weight hyaluronic acid versus low molecular weight hyaluronic acid)
Zhao 2018[538]	Systematic review: study designs inappropriate (included observational studies)
Zhilyayev 2012[539]	Conference abstract only
Zhou 2018[540]	Systematic review is not relevant to review question or unclear PICO (monitoring the effects of mesenchymal stem cells). Incorrect interventions
Zhuang 2007[541]	Not available in English language

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 78: Studies excluded from the health economic review

Reference	Reason for exclusion
Delbarre 2017	Excluded due to a combination of applicability and methodological limitations. French cost comparison study of ambulatory care resource use from registry data. French resource use and unit costs may not reflect the current NHS context; inappropriate comparison as some of those receiving hyaluronic acid injections also received corticosteroid injections; baseline characteristics not controlled for in cost comparison.

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the clinical and cost-effectiveness of intra-articular corticosteroids for managing osteoarthritis-affected joints other than the knee?

K.1.2 Why this is important

Intra-articular corticosteroids were found to have sufficient evidence of benefit for people with knee osteoarthritis and limited but consistent evidence for people with hip osteoarthritis. In this guideline, it was recommended to consider intra-articular corticosteroids for people with osteoarthritis. Given the limited evidence for joint sites other than the knee and hip, the committee agreed it was important for further research to establish if the treatment is effective for all joint sites.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Currently there are no randomised controlled trials investigating the use of corticosteroid injections for joint sites other than the hip and knee, adding uncertainty for using this treatment for other joint sites. This research could allow further understanding of the benefits and the adverse events the treatment could cause to those joint sites. Long term use of corticosteroids may be associated with adverse events that have been identified in non-randomised evidence. Investigating the long term effects in a randomised trial may allow this to be further understood.
Relevance to NICE guidance	There were no trials included in this guideline that investigated the use of corticosteroid injections for joint sites other than the hip and knee. There was limited evidence investigating the long term effects of corticosteroid injections. Work in these areas would allow for more confident recommendation making in future versions of the guideline.
Relevance to the NHS	No economic evidence was identified investigating the cost-effectiveness of corticosteroids for people with osteoarthritis. This research could capture this information and so allow the costs to resources to be understood better.
National priorities	There is not a national priority area.
Current evidence base	Currently RCT evidence for intra-articular corticosteroid injections is limited to osteoarthritis affecting the knee and hip. The majority of this evidence investigates short term benefits (≤3 months). Given this, longer term studies investigating the diversity of joint sites

	that can be affected by osteoarthritis would be beneficial at increasing knowledge.
Equality considerations	The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

K.1.4 Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies with an unclear population (e,g, type of arthritis, proportion of participants with osteoarthritis) • Spinal osteoarthritis • Knee osteoarthritis
Intervention	Intra-articular corticosteroids (of any type) – these may be delivered with or without image guidance as required
Comparator	Placebo injection
Outcome	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flare [dichotomous data]

	• Serious adverse events [dichotomous data]
Study design	Randomised control trial
Timeframe	Long term (at least 1 year)
Additional information	Subgroup analyses: • Image guided compared to non-image guided • Multimorbidity (high versus low morbidity score) • Site of osteoarthritis ○ Hip ○ Ankle ○ Foot ○ Toe ○ Shoulder ○ Elbow ○ Wrist ○ Hand ○ Thumb ○ Finger ○ Temporomandibular joint (TMJ)

K.1.5 Research recommendation

What is the clinical and cost-effectiveness of intra-articular stem cells for managing osteoarthritis?

K.1.6 Why this is important

Intra-articular stem cells were considered in this review. However, only limited evidence in trials with small sample sizes were available. Based on this, the committee agreed that there was currently insufficient evidence to make a recommendation for people with osteoarthritis. However, further research with larger sample sizes that investigated the long term effectiveness of the injections would provide more confidence for a potential therapy.

K.1.7 Rationale for research recommendation

Importance to 'patients' or the population	Currently stem cell therapy is not routinely available and so further work is needed to understand the potential benefits and harms of the treatment for people with osteoarthritis.
Relevance to NICE guidance	Insufficient evidence was found in this review to make a recommendation regarding the use of intra-articular stem cells. Given this, research with larger sample sizes investigating the long term effects would have the potential to change recommendations in the future.
Relevance to the NHS	Stem cell therapy is not routinely available on the NHS but is a new technology that is being delivered. If it becomes an important part of treatment, then there will be impacts on the

	NHS. Therefore, having a clear understanding of the cost effectiveness would be important.
National priorities	There is not a national priority area.
Current evidence base	Currently RCT evidence for intra-articular stem cells is limited to trials with a small sample size that does not report all outcomes important to the committee while making recommendations. The quality of the evidence was generally low due to problems with risk of bias and imprecision. Trials with a larger sample size that are well conducted would be required to make stronger conclusions.
Equality considerations	The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

K.1.8 Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies with an unclear population (e,g, type of arthritis, proportion of participants with osteoarthritis) • Spinal osteoarthritis
Intervention	Intra-articular stem cells – these may be delivered with or without image guidance as required
Comparator	Placebo injection
Outcome	Stratify by ≤/>3 months (longest time-point in each):

	• Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flare [dichotomous data] • Serious adverse events [dichotomous data]
Study design	Randomised control trial
Timeframe	Long term (at least 1 year)

Additional information	Subgroup analyses:
	• Image guided compared to non-image guided
	• Multimorbidity (high versus low morbidity score)
	• Site of osteoarthritis
	  ○ Hip
	  ○ Knee
	  ○ Ankle
	  ○ Foot
	  ○ Toe
	  ○ Shoulder
	  ○ Elbow
	  ○ Wrist
	  ○ Hand
	  ○ Thumb
	  ○ Finger
	  ○ Temporomandibular joint (TMJ)