International Centre for Allied Health Evidence

University of South Australia

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Systematic Review of the Literature

The Effectiveness of Knee Injection of Steroid with or without Local Anaesthetic

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Abbreviations

The following abbreviations are used in this report and are collated here for readers convenience

Abbreviation		Abbreviation	
AL	Anterolateral	**PAI**	Peri-articular Injection
AM	Anteromedial	**PICO**	Population, Intervention, Comparator, Outcome
BM	Betamethasone	**PLA2**	Phospholipase A2
CI	Confidence Interval	**PFPS**	Patello Femoral Pain Syndrome
COGA	Clinical observer global assessment	**PTGA**	Patient global assessment
HA	Hyaluronic acid	**RCT**	Randomised Controlled trial
HI	Hyaluronate injection	**ROM**	Range Of Movement
IASI	Intra-articular Steroid Injection	**RR**	Risk Ratio
iCAHE	International Centre for Allied Health Evidence	**SD**	Standard Deviation
JL	Joint Lavage	**SIGN**	Scottish Intercollegiate Guidelines Network
KSS	Knee Society Score	**SL**	Superolateral,
KOOS	Knee Injury and osteoarthritis outcome score	**SMD**	Standard Mean difference
MA	Meta-analysis	**SR**	Systematic Review
MDPS	Mean daily pain score	**TA**	triamcinolone acetonide
MRI	magnetic resonance imaging	**THA**	Triamacinolone hexacetonide
MPA	methylprednisolone acetate	**TCA - IR**	triamcinolone acetonide - immediate release
NASHA	non-animal stabilised hyaluronic acid	**USD**	United States dollar
NNT	Number needed to Treat	**VAS**	Visual Analogue Scale
NRS	Numerical Rating Scale	**WMD**	Weighted Mean Difference
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs	**WOMAC**	Western Ontario and McMaster Universities Arthritis Index
OA	Osteoarthritis		
	Quality Ratings		
AQ	Acceptable Quality	**LQ**	Low Quality
CS	Can't say	**NA**	Not Applicable
HQ	High Quality	**R**	Reject (Unacceptable Quality)
QS	Quality of Study		

EXECUTIVE SUMMARY

Objective of the Review	The objective of this systematic review is to synthesise the evidence related to the effectiveness of injection of steroid with or without local anaesthetic to the knee as a form of interventional pain management. In order to review the evidence this review aims to answer the following research questions 1. What is the evidence for the effectiveness of steroid injections into the knee with or without local anaesthetic in relieving pain and/or in improving functional outcomes in patients with pain? 2. What is the evidence for the safety of steroid injections into the knee with or without local anaesthetic?
Evidence sourced	The search yielded 2533 articles. After scrutiny, 1469 articles were excluded as duplicates or failing to meet the inclusion criteria (shown in Figure 1), leaving 31 studies for inclusion in this review including 13 systematic reviews (SRs) and 18 randomised controlled trials (RCTs).
What is the evidence for the effectiveness of steroid injections into the knee with or without local anaesthetic in relieving pain and/or in improving functional outcomes in patients with pain?	**Knee Osteoarthrosis** 1. **The evidence indicates that intra-articular steroid injections reduce pain in the short term (< 4 weeks) better than placebo or hyaluronic acid and their derivatives in patients with knee osteoarthritis**. *Level A recommendation* 2. **The evidence indicates that after four weeks intra-articular steroid injections are less effective than hyaluronic acid for pain reduction in patients with knee osteoarthritis.** *Level A recommendation* 3. **The evidence indicates that 40mg of slow release steroid is more effect than 10mg or 60mg in patients with osteoarthritis.** *Level B recommendation* 4. **The evidence indicates that the addition of intra-articular steroids in conjunction to a 12 week exercise program offers no additional benefit than the exercise program alone in patients with osteoarthritis.** *Level B recommendation* **Patella tendinopathy** **The evidence indicates that steroid injections offer little additional benefit over an exercise program comprising of either eccentric exercises or heavy slow repetitions, with the latter two providing a gradual decrease in pain while the steroid effect diminishes** *Level C recommendation*
What is the evidence for the safety of steroid injections into the knee	**Knee Osteoarthrosis** **Minor complications associated with intra-articular steroid injections into the knee are not uncommon but rarely require significant medical attention. Adverse effects occur in 3.5-21% of participants, and include arthralgia, joint stiffness, joint swelling, joint effusion, joint warmth, joint crepitation, injection site pain and joint instability.** *Level A recommendation* **Patella tendinopathy** **Adverse events associated with steroid injections for patellar tendinopathy are rare**. *Level C recommendation*

What is the evidence for differences in effectiveness if imaging is used?	**Knee Osteoarthritis** **The evidence indicates that sonographically guided injections are more effective than palpation guided injections for pain relief in both the short and long term term.** *Level D recommendation*
Does the evidence report any information about cost effectiveness?	**Knee Osteoarthritis** **The evidence indicates that intra-articular steroids injections were more expensive than ketorolac (NSAID) and whilst provided additional benefit on function, steroids were not as cost effective as NSAIDs.** *Level D recommendation*
Does the evidence change the 2005 recommendations	**2005 Summary of Evidence** *"There is medium to high quality evidence from two systematic reviews and sixteen randomised controlled trials (RCTs) that intra-articular steroid injection into the knee joint is effective in the short term (up to two weeks) for the treatment of adults with osteoarthritic knee pain. There was also some limited evidence to suggest that high doses of steroid may provide longer term effectiveness."* **Despite an increase in evidence the recommendations do not change significantly**

1. Background

1.1 Objective of this Review

The objective of this review is to synthesise the evidence related to the effectiveness of injection of steroid with or without local anaesthetic into the knee as a form of interventional pain management. This review will carry out a systematic review of the best available research evidence.

This review aims to answer the following research questions:

a) What is the evidence for the effectiveness of steroid injections with or without local anaesthetic in relieving pain in patients with knee pain?
b) What is the evidence for the effectiveness of steroid injections with or without local anaesthetic in improving functional outcomes in patients with knee pain?
c) What is the evidence for the safety of steroid injections with or without local anaesthetic in patients with knee pain?

1.2 Description of the Intervention

Knee pain is a common complaint with a reported prevalence of 25% in older adults (McAlindon et al., 1992; O'Reilly et al., 1996; Turkiewicz et al., 2014). In a population based survey of Chinese subjects aged 70 years and over, the knee was the most commonly reported site of pain complaints (Woo et al., 1994). A recent study conducted in Sweden found the prevalence of frequent knee pain in one or both knees during the last 12 months was 25.1% and the prevalence of knee pain on most days of the previous month was 20.3% in individuals aged between 56-84 years of age (Turkiewicz et al., 2014). Similar findings were reported in the United States, with 30% of adults 65 years of age reporting knee pain of stiffness in the preceding 20 days (Health, United States 2006).

Knee pain can affect all age groups and can arise from a multitude of pathologies including patellofemoral syndrome, patella tendinopathy, patellofemoral instability, fat pad impingement, bursitis, tendonitis, ligament injuries, bakers cyst and osteoarthritis (Ptasznik 1999). For adults over the age of 55 knee pain is most often attributable to osteoarthritis (Peat, McCarney and Croft 2001) a disease which is expected to become increasingly common due to aging and the increasingly obese population in many countries (Turkiewicz et al., 2012). For individuals below the age of 55, there are a range of potential knee pain causes – notably injuries to cartilage, ligaments and soft tissue structures around the joint, with patellofemoral joint pain the most commonly identified cause in this younger population (Peat, McCarney & Croft 2001).

Although knee pain can originate from diverse origins, management options tend to be similar and include non-pharmalogical measures, such as exercise and weight loss, medications, including analgesics and non-steroidal anti-inflammatory drugs, injections such as corticosteroids and viscosupplementation and, finally, surgery which can include a total knee replacement or reconstruction (Neustadt 2006; Richards et al., 2016).

Steroids - Rationale

Locally, corticosteroids act to inhibit the inflammatory response induced by mechanical, chemical, or immunologic agents. This inhibition occurs in specific leukocyte functions, including leukocyte aggregation at inflammatory sites, prevention of degranulation of granulocytes, mast cells, and macrophages, and stabilization of lysosomal and other membranes (Di Rosa et al., 1986). Corticosteroids also inhibit PLA2 activity, therefore interrupting the arachidonic acid cascade. It has also been shown that local application of cortisone blocks transmission in normal nociceptive C-fibres, potentially blocking nociceptive nerves in the manner of local anaesthetics.

Several different steroid preparations may be used, with or without local anaesthetic or normal saline to increase the volume of the injectate. Typical steroids used include methylprednisolone acetate, betamethasone acetate/propionate, and triamcinolone acetate. The benefits of adding a local anaesthetic include potential immediate pain relief for the patient which provides feedback to the practitioner that the steroid solution is near the presumed site of pathology.

2. Methodology

2.1 Review question

What is the effectiveness of knee injection of steroid with or without local anaesthetic?

2.2 Methods

A systematic review of published research literature was undertaken to provide a synthesis of the currently available research evidence related to the effectiveness of knee steroid injections with or without local anaesthetic as a form of interventional pain management. A systematic and rigorous search strategy was developed to locate all published and accessible research evidence. The evidence base for this review included research evidence from existing systematic reviews, meta-analyses, and high-level primary research (randomised controlled trials). Where no systematic reviews or randomised controlled trials were located then other primary study designs (excluding commentary /expert opinion) were considered.

2.3 Search strategy

The search was developed using a standard PICO structure (shown in Table 1). Only English articles published, using human participants, which were accessible in full text were included.

Table 1: Criteria for considering studies in the review

Population	Humans with knee pain
Intervention	Steroid injection to the knee with or without local anaesthetic as a form of interventional pain management
Comparator	Any active treatment or placebo.
Outcomes	• Pain-related primary outcome; • Functional outcomes (range of motion, reduction of disability, return to work, quality of life) • Safety and Risk • Relationship to Imaging • Best Practice recommendations • Cost effectiveness

A combination of search terms (shown in Table 2) were used to identify and retrieve articles in the following databases:

- OVID
  - EMBASE,
  - MEDLINE,
  - AMED,
- ICONDA,
- CINAHL,
- PubMed,
- Pre-Medline,
- The Cochrane Library,
- Scopus,
- TRIP database

Table 2: Search terms for the review

Search term 1	Search terms 2	Search terms 3	Search terms 4
• Pain	• Injections • Intra-articular .	• Knee • Patellofemoral joint • Tibio-femoral joint	• Steroid • Betamethasone • Dexamethasone • Fluocortolone • Methylprednisolone • Paramethasone • Prednisolone • Prednisone • Triamcinolone • Hydrocortisone • Cortisone • Methandrostenolone • Stanozolol • Methenolone • Oxymetholone • Oxandrolone • Nandrolone • Diflucortolone • Fluprednisolone

The titles and abstracts identified from the above search strategy were assessed for eligibility by the *i*CAHE researchers. Full-text copies of eligible articles were retrieved for full examination. Reference lists of included full-text articles were searched for relevant literature not located through database searching.

2.4 Study Selection

Inclusion Criteria

- Study types: systematic reviews, all primary research designs (randomised controlled trials (RCTs), cohort studies (prospective or retrospective), case studies or case series.
- Participants: Patients with knee pain.
- Intervention: Steroid injections with or without local anaesthetic
- Controls: any active treatment or placebo, or no intervention control
- Outcomes: Pain relief (primary) functional outcomes, safety, and risk (secondary)
- Publication criteria – English language, full text available, in peer reviewed journal

Exclusion criteria

- Studies only available in abstract form e.g. conference presentations
- Grey literature and no-English language material
- Studies involving healthy volunteers or experimentally induced pain

2.5 Critical Appraisal

The SIGN (Scottish Intercollegiate Guidelines Network) checklist specific to the study design of the included studies was used to assess the methodological quality of the included studies. The SIGN checklist asks a number of questions with yes, no, can't say or not applicable as responses with the appraiser giving an overall rating of quality, based on the responses to questions of either high quality (++), acceptable (+), low quality (-) or unacceptable. As there is no SIGN Checklist for Case studies these study designs will not be quality scored

2.6 Data Extraction

Data were extracted from the identified publications using a data extraction tool which was specifically developed for this review. The following information were extracted from individual studies:

- Evidence source (Author, date, country)
- Level of evidence
- Characteristics of participants
- Interventions
- Outcome measures
- Results

For this review the studies that met the inclusion criteria were assessed for internal validity using the Scottish Intercollegiate Guidelines network (SIGN) Checklist for the relevant study design. Each study was graded for overall methodological quality using the SIGN Levels of evidence model

2.7 Data Synthesis

As described, for this review each study was graded for overall methodological quality using the SIGN checklist specific to the study design of the included studies.

Recommendations from the literature were made and scored according to a modification of the SIGN Evidence Grading matrix (see Table 3). The modification was to add levels 1 and 2 to differentiate between the 1+ and 1-, 2+ and 2- levels of evidence.

Table 3 : Modified SIGN Evidence Grading Matrix

Levels of scientific evidence	
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias
1	Meta-analyses, systematic review of clinical trials or clinical trials with a moderate (acceptable) level risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship
2	Cohort or case and control studies with moderate risk of bias and potential risk that the relationship is not causal.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

To standardise the strengths of recommendations from the extensive literature used for this review a structured system was developed to incorporate a number of quality measures. Four measures were selected as important variables for the assessment of strength of recommendations from the primary and secondary research sources. These were

a) Combination of data via meta-analysis

b) Quality of systematic review/trials

c) Number of RCTs

d) Consistency of the evidence

A scoring system was developed, based on a 0 and 1 score for each of these variables.

1. Combination of data via meta-analysis : Yes = 1, No = 0
2. Quality of systematic review: HQ/AQ (+) =1, LQ(0)/R = 0
3. Number of RCTs: ≥ 5RCTs = 1, < 5=0
4. Consistency: ≥ 75% agreement = 1, < 75% agreement = 0

This allowed for a maximum potentials core of 4 and a minimum score of 0, which reflected a measure of the evidence strength across a range of studies. The resultant score was transferred to the SIGN Evidence Grading matrix

Total Score	SIGN Evidence Grading matrix score
4	1++
3	1+
2	1
1/0	1-

2.8 Grade of Recommendations

Recommendations will be graded according to the Scottish Intercollegiate Guidelines network (SIGN) Grades of Recommendations (Table 4)

Table 4: Scottish Intercollegiate Guidelines network (SIGN) Grades of Recommendations

Grades of Recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+

3. Results

3.1 Evidence Sources

The search yielded 2533 articles; following removal of duplicates 1,500 articles were identified for screening of title and abstract. After scrutiny, 1469 articles were excluded for failing to meet the inclusion criteria (shown in Figure 1), leaving 31 studies for inclusion in this review. Figure 1 illustrates the process involved in study selection.

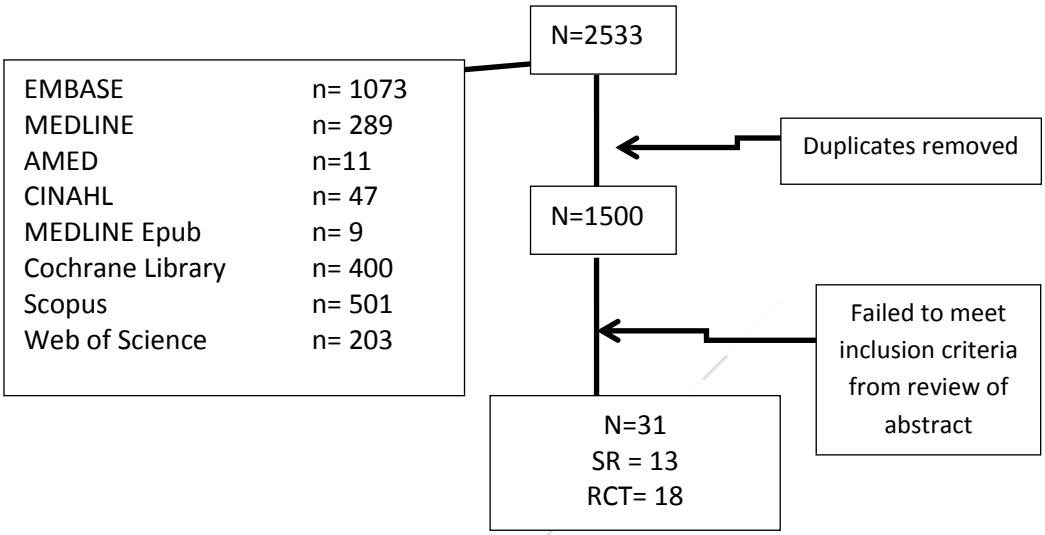

Figure 1: Flow chart of search results

13 systematic reviews met the inclusion criteria for this review. Randomised controlled trials were only included if they were published from 2005 onwards and were not already included within the SRs.

3.2 Quality of the Evidence

The overall quality of the studies included in this review ranged from high quality to low quality. Three SRs were of high quality (1++), three were of average quality (1+) and seven were of low quality (1-). In regards the RCTs, eight were of high quality, three were deemed to be of average quality and seven were of low quality.

The overall quality of the studies included in this review ranged from high quality to low quality.

	N=	HQ(++)	AQ(+)	LQ(-)	R(0)
Systematic reviews	13	3	3	7	3
RCTs	18	8	3	7	0

Appendices 2 and 3 present the critical appraisal scores for the SRs and RCTs included in this review

Systematic reviews

A) Studies did not address the potential for publication bias in reporting their reviews.
B) Conflicts of interest were often not identified or reported

C) Excluded studies were not listed
D) Reviews often failed to differentiate between primary and secondary outcomes when synthesising their findings. Most systematic reviews used pain as a primary outcome and functional disability, etc, as secondary outcomes, but failed to differentiate between the two when synthesising the study findings in their reviews.
E) Reviews did not differentiate between primary osteoarthritis (OA due to degenerative changes) or secondary osteoarthritis (OA due to a significant injury or other pathology)

Randomised controlled trials

A) The studies often failed to ensure that the only difference between the two groups (Intervention vs control) was the treatment under investigation. With the small numbers reported in the RCTs it was difficult to ensure that the effect of confounders was dealt with. This was particularly important when considering the effect of secondary outcomes.
B) A number of studies failed to report the use of intention to treat analysis when reporting the study's findings.
C) Subjects and investigators were rarely blinded to the intervention involved.
D) Studies rarely controlled for the patients involvement in co-interventions such as exercise/medication etc.
E) Trials did not differentiate between primary osteoarthritis (OA due to degenerative changes) or secondary osteoarthritis (OA due to a significant injury or other pathology)

3.3 Findings

Ten (10) systematic reviews (Campbell et al., 2015; Bjordal et al., 2007; Hepper et al., 2009; Godwin & Dawes 2004; Cheng et al., 2012; Wang & He 2015; van Middlekoop et al., 2016; Bannuru et al., 2009; Bellamy et al., 2006; Juni et al., 2015) reviewed the efficacy of intra-articular steroid injections for knee osteoarthritis compared to either a placebo, another intervention or to baseline scores. Two low quality systematic reviews (Maricar et al., 2013; Hirsh, Kitas & Klocke 2013) specifically reviewed factors that influence and/or predict the effect of intra-articular steroids including different steroid preparations and administration techniques. One high quality systematic review (Heintjes et al., 2004) took a broad approach, analysing pharmacotherapies for patellofemoral pain syndrome, which included steroid injections.

Of the RCTs included, two studies specifically looked into the economic values of steroid injections (Sibbitt et al., 2011; Bellamy, Goff & Sayeed 2016). Three studies specifically analysed effectiveness on pain from different treatment approaches (Wagner et al., 2015; Pierce et al., 2016). 11 studies examined the efficacy of intra-articular steroid injections for knee osteoarthritis (Bodick et al., 2015; Davalillo et al., 2015; De souza, Issy & Sakata 2010; Dieu-Donne et al., 2016; Folman and Shabat 2011; Housman et al., 2014; Leighton et al., 2014; Tammachote et al., 2016; Parmigiana et al., 2010; Sari et al., 2016; Skwara et al., 2009). Two studies used steroids as an adjunct therapy for exercise for individuals with knee osteoarthritis (Henriksen et al., 2015; Soriano-Maldonado et al., 2016). One study looked at the efficacy of steroid injections for the pathology of patellar tendinopathy compared to exercise (Konsgaard et al., 2009).

3.4 Outcome Measures – Pain and Function

This review took a pragmatic approach to the presentation of the literature, sub-dividing the studies into the most common major clinical presentations reported in the literature. For the knee these were osteoarthritis and patellofemoral pain syndrome. Where systematic reviews reported studies involving a range of pathologies, if possible the data for each pathology has been extracted from the individual SR and is presented separately below.

Both presentations may result from traumatic injury and/or degenerative changes. In terms of osteoarthritis this is differentiated as primary OA (considered "wear and tear" osteoarthritis, which usually develops after 50 years of age) and secondary OA (osteoarthritis with a specific cause, such as an injury, an effect of obesity, genetics, inactivity, or other diseases). Where the studies have differentiated between the two types this is presented in the descriptions of the studies. The majority of studies did not differentiate between the two types of osteoarthritis.

3.4.1 Osteoarthritis - Systematic reviews

Godwin & Dawes (2004)

Godwin & Dawes (2004) (QS:LQ(-)) completed a systematic review/meta-analysis of the evidence related to whether intra-articular injections of a depo-steroid preparation decreased knee pain secondary to osteoarthritis (both primary and secondary), and specifically if it could decrease pain without causing any serious side effects. The paper included five high quality RCTs, without providing a specific description of the critical appraisal results.

The results found that at 1 week, the depo-corticosteroid group scored significantly lower on the visual analogue scale (VAS) compared to the control group (placebo in all five studies), at three to four weeks the reduction of target pain remained significant but the difference in the VAS scores were no longer significant and at six to eight weeks there was no difference in achievement of target pain reduction or in VAS score between the treatment and the control groups.

The authors also looked into different treatment techniques using different steroid preparations and the results showed that treatment effects were consistent among the five studies and no study showed an effect of triamcinolone beyond 1 week. Methylprednisolone however showed a continuing effect at 3 weeks, and Cortivazol at 4 weeks.

The meta-analysis concluded that intra-articular depo-steroids resulted in a clinically and statistically significant reduction in knee pain 1 weeks after injection that continues for three to four weeks

Study	QS	Conclusions	Level of Evidence
Godwin & Dawes (2004)	LQ (-)	• At 1 week post injection 2 of 2 studies showed depo-steroid statistically significantly reduced VAS compared to the control	1
		• At week 3 to 4 there was no significant difference in VAS score between the steroid group and the control group	1
		• At week 6 to 8 there was no significant difference in VAS score between the steroid group and the control group	1

Bellamy et al, (2006)

Bellamy et al., (2006) (QS:HQ(++)) completed a Cochrane systematic review into the efficacy and safety of intra-articular steroids in patients with osteoarthritis of the knee (both primary and secondary). They identified 26 RCTs which involved intra-articular steroid injections for knee osteoarthritis (see table below).

Study	Comparator	Co-treatment	Outcome
Bias, Labrenz and Rose (2001)	Dexamethasone palmitate (lipotalon) [4mg vs 12mg]		**Pain** • Lowest reduction in pain after an average of four days **Adverse Events** • No adverse events were recorded
Caborn et al., (2004)	Hyalgan G-F 20		**Pain** • The onset of action faster in the steroid group, comparator resulted in longer duration of effect **Adverse Event** • 10% of patients reported an adverse event
Cederlof & Jonson (1996)	Saline		**Pain** • No difference reported
Dieppe et al., (1980a, 1980b)	Saline		**Pain** • Maximum benefit in pain score reported in the steroid group 1 week post injection
Friedman & Moore (1980)	Placebo		**Pain** • No statistically significant difference between groups **Adverse Events** • Post injection flares occurred in similar frequencies in both groups
Frizziero, Pasquali & Ronchetti (2002)	5 weekly injections of Hyaldan		**Pain** • Significant difference in favour of steroid at day 35 but not day 180 • Hyalgan was superior in reducing the extent and grade of cartilage damage **Adverse Event** • Two patients in steroid group withdrew due to adverse event
Gaffney et al., (1995)	Saline		**Pain** • Pain relief significantly greater (P<0.01) in the steroid group 1 week post injection **Function** • No significant difference detected at 1,6 weeks post injection
Jones et al., (1995)	Saline		**Pain** • No difference found, **Adverse Events** • 57% of patients withdrew from steroid group due to worsening of knee symptoms and slow improvement
Jones & Doherty (1996)	Saline		**Pain** • Pain was significantly (P<0.0001) reduced at 3 weeks in steroid group • A significant difference was detected in the number of responders at 3 weeks post injection (RR=3.11; 95% CI 1.61 to 6.01; p value = 0.0007; NNT = 3) **Adverse events** • Two patients withdrew from steroid, one from saline due to worsening symptoms

	Leardini et al., (1987)	3 weekly injections of Hyalgan		**Pain** • No statistical difference were found between groups
	Leardini et al., (1991)	3 weekly injection of Hyalgan		**Pain** • At 1 week no difference • In long term pain reduction in favour of comparator
	Leopold et al., (2003)	3 weekly injections of Hylan G-F 20		• No difference in pain or function between the 2 groups was found at 6 month follow up
	Miller et al., (1958)	Saline		• 6 weeks post injection no difference between groups based on percentage of patients improved • At 6 month no significant difference between the groups
	Pietrogrande et al., (1991)	5 weekly injections Hyalgan		• Both groups reduced symptoms, steroid had a rapid action, comparator lasted longer
	Popov et al., (1989)	Triamcinolone aectonide, hydrocortisone acetate, aprotinin, polyvinylpyrrolidone and physiologic solution		• Triamcinolone acetonide and hydrocortisone acetate were significantly better than other groups, no difference was found between two steroid groups
	Pyne et al., (2004)	Triamcinolone hexacetonide with methylprednisolone acetate		**Pain** • Both steroids provided short term relief, THA more effective than MPA at week 3, lost its effect by week 8 • MPA lasted to 8 weeks
	Ravaud et al., (1999)	Saline		**Pain** • Steroid group had significantly P=0.02 improved VAS score at week 4. • Significant difference found in number of responders (64% steroid vs 25% saline) at 1 week post injection (RR=2.56; 95% CI 1.26 – 5.18; p =0.009; NNT = 2.6) no difference was found at 4,12,24 weeks. **Function** • Significant difference were detected at 1,4,12,24 weeks post injection
	Raynauld et al., (2003)	Saline		**Pain** • Steroid group reported greater improvement in pain **Function** • Significant difference between steroid and saline at 2 years post injection for ROM (WMD 10.40; 95% CI 8.45 to 12.35; p value 0.00001) but not 1 year
	Smith et al., (2003)	Joint Lavage with and without steroid		• No significant difference between the two groups for pain, stiffness or WOMAC or Lequesne assessments • Significant difference at 4 weeks in the OARSI response criteria in favour of the steroid group compared to placebo group
	Tascioglu & Oner (2003)	3 weekly injections of Orthovisc	Paracetamol (maximum 3g daily)	• Significant improvement was reported in both groups at week 4 in pain and Lequesne Index outcome measures • At 3 months a significant improvement in pain and Lequesne in favour of comparator • 6 months no difference between groups
	Tekeoglu et al., (1998)	3 weekly injections of Orthovisc	Paracetamol permitted	• Short term steroid more effect (week 3) • Long term comparator more effective (week 15)

Thorpe (1985)	Triamcinolone acetonide and methylprednisolone acetate		• No difference between the two groups
Valtonen (1981)	Triamcinolone hexacetonide with combination betamethasone acetate and betamethasone disodium phosphate		• Both groups had significant improvements in pain 1 week post injection, triamcinolone hexacetonide was significantly superior (P=<0.005) • The duration of effect was significantly longer with triamcinolone hexacetonide
Wright et al., (1960)	Hydrocortisone acetate; hydrocortisone tertiary-butylacetate and placebo		• No significant difference found between steroid groups • Hydrocortisone tertiary-butylacetate group significant pain improvement compared to placebo at 2 weeks (RR= 1.81; 95% CI 1.09-3.00 p=0.02;NNT=3)
Young et al., (2001)	Arthroscopy with and without steroid		• Significant reduction in WOMAC score within the MPA; no decrease in placebo group

They concluded that for knee osteoarthritis, there is some evidence for efficacy of pain reduction and patient global assessment at one week post injection, with evidence also for continuing efficacy at two and three weeks post injection. They also concluded that there was little or no effect (versus placebo) on function and that trimacinoline hexacetonide was superior to betamethasone for the number of patients reporting pain reduction up to four weeks post injection, but no other clinically or statistically important differences were detected in comparisons of different corticosteroid products.

Study	QS	Conclusions	Level of Evidence
Bellamy et al., (2005)	HQ(++)	• Steroids are effective at pain reduction in osteoarthritic knees in the short term (up to 4 weeks)	1++
		• Steroids offer little to no effect on function	1+

Bjordal et al., (2007)

Bjordal et al., (2007) (QS:LQ(-)) conducted a meta-analysis to determine the short term pain relieving effects of commonly used pharmacological agents for osteoarthritic knee pain (both primary and secondary), for which six RCTs using intra-articular steroid injections versus a placebo control group were included.

Four of the studies were deem to be of high quality and two of the included studies rated poorly for their methodological qualities (Friedman 1980; Jones 1996; Ravaud 1999; Smith 2003; Gaffney 1995; Dieppe 1980) respectively. The review showed that intra-articular steroids injections for osteoarthritic knees produced a mean effect size over placebo which was large enough to exceed the mean threshold for "slight improvement" and with intra-articular steroid injection, efficacy gradually declined during follow up.

The authors concluded that for the first four weeks post treatment intra-articular steroid injection offer limited pain relief over placebo within the 1-2 week time period, but the intervention did not seem to offer meaningful pain relief beyond the first month.

Study	QS	Conclusions	Level of Evidence
Bjordal et al., (2006)	LQ (-)	• During the first four weeks after treatment initiation intra-articular steroid injections offer limited pain relief over the placebo within 1-2 weeks	1-
		• Intra-articular steroid injections don't offer meaningful pain relief beyond the first month	1-

Hepper et al., (2009)

Hepper et al., (2009) (QS:LQ(-)) completed a systematic review into the efficacy and duration of the benefit from steroid injections in reducing knee pain secondary to osteoarthritis (both primary or secondary). It also looked at whether there was a difference between various steroids in efficacy of pain reduction for knee osteoarthritis. Five studies met the inclusion criteria (Ravaud et al., 1999; Friedman and Moore 1980; Gaffney et al., 1995; Dieppe et al., 1980; Jones and Doherty 1996). In each of the studies, normal saline solution was used as the comparator.

The results showed that at week 1, four of the studies assessing VAS pain reported a statistically significant decrease between the steroid and placebo group and a decrease in pain from the baseline measures. Three to four weeks post injection, no statistically significant decreases in pain were found between the treatment and placebo group. Only one study (Ravaud et al., 1999) reported a statistically decrease from baseline with the steroid group at week 4 and at week six to eight no study demonstrated statistically significant difference between the steroid and placebo group.

In regard to the use of different preparations, two of four studies favoured the use of triamcinolone; one study reported a statistically significant decrease in pain favouring triamcinolone compared with methylprednisolone at week three (but at no other time point).

They concluded that patients receiving steroids experience approximately a 22% greater reduction in pain within the first week than did patients receiving placebo however this efficacy is seen consistently only at one week post injection, not beyond there when longer term pain reduction is desirable, other treatment modalities may be able to attain the goal better.

Study	QS	Conclusions	Level of Evidence
Hepper et al., (2009)	LQ(-)	• There was a statistically significant decrease in pain from baseline at week 1 following steroid injections	1
		• Only one study reported a statistically significant decrease from baseline within the steroid group at week 4	1-
		• At week 4-3, 6-8 and 12-24 no statistically significant differences were found between the steroid and the placebo group	1-
		• One study found at week 1 triamcinolone to be more effective than betamethasone in pain scores	1-
		• One study found triamcinolone to be more efficacious than methylprednisolone at week 3	1-
		• Two studies failed to find any statistically significant difference between triamcinolone and methylprednisolone	1-

Bannuru et al., (2009)

Bannuru et al., (2009) (QS:AQ(+)) conducted a systematic review/meta-anaysis comparing the efficacy of intraarticular hyaluronic acid with for knee osteoarthritis (OA) (both primary and secondary). They identified 7 RCTs which compared the therapeutic effects of intraarticular hyaluronic acid with that of intraarticular corticosteroids to treat knee osteoarthritis (see table below).

Study	Comparator	Co-treatment	Outcome
Leardini et al., (1987)	Hyalgan 2ml (20mg), 3 weekly injections		**Pain** • Effect size from baseline at 2/52 = 0.069 [-0.530, 0.708] favouring Hyaluronic acid • Effect size at 4/52 = 0.182 [-0.439,0.803] favouring Hyaluronic acid
Leardini et al., (1991)	Hyalgan 2ml (20mg), 3 weekly injections		**Pain** • Effect size from baseline at 2/52 = -0.355 [-0.981,0.270] favouring corticosteroids • Effect size from baseline at 4/52 = 0.274 [-0.349,0.897] favouring Hyaluronic acid
Pietrogrande et al., 1991	Hyalgan 2ml (20mg), 5 weekly injections		**Pain** • Effect size from baseline at 2/52 = -0.443 [-0.863,0.024] favouring steroids • Effect size from baseline at 4/52 = 0.241 [-0.174,0.657] favouring Hyaluronic acid
Jones et al., 1995	Hyalgan 20mg, 5 weekly injections		**Pain** • Effect size from baseline at 4/52 = -0.047 [-0.476,0.570] favouring steroids • Effect size from baseline at 26/52 = 0.353 [-0.550,1.257] favouring Hyaluronic acid
Frizziero, Pasquali & Ronchetti 2002	Hyalgan 2ml (20mg), 5 weekly injections		**Pain** • Effect size from baseline at 2/52 = -0.819 [-0.476,0.570] favouring steroids • Effect size from baseline at 4/52 = -0.548 [-0.950,-0.420] favouring steroids • Effect size at 12/52 = 0.027 [-0.367,0.420] favouring hyaluronic acid • Effect size at 26/52 = 0.238 [-0.158, 0.634] favouring hyaluronic acid
Tascioglu & Oner 2003	Orthovisc 2ml (30mg), 3 weekly injections		**Pain** • Effect size from baseline at 4/52 = -0.038 [-0.567, 0.491] favouring steroids • Effect size at 12/52 = 0.0577 [0.036,1.118] favouring hyaluronic acid • Effect size at 26/52 = 0.450 [-0.085, 0.985] favouring hyaluronic acid
Caborn et al., 2004	Synvisc 2ml (16mg), 3 weekly injections	+ Subacromial steroid injection	**Pain** • Effect size from baseline at 2/52 = -0.256 [-0.524, 0.013] favouring steroids • Effect size from baseline at 4/52 = 0.000 [-0.269, 0.269] • Effect size at 12/52 = 0.467 [0.196,0.737] favouring hyaluronic acid • Effect size at 26/52 = 0.440 [0.169, 0.710] favouring hyaluronic acid

The authors reported that when reviewing the effect on pain compared to hyaluronic acid, at 2 weeks there was a mean effect size of -0.39 (95% CI -0.65 to -0.12) favouring steroids, at week

4 the effect size was -0.01 (95% CI -0.23 to 0.21) suggesting equal efficacy with hyaluronic acid and at week 8, 12 and 26 the results favoured hyaluronic acid. They concluded that in the short term (up to 4 weeks) steroids appear to be more effective for pain, there is equal efficacy 4 weeks after initiation of treatment compared to hyaluronic acid and by 8 weeks and beyond, hyaluronic acid products demonstrated greater relative effects.

Study	QS	Conclusions	Level of Evidence
Bannuru et al., (2009)	AQ(+)	• Steroids are effective at pain reduction in osteoarthritic knees in the short term (up to 4 weeks)	1+
		• The effect is largely absent by 26 weeks	1++

Cheng at al (2012)

Cheng at al (2012) (QS:LQ(-)) conducted a systematic review of the evidence related to injections for the management of knee arthritis, which included intra-articular steroids for knee osteoarthritis (both primary and secondary). The systematic review included two meta-analysis that evaluated the effect of intra-articular steroids injections (IASI) on osteoarthritis of the knee. Included in these papers were five RCTs of high methodological quality, which showed clinically and statistically significant reductions in knee pain one week post injection. It was reported that the beneficial effect could last for three to four weeks, but was unlikely to continue beyond that.

They concluded there was strong evidence that supported the use of intra-articular steroid injections for osteoarthritis, leading to significant pain relief and functional improvements for only four weeks.

Study	QS	Conclusions	Level of Evidence
Cheng et al., (2012)	LQ(-)	• One meta-analysis showed clinically and statistically significant reduction in knee pain 1 week after injection which could last for 3-4 weeks but is unlikely to continue beyond that	1-
		• Second meta-analysis showed that the improvement in symptoms after steroid injection only lasted up to 2 weeks	1-

Maricar et al (2012)

Maricar et al (2012) (QS:LQ(-)) conducted a systematic review which included a section regarding treatment factors which can predict either the magnitude or duration of response to intra-articular steroid injections in the knee for knee osteoarthritis (both pruimary and secondary). One study looked into sonographically guided injections compared with blind injections. The sonographically guided injections led to a further 42% decrease in absolute pain from baseline scores at two weeks, however pain outcomes at six months were similar whether these injections were performed blind or sonographically guided.

Two other studies investigated whether different injection sites and approaches influenced the outcome from intra-articular steroid injection; both studies found no difference in the

therapeutic response between infrapatella, medial knee, lateral mid-patella and anterolateral joint line with the knee flexed.

The authors concluded that sonographically guided injections when compared to blind injections led to a greater decrease in pain from baseline scores at two weeks and there was no difference in outcome using different injection approaches.

Study	QS	Conclusions	Level of Evidence
Maricar et al., (2012)	LQ(-)	• Sonographically guided injections when compared to blind injection led to a greater decrease in pain from baseline scores at two weeks	1-
		• There was no difference in therapeutic response between infrapatella, medial knee, lateral mid-patella and anterolateral joint line with the knee flexed	1-

Hirsch, Kitas & Klocke (2013)

Hirsch, Kitas & Klocke (2013) (QS:LQ(-)) conducted a systematic review relating the predictors of pain reduction following intra-articular steroid injections in patients with knee arthritis, four of the included studies described knee osteoarthritis and factors related to the technique or the corticosteroid preparations used. One study (Sambrook et al., 1989) showed no significant difference in pain relief between intra-articular injection to injection into the patellar margin. Two trials included comparisons of triamcinolone hexacetonide with betamethasone (Valtonen 1981) and methylprednislonone (Pyne et al., 2004), showing varied results at different time points for efficacy. One trial (Wright et al., 1960) compared hydrocortisone tertiary-butyl-acetate with hydrocortisone with direct comparison of the two drugs showing no statistical difference. The SR found very limited evidence for predictive factors of pain relief following intra-articular steroid injections in osteoarthritic knees.

They concluded that evidence for predictors of pain relief after intra-articular steroid injection, these being steroid preparations or injection administration techniques, in knee osteoarthritis was weak.

Study	QS	Conclusions	Level of Evidence
Hirsch, Kitas & Klocke (2013)	LQ(-)	• When comparing THA vs MPA at 3 weeks THA had greater pain reduction than MPA (P<0.01) at 8 weeks there was no statistical significant difference between the two	1-
		• When comparing THA vs BM at week 1 follow up THA had greater reduction of pain than BM (p<0.005) at the week 2 and 4 follow up there was no significant difference	1-
		• When comparing hydrocortisone acetate vs hydrocortisone tertiary butyl acetate at 2 weeks only hydrocortisone tertiary butyl acetate was statistically superior to placebo at 2 weeks (p< 0.02) and at 4 weeks both were non-significant	1-
		• When comparing intra-articular vs peripatella there was no significant difference between the two injection approaches	1-

Wang & He (2014)

Wang & He (2014) (QS:AQ(+)) conducted a systematic review/meta-analysis to compare the therapeutic effect of intra-articular steroids for knee osteoarthritis compared to hyaluronic acid. This study also compared the incidence of adverse events between the two interventions. The MA was performed on seven studies with six of the studies being deemed to be of high quality (Jones 1995; Frizziero 2002; Caborn 2004; Skwara 2009; Skwara 2009; Shimizu 2010) and one to be deemed low quality (Tasciotaoglu 2003).

The study found that steroids reduce pain on the VAS after one month, after three months and six months hyaluronic acid reduced pain to a greater extent than steroids. The study also found that adverse effects are rare or insignificant, the most common side effects were arthralgia, injection site pain, joint swelling and injection site oedema.

The authors conclude that steroids were more effective at pain relief compared to hyaluronic acid in the short term (up to one month) and that hyaluronic acid was more effective than steroids over a longer period of time (up to six months)

Study	QS	Conclusions	Level of Evidence
Wang & He (2014)	AQ(+)	• The two drugs (steroids and hyaluronic acid) appear to be equally effective for pain relief in the short term.	1+
		• From 3 months onwards, hyaluronic acid was found to have a greater relative effect compared with steroids for reducing pain	1++
		• In other outcome measures (Lequense Index of knee OA, KSS of knee OA, maximum flexion of knee OA and adverse events) there was no statistically significant difference between the two groups	1++

Campbell et al., (2015)

Campbell et al., (2015) (QS:LQ(-)) conducted a systematic review comparing a number of different non-operative modalities for knee osteoarthritis, which included intra-articular steroids. Two studies were included in the analysis (Bellamy et al., 2006; Bannuru et al., 2009), both of which were deemed to be of high methodological quality by the authors.

The SR found that intra-articular steroids provided pain relief, this being a greater reduction during the first four weeks after injection compared to hyaluronic acid. The comparator, hyaluronic acid, had greater positive effect at the 5 to 13 weeks post injection time point and this relief persisted for up to 26 weeks.

The authors concluded that intra articular steroids were effective in controlling pain; however these provided a better short term relief while hyaluronic acid had a longer lasting effect.

Study	QS	Conclusions	Level of Evidence
Campbell et al., (2015)	LQ (-)	• Steroids are effective in controlling pain secondary to knee osteoarthritis in the short term (first four weeks)	1-
		• From the 5th to 13th week intra-articular hyaluronic acid was more effective and this relief lasted for up to 26 weeks in two studies	1-

Juni et al (2015)

Juni et al (2015) (QS:HQ(++)) conducted a Cochrane systematic review looking into the effectiveness of intra-articular steroids for people with knee osteoarthritis in terms of pain and safety, amongst other outcome measures. Included in the review were 27 randomised or quasi controlled trials, for which the authors deemed the quality of evidence to be low for all outcomes with most trials having a high or unclear risk of bias.

The authors concluded that they were confident that there was no effect of intra-articular steroids remaining after six months and it remained unclear whether there were clinically important benefits one to six weeks post steroid injection. The authors deemed that intra-articular steroids should be considered experimental in knee osteoarthritis and should not be routinely used until adequately powered and properly designed studies are completed and clearly indicate a short to mid-term effect of the intervention.

Study	QS	Conclusions	Level of Evidence
Juni et al., (2015)	HQ(++)	• Intra-articular steroids appear to be more beneficial in pain reduction than control interventions up to the 3 month mark	1+
		• When stratifying results according to length of follow up benefits were moderate at 1 to 2 weeks after end of treatment (SMD -0.43, 95% CI -0.70 to 0.27), small to moderate at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to 0. 21), small at 13 weeks (SMD -0.22; 95% CI -0.44 to 0.00) and no evidence of an effect at 26 weeks	1+
		• There was no effect of intra-articular steroid injections post six months	1+
		• It remains unclear whether there are clinically important benefits one to six weeks post injection	1+

Van Middlekoop et al (2016)

Van Middlekoop et al (2016) (QS:AQ(+)) conducted a meta-analysis into evaluating the efficacy of intra-articular steroids for knee osteoarthritis, the study divided the subjects into subgroups according to the severity of pain and inflammation signs. The paper included five RCTs looking at knee osteoarthritis with the steroid injections. Four of the five studies were of high methodological quality (Boon et al., 2010; Chao et al., 2010; de Campos et al., 2013; Ravaud et al., 1999).

The results revealed an overall significant effect of steroid injection compared to placebo in the short term in the knee osteoarthritis population. There were no significant treatment effects compared to the placebo at mid-term and long term follow up.

The authors also found that delivering the injection under ultrasound guidance were reported as enhancing the response of intra-articular steroid injection.

The authors concluded that patients with severe pain at baseline benefitted significantly more from intra-articular steroid injection than those with less severe pain at short term follow up. Both patients with and without severe pain show clinically relevant effects of intra-articular steroid at short term follow up.

Study	QS	Conclusions	Level of Evidence
Van Middlekoop et al (2016)	AQ(+)	• A significant overall effect on the primary outcome pain severity at short term follow up was seen in the intra-articular steroid group compared to the placebo 13.93 (95% CI 6.41-21.46)	1+
		• At mid-term no significant overall effects was seen in the IA steroid group compared to the placebo group (6.90; 95% CI -0.66 to 14.47)	1+
		• No significant differences were found at long term follow up between the groups	1+
		• A significant interaction (18.04; 95% CI 1.87 – 34.20) was observed between severe pain and IA steroid injection compared to placebo at short term follow up	1+

3.4.2 Osteoarthritis - Randomised Controlled Trials

Eighteen RCTs that were not included in the previously reported systematic reviews were identified that investigated the effectiveness of steroid injections for knee osteoarthritis. For this analysis we have reviewed the effectiveness of the steroid injections against baseline measures and then against other intervention or comparing different techniques.

Intervention	Study	QS	Outcome measure	Result
Steroid compared to baseline				
80 mg methylprednisolone acetate with lidocaine for low grade OA (primary and secondary)	Folman and Shabat (2011)	LQ	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) @ baseline and 3 months	• Pain improved @ 3/12 from 56.6 (9.7) to 24.0 (25.0) (P= 0.001) • 21.8% of patients had increased pain for 24-48 hours post injection
40mg methylprednisolone acetate for primary OA	Housman et al (2014)	AQ	WOMAC, Patient global assessment (PTGA), Clinical observer global assessment (COGA) @ Baseline and 4,8,12,16,20,26 weeks	• WOMAC pain score decreased -0.9 (95% CI -1.0 - -0.8) from baseline to 26/52 • Improved in PTGA for target knee Mean (SD) 2.4 (0.6) at baseline to 1.6 (0.9) @ 26/52 • COGA target knee 2.3 (0.8) at baseline to 1.5 (1.1) @ 26/52 • Walking pain from 2.3 (0.5) at baseline to 1.5 (0.8) @ 26/52
Betamethasone with Bupivacaine and morphine for medium grade OA (primary and secondary)	Sari et al., (2016)	LQ	Visual Analogue Scale (pain), WOMAC @ baseline and 1, 3 months	• VAS: baseline = 8 reduced to 5 @ 1/12 and 5.5 @ 3/12 • WOMAC: baseline 47.19 reduced to 37.53 @ 1/12 then increased to 42.33 @ 3/12
10mg triamcinolone acetonide for medium grade OA (primary)	Skwara et al., (2009)	LQ	VAS (pain), Knee Society Score, Lequesne Score @ baseline and 12 weeks	• VAS @ baseline = 52.9 reduced to 45.8 @ 12/52 • Lequesne @ baseline = 11.6 reduced to 9.7 @ 12/52
FX006 (10, 40, or 60-mg triamcinolone acetonide for medium grade OA	Bodick et al., (2015)	HQ	Mean daily pain score (MDPS), WOMAC (function, stiffness, pain)	• MDPS (compared to baseline MDPS); 10mg FX006 reduced 3.9 @ 8/52, 3.8 @ 10/52 and 3.6 @ 12/52; 40mg FX006 reduced 4.3 @ 8/52, 4.1 @ 12/52 and 3.7 @ 12/52; 60mg FX006 reduced 3.9 @ 8/52, 3.6 @ 10/52 and 3.2 @ 12/52

(primary and secondary)			@ baseline and 2,8,15,29,57 and 85 days	• WOMAC (function) least mean difference from baseline @8/52 = 10mg reduced 1.22, 40mg reduced 1.31 and 60mg reduced 1.13

Steroid compared to baseline

- Steroids may effective at reducing pain in osteoarthritic knees in the short term (up to 12 weeks) (2 x LQ studies 1 x AQ and 1 x HQ RCT)
- Steroids may have a deteriorating effect after 6 weeks (1 x LQ RCT)
- Steroids can be effective at improving function in the short term (up to 8 weeks) (1 x HQ RCT)
- Patients may have increased pain post steroid injection (1 x LQ RCT)

Intervention	Comparator	Study	Quality Score	Results
Dosage Parameters				
FX006 (10, 40, or 60-mg triamcinolone acetonide) for medium grade OA (primary and secondary)	Immediate release steroid (triamcinolone acetonide) x 1 injection	Bodick et al., (2015)	HQ	• Compared to TCA IR Mean daily pain score; FX006 10mg 0.5 greater reduction @8/52 and 10/52 and 0.3 @ 12/51; FX006 40mg 0.9 greater reduction @ 8/52 and 10/52 and 0.4 @ 12/52; FX006 60mg 0.5 greater reduction @ 8/52, 0.4 @ 10/52 and 0.1 @ 12/52 • Greater improvements in pain, pain on walking, stiffness, function and responder scores for the FX006 40mg
80mg methylprednisolone for all OA (primary and secondary)	80mg prednisolone with 2mg morphine x 1 injection	De souza, Issy & Sakata (2010)	LQ	• Two groups did not differ in terms of the time for first analgesic supplementation (steroid and morphine 19.5 (4.2), steroid alone 13.2 (6.5) p= 0.1274 • Two groups did not differ in total paracetamol dose used over the one week Steroid and Morphine = 3.6 (6.2), steroid alone = 3.4 (5.7) p= 0.4160 • No statistically significant difference between the intensity of pain during movement from baseline to 1 week, the steroid alone group had a statistically significant reduction in pain @ 1/52 • No significant difference in knee flexion or extension angle was observed between the two groups • Quality of analgesia was reported to be excellent or good by 78.5% of the steroid and morphine group and 85.7% of steroid group after week 1 – no significant difference between the groups.
Dosage Parameters • 40mg FX006 extended release triamcinolone acetonide shows greater improvements than 40mg immediate-release triamcinolone acetonide (1x HQ RCT) • 40mg FX006 also showed greater improvements that the other dosages of FX006 (10mg and 60mg) (1xHQ RCT) • Adding 2mg of morphine added no statistically significant benefit to using 80mg of methylprednisolone for osteoarthritic knee pain and function.				
Steroid versus hyaluronic acid injectates				
5mg Bethamethasone dipropionate with 2mg betamethasone sodium phosphate x 2 injections (day 0 and week 4) for	Hyaluronic Acid X 5 injections weekly	Davalillo et al., (2015)	LQ	• @3/12 BM greater pain reduction (66.3% compared to 48.5) • @6/12 and 1 year HA greater pain reduction (33.6% compared to 8.2%) • WOMAC function scores favour HA in all visits • WOMAC pain, total and stiffness favour HA in all visits

medium grade OA (primary and secondary)				
40mg methylprednisolone acetate then arthrocentesis week 2 for primary OA	Hyalstan Injection X 1 or 2 injections	Housman et al., (2014)	A	• All treatments had a statistically significant improvement from baseline to 26 weeks in reducing OA knee pain • All treatments demonstrated similar reductions by approx. 1 point on the WOMAC pain score • No statistically significant difference between steroid and hyalstan with secondary outcomes
40mg methylprednisolone acetate x 1 injection for medium grade OA (primary and secondary)	NASHA (hyaluronic acid gel) X 1 injection	Leighton et al., (2014)	HQ	• Both treatment groups reduced pain in the short term • After week 6 the steroid effect started to deteriorate while NASHA provided a longer lasting effect • Significantly improved pain response at 26 with NASHA compared to steroid
40mg triamcinolone acetonide with lidocaine with epinephrine x 1 injection	Hylan GF 20 X 1 injection	Tammachote et al., (2016)	HQ	• VAS @ 6/12 from baseline; Hylan GF 20 reduced 29 compared to steroid reduction of 30 • WOMAC @ 6/12 from baseline; Hylan GF reduced by 22 compared to steroid reduction of 18 • Knee flexion (deg) @ 6/12; 6 Hylan GF 20 compared to 8 steroid.
10mg triamcinolone acetonide x 1 injection for medium grade OA (primary)	Hyaluronan x 1 injection	Skwara et al., (2009)	LQ	• VAS Score; Steroid group reduced 52.9 to 42.5 (P=0.2311); HA group reduced 54.9 to 44.0 (P=0.0416) • KSS Function score; Steroid group increased 71.9 to 73.5 (p=0.2367); HA group increased 70.2 to 72.7 (p= 0.0416) • Lequesne score; TA group achieved a significant increase from 11.6 to 9.7 (P<0.0001); HA achieved a significant increase from 11.9 to 10.1
Steroid versus hyaluronic acid injectates • In the short term, steroids can be equally or more effective at decreasing pain in osteoarthritic knees (2 x LQ, 2 x HQ, 1 x AQ RCT) • After 6 weeks, hyaluronic acid injectates may have greater efficacy for pain reduction as the effect of steroids may start to deteriorate (1 x LQ, 1 x HQ RCT) • Steroids showed no significant effect on function (1 x LQ RCT)				
Steroid versus NSAIDs				
Cortivazol 3.75 mg or betamethasone 2 mg x 3 each 1 week apart for all OA (primary and secondary)	NSAIDs (Diclofenac 150mg and aceclofenac 200mg) X 2 daily for 21 days	Dieu-Donne et al., (2016)	LQ	• NSAIDS had a greater reduction in pain from baseline to 6 weeks compared to the steroid injection group • NSAIDs group had lower percentage and greater reduction of participants with spontaneous pain from baseline to 6 weeks compared to the steroid injection group
ketorolac tromethamine in bupivacaine hydrochloride without epinephrine or 40mg triamcinolone acetonide in bupivacaine hydrochloride without epinephrine x 1 injection for all OA	NSAID (ketorolac tromethamine with bupivacaine hydrochloride) x 1 injection	Bellamy et al., (2016)	HQ	• Mean VAS for both ketorolac and corticosteroid decreased significantly from baseline at 2 weeks, 6.3-4.6 (P=.003) and 5.2-3.6(P =.003), respectively and remained decreased throughout the 24 weeks. Data were normalized for VAS over time with no difference between the 2 treatments (P =0 .98) • Mean WOMAC score for both ketorolac and corticosteroid increased from baseline at 2 weeks, 49-53 (P = .003) and 53-68 (P = .003), respectively. Corticosteroid appeared to have higher function scores than ketorolac at final follow-up.

(primary and secondary)				
Steroid versus NSAIDs • Both steroids and non-steroidal anti-inflammatories are effective at reducing knee osteoarthritic pain throughout the 24 week period post injection (1xHQ) • Corticosteroids may be more effective at providing functional improvement at two weeks post injection in osteoarthritic knees (1 x HQ) • NSAIDs may be more effective at reducing spontaneous knee pain than steroids in the short term (6 weeks) (1xLQ)				
Steroid Versus Other Intervention				
Betamethasone with Bupivacaine and morphine x 1 injection for medium grade OA (primary and secondary)	Radiofrequency (RF) neurotomy of genticular nerve	Sari et al., (2016)	LQ	• Significant short-term and long-term clinical improvements were observed in patients from both groups (P<0.001) • RF group had significant reduction in pain perception both in short and long term compared to steroid group
Steroid Versus Other Intervention • Both steroids and radiofrequency neurotomy of the genticular nerve are effective at significantly reducing pain in the short and long term for patients with knee osteoarthritis (1xLQ) • The RF had a significantly greater reduction in their pain perception compared to the steroid group in both the short and the long term (1xLQ)				
Steroid – As an adjunct therapy (i.e Exercise with and without steroid)				
60mg triamcinolone hexacetonide x 1 injection for medium grade OA (primary)	Joint lavage with steroid x 1 injection	Parmigiana et al., (2010)	HQ	• Maximum improvement of 80% by the JL/HT group and 73% for the HT group • Patients with severe arthritis had significantly greater improvement with JL/TH with WOMAC pain (p=0.01), Lequesne's index (p=0.021) and the likert improvement scale according to patient (p=0.013) and according to the physician (p=0.035) @ 8/52
40mg methylprednisolone acetate with lidocaine hydrochloride + 12 week supervised exercise program for all OA (primary and secondary)	Placebo (with lidocaine hydrochloride) and exercise	Henrikson et al., (2015)	HQ	• Steroid + exercise program showed greater improvement in hamstring isometric strength than placebo + exercise, statistically significant • All other outcomes no differences in change were found between groups • Mean (SD) difference KOOS pain scale from baseline @ week 14; Placebo 14.8 (1.8) to steroid 13.6 (1.8) with mean difference 1.2 (3.8 – 6.2) (P=0.64)
40mg methylprednisolone acetate with lidocaine hydrochloride + 12 week supervised exercise program for all OA (primary and secondary)	Placebo (with lidocaine hydrochloride) and exercise	Soriano-Maldonado et al., (2016)	HQ	• There were no significant group difference changes between pressure pain sensitivity threshold or temporal summation at week 14 or week 26 • There was no overall benefit of the steroid injection to the pain sensitivity measures regardless of allocation

Steroid – As an adjunct therapy (i.e Exercise with and without steroid)

- Both groups with steroid injection and joint lavage and just steroid injection had improvement in their pain symptoms post intervention (1xHQ)
- Steroid and exercise compared to steroid and placebo only had a significantly greater in hamstring isometric strength in favour of the steroid group (1xHQ)
- Both steroid and exercise and steroid and placebo reduced pain in osteoarthritic knees with no significant difference between the two groups (1xHQ)
- The addition of intra-articular steroid injection to an exercise program does not provide any additional benefit on pain sensitivity in comparison to a placebo in patients with knee osteoarthritis (1xHQ)

Steroid – Technique used (i.e. Location of injection, ultrasound guided)

60mg Depo-Medrol with lidocaine x 1 injection for all OA (primary and secondary)	superolateral, anteromedial or anterolateral approach to injection	Wagner et al., (2015)	HQ	• No statistical differences between procedural pain between the groups • WOMAC scores decreased @ 1/52 and 4/52 for all groups, no significant difference between the 3 groups • WOMAC scores for the SL, AM and AL groups were 701 (687), 593 (555) and 891 (714) @ 1 week follow up and 600 (610), 665 (683) and 954 (699) at 4 weeks respectively
80mg triamcinolone acetonide for all OA (primary and secondary)	Anatomic palpation guided or sonographically guied	Sibbit et al., (2011)	LQ	• Anatomic palpation guidance = 69% reduction in absolute pain score @2/52 (baseline VAS: 7.8 (1.8); 2 week VAS: 2.4 (2.8) P<0.001) • Duration of therapeutic effect was: mean (SD) 3.1 (2.1) Months • Time to reinject: 6.0 (2.8) months • Sonographically guided = 42% less pain than palpation method @2/52 (p<0.03) • Absolute pain score @2/52 (baseline VAS 7.5 (2.0); 2/52 VAS: 1.4 (2.1) • Pain @ 6/12 mean (SD) for palpation was 6.3 (2.9) and sonographically guided 6.3 (2.6) • Time to next procedure mean (SD): Palpation = 6.0 (2.8) months and sonographically guided = 7.1 (3.2)
80 mg methylprednisolone acetate with lidocaine (intra-articular injection) for all OA (primary and secondary)	Periarticular Steroid X 1 injection	Folman and Shabat (2011)	LQ	• All patients reported immediate and considerable pain relief post intervention • PAI pain from baseline decreased from 62.5 to 27 while IASI decreased from 56.6 to 24 • 21.8% of patients had increased pain for 24-48 hours post injection in IASI group compared to 80.6% in PAI group

Steroid – Technique used (i.e. Location of injection, ultrasound guided)

- No differences were found between using the superolateral, anteromedial or anterolateral approach to injection, all were effective at decreasing osteoarthritic knee pain in the short term (up to 4 weeks) (1xHQ)
- Sonographically guided injections produced 42% less pain at the two week post injection mark in osteoarthritic knees than palpation guided injections (1xLQ)
- Sonographically guided and palpation guided injections both provide pain relief in the short term for osteoarthritic knees (up to 6 weeks) (1xLQ)
- Sonographically guided injections provide a longer therapeutic effect than palpation guided injections (1xLQ)
- Both peri-articular and intra-articular injections provided pain relief post injection (1xLQ)
- Patients with peri-articular injections had a greater increase in pain in the 24-48 period post injection than the intra-articular group (1xLQ)

3.4.3 Patellofemoral pain syndrome - Systematic reviews

Heintjes et al (2004)

Heintjes et al (2004) (QS:HQ++)) undertook a Cochrane systematic review to look at a variety of pharmacotherapies for patellofemoral pain syndrome; this included a section for intramuscular injections of anabolic steroids and glucocorticoids. One study was included in this review (Darracott 1973) who performed a low quality study using intramuscular administration of an anabolic ester nandrolone phenylpropionate (Durabolin) 25mg compared to intramuscular administration of a placebo, both weekly for 6 weeks. There was a significant difference in the number of participants that improved clinically observed; 1 out of 20 participants in the placebo group improved clinically compared to 20 out of 23 in the Nandrolone group.

The authors concluded, that in regard to anabolic steroids, it was stated that there is limited evidence that the anabolic steroids Nandrolone may be effective; the drug however is too controversial for use in the treatment of PFPS due to its inclusion in the international doping list and significant side effects such as premature close of epiphyses, virilisation, liver insufficiency and heart failure.

Study	QS	Conclusions	Level of Evidence
Heintjes et al., (2004)	HQ(++)	• Significant difference were found in the number of participants that improved clinically; 20 out of 23 improved in the steroid group compared to 1 out of 20 in the placebo group	1-
		• Anabolic steroids have limited evidence on their efficacy but are too controversial for use on the treatment of PFPS	1-

3.4.4 Patellofemoral pain syndrome - Randomised Controlled Trials

Konsgaard et al (2009) conducted a RCT analysing the efficacy of cortisone injections compared to eccentric exercises and heavy slow repetition exercises for pain reduction in individuals diagnosed with patellar tendinopathy. The results showed that in the short term (12 weeks), all three modalities were effective at reducing pain with similar responses. The relative improvement from baseline to the end follow up at 2 weeks showed the eccentric exercises and heavy slow repetitions were able to maintain their efficacy and gradually reduced pain while the steroid injection had a diminishing effect. The overall change in VAS was 47% reduction in the steroid group, 55% reduction in eccentric exercise group and a 70% reduction in the heavy slow repetition group

Study	QS	Conclusions
Konsgaard et al., (2009)	AQ(+)	CORT has good short-term but poor long-term clinical effects, in patellar tendinopathy. HSR has good short- and long-term clinical effects.

3.5 Outcome Measures – Safety and Risk

3.5.1 Safety And Risk - General

In previous literature, some concerns have been raised regarding the use of repeated intra-articular steroid injections and progressive cartilage damage. Lane (1997) recommended that intra-articular steroid injections should not be given in a single joint at more than three monthly intervals. Similarly, Ratiner (2001) recommended that there should be no more than two to three injections per joint per year in routine cases. Gosal (1999) has suggested that the short term benefit of reduced pain and inflammation has to be weighed against possible adverse effects concerning the articular cartilage, the synovium and the host immune response.

Although uncommon, complication of intra-articular steroids include the following; post injection flare, crystal–induced synovitis, tissue atrophy, fat necrosis, calcification, sepsis, steroid arthropathy, vascular necrosis, haematomoa (Ayral 2001; Lawford 1994; McColl 2000; Noerdlinger 2001; Ratiner 2001; Rozental 2000; Seror 1999; Wada 1993). Rarely, absorption of intra-articular steroids from the joint through the body may result in fluid retention, hyperglycaemia and hypertension (Ratiner 2001). It has been commented on that the risk of these adverse effects can be minimised by the accuracy of the intra-articular injection (Jones 1993) and the adherence to an appropriate sterile technique (McColl 2000).

3.5.2 Safety And Risk - Osteoarthritis

Juni et al., (2015) reported on adverse events within a systematic review on steroids for knee osteoarthritis. Two trials reported on any type of adverse events (Petrella 2015; Wright 1960) and the authors concluded the participants administered steroids were 11% less likely to experience adverse events however these findings were not statistically significant. They found from two studies (Campos 2013; Henriksen 2015) that participants on steroids were 67% less likely to withdraw because of adverse events, but again these findings were statistically insignificant. Five trials (Henriksen 2015; Lyons 2005; Ozturk 2006; Petrella 2015; Ravaud 1999) found that participants on steroids were 27% less likely to withdraw because of adverse events; again findings were not statistically significant.

The authors concluded that intra-articular steroids appeared to cause as many side effects as the placebo however the findings were not precise or reliable due to the grade of the evidence.

Wang & He (2015) compared intra-articular hyaluronic acid and steroids in the treatment of knee osteoarthritis, and from the three studies, which included 171 hyaluronic acid participants and 144 steroids participants, reported detailed data on the adverse events. They found there was no statistically significant difference in the adverse events observed between the two groups.

Davalillo et al., (2015) in a RCT compared hyaluronic acid (HA) and betamethasone (BM) and found that all adverse reactions were related to the administration procedure and were experienced by 3.5% of the patients. Pain was experienced in four HA patients compared to two BM patients and effusion was detected in five HA patients compared to two BM patients.

Housman et al, (2014) in a RCT compared intra-articular hylastan to intra-articular methylprednisolone acetate, overall It was found the adverse events were comparable to the two pharmacotherapy preparations. Overall 81 (of the 131) patients injected with steroid had

an adverse event; 13 being injection related, 29 being treatment related, eight being serious with seven individuals discontinuing due to the adverse events. The adverse events occurring in the 21% of the patients were; arthalgia 29.8%, joint stiffness 19.1%, joint swelling 13.7%, joint effusion 12.2%, joint warmth 2.3%, joint crepitation 3.8%, injection site pain 1.5% and joint instability 1.5%.

Leighton et al., (2014) conducted a RCT which used methylprednisolone compared to hyaluronic acid for the treatment of knee osteoarthritis. The authors reported that the adverse effects were largely anticipated and there was a lack of differences between the two groups. During the blinded stage of the study, within the steroid group 3.2% of patients had arthralgia, 0.5% had injection site pain and 0.5% had joint stiffness. Once this trial progressed to the open label stage the percentage of adverse events occurring within the steroid group increased; with arthralgia increasing to 17.3%, joint stiffness 1.7% and joint swelling 0.6%.

Bodick et al., (2015) in a RCT comparing three different steroid preparations of FX006 and TCR IR found that for 10mg 27 patients had at least one treatment emergent adverse event of which 7 were deemed to be "possibly, probably or definitely" related to the intervention. 40mg group had 33 patients with 5 in the possibly, probably or definitely group and the 60mg group had 34 for which seven were in the possibly, probably or definitely group. The TCR-IR group had 28 of which 9 were in the possibly, probably or definitely group. These adverse reactions included; nasopharyngitis, upper respiratory tract infection, neutrophin count increase, white blood cell count increase, arthralgia, joint stiffness and headache.

De souza, Issy and Sakata (2010) in a RCT comparing methylprednisolone with methyprednisolne with an additional 2mg of morphine found that in the steroid group A, three patients had adverse effects, these included limb itching reported in one patient, dizziness by two patients and nausea and vomiting, weakness and sleepiness by one. The group with the additional morphine had two participants suffer adverse responses and these were tremor and preorbital erythema in one patients, dizziness in two patients, nausea and vomiting in one, dizziness in one and neck pain in two.

3.5.3 Safety And Risk - Patella Tendinopathy

Kongsgaard et al., (2009) in a RCT comparing steroid injections, eccentric decline squats and heavy slow resistance training found that no adverse events occurred within any of the three groups.

3.5.4 Safety And Risk - Recommendations

Minor complications associated with intra-articular steroid injections into the knee are not uncommon but rarely require significant medical attention Prevalence rates of minor complications associated with intra-articular injections such as increased pain after injection (3%–17.3%) Level A recommendation based on one HQ SR, one LQ SR

3.6 Economic analysis

Bellamy et al, (2016) conducted a review into the cost effectiveness and efficacy between ketorolac and steroids for knee osteoarthritis in Texas, USA. The results for the efficacy showed no statistically significant difference in outcome between the two for pain, however the steroids had a higher functional improvement at the final follow up. The results also showed that the price difference between the two injections to be 143% with the institutional cost of

triamcinolone being $12.28USD per injection compared to ketorolac at $2.01USD. The authors concluded that at their institution they estimated a total saving of $12 601.29USD over a three year period if using ketorolac instead of the steroid. The authors did note that both solutions had an anaesthetic component and they are unsure if the pain reduction was purely from the compared preparations of the bupivacaine included.

Sibbit et al, (2011) completed a RCT evaluating the cost-effectiveness of different techniques of administration in particular sonographic guidance for intra-articular steroids injections in New York, USA. The authors used 80mg of triamcinolone acetonide suspension, either administered with palpation guidance or sonographic guidance. They concluded that for the use in hospital outpatients it modestly reduced the cost for the patient 13% ($17USD) relative to the palpation method and it significantly reduced the cost per responder (those with asymptomatic joints two weeks post injection) by 58% ($224USD). This was due to the ultra-sound guided procedure having a longer therapeutic duration, longer time to the next injection which in turn resulted in fewer costs per year.

Recommendation

- **The evidence indicates that intra-articular steroids injections were more expensive than ketorolac (NSAID) and provided the same effect, steroids are not as cost effective as NSAIDs.** Level D recommendation based on one LQ RCT
- **The evidence indicates that ultrasound guided intra-articular steroid injections were more cost effective than palpation guidance due to better therapeutic effect.** Level D recommendation based on one LQ RCT

4. Recommendations

Recommendation:

<u>Knee Osteoarthrosis</u>

The evidence indicates that intra-articular steroid injections reduce pain in the short term (< 4 weeks) better than placebo or hyaluronic acid and their derivatives in patients with knee osteoarthritis. The evidence indicates that after four weeks intra-articular steroid injections are less effective than hyaluronic acid for pain reduction in patients with knee osteoarthritis Level A recommendation based on one x HQ SRs with Level 1++ evidence, one HQ SRs and two AQ SRs with level 1 evidence, two LQ SRs with level 1 Evidence, three HQ and 2 AQ RCTs

The evidence indicates that 40mg of slow release steroid is more effect than 10mg or 60mg in patients with osteoarthritis. Level B recommendation based on results from one AQ SR with level 1++ evidence, one AQ SR with level + evidence and one HQ and one LQ RCT

The evidence indicates that the addition of intra-articular steroids in conjunction to a 12 week exercise program offers no additional benefit than the exercise program alone in patients with osteoarthritis. Level B recommendation based on one HQ RCT

Minor complications associated with intra-articular steroid injections into the knee are not uncommon but rarely require significant medical attention. Adverse effects occur in 3.5-21% of participants; some of the adverse effects can be arthralgia, joint stiffness, joint swelling, joint effusion, joint warmth, joint crepitation, injection site pain and joint instability. Level A recommendation based on one HQ SR, one HQ and one AQ RCT

The evidence indicates that sonographically guided injections are more effective than palpation guided injections for pain relief in both the short and long term term. Level D recommendation based on one LQ RCT

The evidence indicates that intra-articular steroids injections were more expensive than ketorolac (NSAID) and provided the same effect, steroids are not as cost effective as NSAIDs. Level D recommendation based on one LQ RCT

The evidence indicates that ultrasound guided intra-articular steroid injections were more cost effective than palpation guidance due to better therapeutic effect. Level D recommendation based on one LQ RCT

<u>Patella tendinopathy</u>

The evidence indicates that steroid injections offer little additional benefit over an exercise program comprising of either eccentric exercises or heavy slow repetitions, with the latter two providing a gradual decrease in pain while the steroid effect diminishes. Level C recommendation based on one AQ RCT

Adverse events associated with steroid injections for patellar tendinopathy are rare. Level C recommendation based on one AQ RCT

5. References

Ayral, X 2001, 'Injections in the treatment of osteoarthritis', Bailliere's Best Practice and Research in Clinical Rheuamtology, vol. 15, no. 4, pp. 609-626.

Bannuru, R, Natov, N, Schmid Obadan, I, Price, L, , C & McAlindon, T 2009, 'Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis (Structured abstract)', Arthritis and Rheumatism (Arthritis Care and Rsearch), vol. 61, no. 12, pp. 1704-1711.

Bellamy, JL, Goff, BJ & Sayeed, SA 2016, 'Economic Impact of Ketorolac vs Corticosteroid Intra-Articular Knee Injections for Osteoarthritis: A Randomized, Double-Blind, Prospective Study', Journal of Arthroplasty, vol. 31, no. 9 Supplement, 01 Sep, pp. 293-297.

Bellamy, N, Campbell, J, Welch, V, Gee, TL, Bourne, R, Wells, GA, Bellamy, N, Campbell, J, Robinson, V, Gee, T, Bourne, R & Wells, G 2006, 'Intraarticular corticosteroid for treatment of osteoarthritis of the knee', Cochrane Database of Systematic Reviews, pp. N.PAG-N.PAG.

Bjordal, JM, Klovning, A, Ljunggren, AE & Slørdal, L 2007, 'Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials', European Journal of Pain, vol. 11, no. 2, pp. 125-138.

Bodick, N, Lufkin, J, Willwerth, C, Kumar, A, Ballal, R, Clayman, M, Bolognese, J, Schoonmaker, C & Hunter, D 2015, 'An intra-articular, extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee: A randomized clinical trial', Journal of Bone and Joint Surgery – American Volume, vol. 97, no. 11, pp. 877-888.

Campbell, KA, Erickson, BJ, Saltzman, BM, Mascarenhas, R, Bach, BR, Cole, BJ & Verma, NN 2015, 'Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses', Arthroscopy – Journal of Arthroscopic and Related Surgery, vol. 31, no. 10, October, pp. 2036-2045.

Campos, GC, Rezende, MU, Pailo, AF, Frucchi, R, Camargo, OP 2013, 'Adding triamcinolone improves viscosupplementation. A randomized clinical trial', Clinical Orthopaedics and related research, vol. 471, no. 2, pp. 613-620.

Cheng, OT, Souzdalnitski, D, Vrooman, B & Cheng, JG 2012, 'Evidence-Based Knee Injections for the Management of Arthritis', Pain Medicine, vol. 13, no. 6, Jun, pp. 740-753.

Davalillo, CÁT, Vasavilbaso, CT, Álvarez, JMN, Granado, PC, Jiménez, OAG, del Sol, MG & Orbezo, FG 2015, 'Clinical efficacy of intra-articular injections in knee osteoarthritis: A prospective randomized study comparing hyaluronic acid and betamethasone', Open Access Rheumatology: Research and Reviews, vol. 7, pp. 9-18.

De Souza, CJ, Issy, AM & Rioko, SK 2010, 'Effect of the combined intra-articular administration of morphine and methylprednisolone in patients with knee osteoarthritis', Journal of Pain Management, vol. 3, no. 2, pp. 201-205.

Di Rosa, M, Calignano, A, Carnuccio, R, Lalenti, A & Sautebin, L 1986, 'Multiple control of inflammation by glucocorticoids,' Inflammation Reseach, vol. 17, no.3, pp. 284-289.

Dieu-Donne, O, Theodore, O, Joelle, ZT, Pierre, D, Smaila, O, Christian, C, Fulgence, K & Joseph, DY 2016, 'An open randomized trial comparing the effects of oral NSAIDs versus steroid intra-articular infiltration in congestive osteoarthritis of the knee', Open Rheumatology Journal, vol. 10, 01 Jan, pp. 8-12.

Folman, Y & Shabat, S 2011, 'Local treatment of a painful knee with cortiscosteroids: The efficacy of intra-articular injection compared with peri-articular soft tissue infiltration', Journal of Musculoskeletal Pain, vol. 19, no. 3, pp. 154-157.

Godwin, M & Dawes, M 2004, 'Intra-articular steroid injections for painful knees. Systematic review with meta-analysis', Canadian Family Physician, vol. 50, no. FEB., pp. 241-248.

Gosal, HS, Jackson, AM, Bickerstaff, DR 1999, 'Intra-articular steroid after arthroscopy for osteoarthritis of the knee,' Journal of bone and Joint Surgery. Vol. 81-B, pp. 952-954.

Health, United States, 2006 with chartbook on trends in the health of Americans, Hyatsville, MD, National centre for health statistics, 2006, p. 82.

Heintjes, EM, Berger, M, Bierma-Zeinstra, SM, Bernsen, RM, Verhaar, JA & Koes, BW 2004, 'Pharmacotherapy for patellofemoral pain syndrome', Cochrane Database of Systematic Reviews,no.3,10.1002/14651858.CD003470.pub2

Henriksen, M, Christensen, R, Klokker, L, Bartholdy, C, Bandak, E, Ellegaard, K, Boesen, M, Riis, R, Bartels, E & Bliddal, H 2015, 'Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: a randomized clinical trial', JAMA Internal Medicine, vol. 175, no. 6, pp. 923-930.

Henriksen, M, Christensen, R, Klokker, L, Bartholdy, C, Bandak, E, Ellegaard, K, Boesen, M, Riis, R, Bartels, E & Bliddal, H 2015, 'Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: a randomized clinical trial', JAMA Internal Medicine, vol. 175, no. 6, pp. 923-930

Hepper, CT, Halvorson, JJ, Duncan, ST, Gregory, AJ, Dunn, WR & Spindler, KP 2009, 'The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies', Journal of the American Academy of Orthopaedic Surgeons, vol. 17, no. 10, Oct, pp. 638-646.

Hirsch, G, Kitas, G & Klocke, R 2013, 'Intra-articular Corticosteroid Injection in Osteoarthritis of the Knee and Hip: Factors Predicting Pain Relief-A Systematic Review', Seminars in Arthritis and Rheumatism, vol. 42, no. 5, pp. 451-473.

Housman, L, Arden, N, Schnitzer, TJ, Birbara, C, Conrozier, T, Skrepnik, N, Wei, N, Bockow, B, Waddell, D, Tahir, H, Hammond, A, Goupille, P, Sanson, BJ, Elkins, C & Bailleul, F 2014, 'Intra-articular hylastan versus steroid for knee osteoarthritis', Knee Surgery, Sports Traumatology, Arthroscopy, vol. 22, no. 7, pp. 1684-1692.

Jones, A Regan, M, Ledingham, J, Pattrick, M, Manhire, A, Doherty, M 1993, 'Importance of placement of intra-articular steroid injections' BMJ, vol. 307, pp. 1329-1330.

Jüni, P, Hari, R, Rutjes, AW, Fischer, R, Silletta, MG, Reichenbach, S & da, CBR 2015, 'Intra-articular corticosteroid for knee osteoarthritis', Cochrane Database of Systematic Reviews, no. 10, 10.1002/14651858.CD005328.pub3

Kongsgaard, M, Kovanen, V, Aagaard, P, Doessing, S, Hansen, P, Laursen, AH, Kaldau, NC, Kjaer, M & Magnusson, SP 2009, 'Corticosteroid injections, eccentric decline squat training and heavy slow resistance training in patellar tendinopathy', Scandinavian Journal of Medicine and Science in Sports, vol. 19, no. 6, December, pp. 790-802.

Lane, NE, Thompson, JM 1997, 'Management of osteoarthritis in the primary care setting: an evidence based approach to treatment,' American Journal of Medicine, vol. 103, no. 6A, pp. 25S-30S

Lawford, R, York, J, Hassal, J, Richards, G, Mchill, N 1994, 'Intra-articular and soft tissue steroid injections: theory versus practice', 38th Annual Scientific conference of the Australian Rheumatology Association, Melbounre, May 22-24, 114.

Leighton, R, Akermark, C, Therrien, R, Richardson, JB, Andersson, M, Todman, MG, Arden, NK & Group, DS 2014, 'NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial', Osteoarthritis & Cartilage, vol. 22, no. 1, Jan, pp. 17-25.

Lyons, C, Majeed, A, Banarsee, R 2005, 'Effectiveness of high volume intra-articular injection of cortisone and lignocaine in osteoarthritis of the knee, pilot study', North and West London Journal of General Practice, vol. 11, no. 1, pp. 23-28.

Maricar, N, Callaghan, MJ, Felson, DT & O'Neill, TW 2013, 'Predictors of response to intra-articular steroid injections in knee osteoarthritis-a systematic review', Rheumatology (United Kingdom), vol. 52, no. 6, pp. 1022-1032.

McAlindon, TE, Cooper, C, Kirwan, JR, Dieppe, PA 1992, 'Knee pain and disability in the community' Brithish Journal of Rheumatology, vol. 31, pp. 189-192.

McColl, GJ, Dolezal, H, Eizenberg, N 2000, 'Common corticosteroid injections. An anatomotical and evidence based review', Australian Family Physician, vol. 29, pp. 922-926.

Nattapol, T, Supakit, K, Thanasak, Y & Phonthakorn, P 2016, 'Intra-Articular, Single-Shot Hylan G-F 20 Hyaluronic Acid Injection Compared with Corticosteroid in Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial', Journal of Bone & Joint Surgery, American Volume, vol. 98, no. 11, pp. 885-892.

Neustadt, D 2006, 'Intra-articular injections for osteoarthritis of the knee,' Cleveland Clinical Journal of Medicine, vol. 73, pp. 897-911.

Noerdlinger, MA, Fadale, PD 2001, ' The role of injectable corticosteroids in orthopedics', Orthopedics, vol. 24, no. 4, pp. 400-405.

O'Reilly, SC, Muir, KR, Doherty, M 1996, 'Screening for pain in knee osteoarthritis: Which question?' Annals of the Rheumatic Diseases, vol. 55, no.12, pp. 931-933.

Ozturk, C, Atamaz, F, Hepguler, S, Argin, M, Arkun, R 2006, 'The safety and efficacy of intra-articular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single blind, randomized study', Rheumatology International, vol. 26, no. 4, pp. 314-319.

Parmigiani, L, Furtado, R, Lopes, R, Ribeiro, L & Natour, J 2010, 'Joint lavage associated with triamcinolone hexacetonide injection in knee osteoarthritis: a randomized double-blind controlled study', Clinical Rheumatology, vol. 29, no. 11, pp. 1311-1315.

Peat, G, McCarney, R, Croft, P 2001, 'Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care,' Annals of the Rheumatic Diseases, vol. 60, no. 2, pp. 91-97.

Petrella, RJ, Eamons, P, Alleyne, J, Dellaert, F, Gill, DP, Maroney, M 2015, 'Safety and performance of hydros and hydro-TA for knee osteoarthritis. A prospective multi-centre, randomized, doub;e-blind feasibility trial', BMC Musculoskeletal Disorders, vol. 16, no. 57, pp. 1-9.

Pierce, TP, Elmallah, RK, Jauregui, JJ, Cherian, JJ, Harwin, SF & Mont, MA 2016, 'Inferomedial or inferolateral intra-articular injections of the knee to minimize pain intensity', Orthopedics, vol. 39, no. 3, May-June, pp. e578-e581.

Ptasznik, R 1999, 'Ultrasound in acute and chronic knee injury,' Radiologic Clinics of North America, vol. 37, pp. 797-829.

Ratiner, B, Gramas, DA, Lane, NE, Osteoarthritis, in Weisman, MH, Weinblatt, ME, Louis, JS editors 'Treatment of the Rheumatic Diseases. Companion to Kellys textbook of Rheumatology. 2nd edition. Philadelphia: WB Saunders Company, 2001, pp. 481-86.

Ravaud, P, Moulinier, L, Graudeau, B, Ayral, X, Guerin, C, Noel, E, Thomas, P, Fautrel, B, Mazieres, B, Dougados, M 1999, 'Effects of joint lavage and steroid injection in patients with osteoarthritis of the knee: results of a multicentered, randomized controlled trial', Arthritis and Rheumatology, vol. 42, no. 3, pp. 475-482.

Richards, MM, Maxwell, JS, Weng, L, Angelou, MG, Golzarian, J 2016, 'Intra-articular treatment of knee osteoarthritis: from anti-inflammatory to products of regenerative medicine,' The Physician and Sports Medicine, vol. 44, no. 2, pp.101-108.

Rozental, TD, Sculco, TP 2000, 'Intra-articular corticosteroids: an updated overview,' American Journal of Orthopedics, vol. 29, no. 1, pp. 18-23.

Sari, S, Aydin, ON, Turan, Y, Ozlulerden, P, Efe, U & Kurt Omurlu, I 2016, 'Which one is more effective for the clinical treatment of chronic pain in knee osteoarthritis: Radiofrequency neurotomy of the genicular nerves or intra-articular injection?', International Journal of Rheumatic Diseases.

Seror, P, Pluvinage, P d'Andre, FL, Benamou, P, Attuil, G 1999, 'Frequency of sepsis after local cortocosteroid injection (an inquiry on 1160000 injections in rheumatological private practice in france)', Rheumatology, vol. 38, pp. 1272-1274.

Sibbitt Jr, WL, Band, PA, Kettwich, LG, Chavez-Chiang, NR, DeLea, SL & Bankhurst, AD 2011, 'A randomized controlled trial evaluating the cost-effectiveness of sonographic guidance for intra-articular injection of the osteoarthritic knee', Journal of Clinical Rheumatology, vol. 17, no. 8, pp. 409-415.

Skwara, A, Ponelis, R, Tibesku, CO, Rosenbaum, D & Fuchs-Winkelmann, S 2009, 'Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee – Hyaluronan versus triamcinolone: A prospective, randomized, doubleblind, monocentric study', European Journal of Medical Research, vol. 14, no. 4, pp. 157-164.

Soriano-Maldonado, A, Klokker, L, Bartholdy, C, Bandak, E, Ellegaard, K, Bliddal, H & Henriksen, M 2016, 'Intra-articular corticosteroids in addition to exercise for reducing pain sensitivity in knee osteoarthritis: Exploratory outcome from a randomized controlled trial', PloS ONE [Electronic Resource], vol. 11, no. 2.

Turkiewicz, A, Gerhardsson de Verdier, M, Engstrom, G, Nilsson, PM, Mellstrom, C, Lohmander, LS, Englund, M 2014, 'Prevalence of knee pain and knee OA in Southern Sweden and the proportipons that seek medical care,' Rheumatology, vol. 54, pp. 827-835.

Turkiewicz, A, Petersson, IF, Bjork, J, Dahlberg, LE, Englund, M 2013, 'The consultation prevalence of osteoarthritis 2030 may increase by 50%: prognosis for Sweden,' Osteoarthritis and Cartilage, vol. 21, pp. 5160 – 5161.

van Middelkoop, M, Arden, NK, Atchia, I, Birrell, F, Chao, J, Rezende, MU, Lambert, RGW, Ravaud, P, Bijlsma, JW, Doherty, M, Dziedzic, KS, Lohmander, LS, McAlindon, TE, Zhang, W & Bierma-Zeinstra, SMA 2016, 'The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids', Osteoarthritis and Cartilage, vol. 24, no. 7, Jul, pp. 1143-1152.

Wada, J, Koshino, T, Marii, T, Sugimoto, K 1993, 'Natural course of osteoarthritis of the knee treated with or without intra-articular corticosteroid injections', Bulletin Hospital for Joint Diseases, vol. 53, no. 2, pp. 45-48.

Wagner, B, Howe, A, Dexter, W, Hatzenbuehler, J, Holt, C, Haskins, A & Lee, LF 2015, 'Tolerability and efficacy of 3 approaches to intra-articular corticosteroid injections of the knee for osteoarthritis a randomized controlled trial', Orthopaedic Journal of Sports Medicine, vol. 3, no. 8, pp. 1-5.

Wang, F & He, XJ 2015, 'Intra-articular hyaluronic acid and corticosteroids in the treatment of knee osteoarthritis: A meta-analysis', Experimental and Therapeutic Medicine, vol. 9, no. 2, Feb, pp. 493-500.

Woo, J, Hos, SC, Lau, J, Leung, PC 1994, 'Musculoskeletal complaints and associated consequences in elderly Chinese aged 70 years and over,' Journal of Rheumatology, vol. 21, pp. 1927-1931.

Wright, V, Chandler, GN, Morison, RA, Hartfall, SJ 1960, 'Intra-articular therapy in osteoarthritis; comparison of hydrocortisone acetate and hydrocortisone tertiary-butylacetate', Annals of the Rheumatic Diseases, vol. 19, pp. 257-261.

6. Appendices

Appendix 1: Sign Checklists Used in this Review

SIGN Critical Appraisal Tool for Systematic Reviews and Meta-analyses

SIGN

Methodology Checklist 1: Systematic Reviews and Meta-analyses

SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al., Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*

Study identification (*Include author, title, year of publication, journal title, pages*)	
Guideline topic:	Key Question No:

Before completing this checklist, consider:

Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.

Checklist completed by:

Section 1: Internal validity

In a well conducted systematic review:		***Does this study do it?***	
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes □ **If no reject**	No □
1.2	A comprehensive literature search is carried out.	Yes □ Not applicable □ **If no reject**	No □
1.3	At least two people should have selected studies.	Yes □	No □ Can't say □
1.4	At least two people should have extracted data.	Yes □	No □ Can't say □
1.5	The status of publication was not used as an inclusion criterion.	Yes □	No □
1.6	The excluded studies are listed.	Yes □	No □
1.7	The relevant characteristics of the included studies are provided.	Yes □	No □
1.8	The scientific quality of the included studies was assessed and reported.	Yes □	No □
1.9	Was the scientific quality of the included studies used appropriately?	Yes □	No □
1.10	Appropriate methods are used to combine the individual study findings.	Yes □ Can't say □	No □ Not applicable □
1.11	The likelihood of publication bias was assessed appropriately.	Yes □	No □

		Not applicable □
1.12	Conflicts of interest are declared.	Yes □ No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) □ Acceptable (+) □ Low quality (-)□ Unacceptable – reject 0 □
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes □ No □
2.3	**Notes:**	

SIGN Critical Appraisal Tool for Controlled trials

SIGN

Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise bias? *Code as follows:*	High quality (++)☐ Acceptable (+)☐ Low quality (-)☐ Unacceptable – reject 0 ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

SIGN Critical Appraisal Tool for Cohort studies

SIGN	**Methodology Checklist 3: Cohort studies**

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than + .

Section 1: Internal validity

	In a well conducted cohort study:	Does this study do it?	
1.1	The study addresses an appropriate and clearly focused question.[i]	Yes □ Can't say □	No □
	SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ Can't say □	No □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □	No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes □ Can't say □	No □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.		
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	Yes □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.[ii]	Yes □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	Yes □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once	Yes □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

Appendix 2: Data extraction from Systematic Reviews used in this Review

Author and year	SIGN Score	Studies	Outcome	Conclusions	Evidence 1	2	3	4	Grade
Knee Osteoarthritis									
Wang & He (2014) SR/MA *Intra-articular corticosteroids vs hyaluronic acid for knee osteoarthritis*	AQ(+)	7 RCT	Pain. Function, ROM	The two drugs (corticosteroids and hyaluronic acid) appear to be equally effective for pain relief in the short term, with one study showing a possible short term benefit over the use of Hyaluronic acid	1	1	1	0	1+
				From 3 months onwards, hyaluronic acid was found to have a greater relative effect compared with corticosteroids	1	1	1	1	1++
				In other outcome measures there were no statistically significant difference between the two groups	1	1	1	1	1++
Van Middlehoop (2006) MA *intra-articular glucocorticoids for knee osteoarthritis*	AQ (+)	7 RCT	Pain, function, ROM, global assessment	A significant overall effect on the primary outcome pain severity at short term follow up was seen in the intra-articular glucocorticoid group compared to the placebo 13.93 (95% CI 6.41-21.46)	1	1	1	0	1+
				At mid-term no significant overall effects was seen in the IA glucocorticoid group compared to the placebo group (6.90; 95% CI -0.66 to 14.47)	1	1	1	0	1+
				No significant differences were found at long term follow up between the groups	1	1	1	0	1+
				A significant interaction (18.04; 95% CI 1.87 – 34.20) was observed between severe pain and IA glucocorticoid injection compared to placebo at short term follow up	1	1	1	0	1+
Maricar (2013) SR *Technique for IACI*	LQ(-)	3 RCTs	Pain	• Sonographically guided injections when compared to blind injection led to a greater decrease in pain from baseline scores at two weeks	0	0	0	0	1-
				• There was no difference in therapeutic response between infrapatella, medial knee, lateral mid patella and antero-lateral joint line with knee flexed	0	0	0	0	1-
Juni et al., (2015) SR *benefits and harms of intra-articular corticosteroids for people with knee osteoarthritis*	HQ(++)	27 RCTs or quasi RCTs	Pain, function, QOL	• intra-articular corticosteroids appear to be more beneficial in pain reduction than control interventions up to the 3 month mark	1	1	1	0	1-
				• When stratifying results according to length of follow up benefits were moderate at 1 to 2 weeks after end of treatment (SMD -0.43, 95% CI -0.70 to 0.27), small to moderate at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to 0. 21), small at 13 weeks (SMD -0.22; 95% CI -0.44 to 0.00) and no evidence of an effect at 26 weeks	1	1	1	0	1-
				• There was no effect of intra-articular steroid injections post six months	1	1	1	0	1-
				• It remains unclear whether there are clinically important benefits one to six weeks post injection	1	1	1	0	1-

Author and year	SIGN Score	Studies	Outcome	Conclusions	Evidence				Grade
					1	2	3	4	
Hirsch, Kitas & Klocke (2013) SR *intra-articular corticosteroid injections preparation in patients with knee arthritis*	LQ(-)	4 RCTs	Pain	• When comparing THA vs MPA at 3 weeks THA had greater pain reduction than MPA (P<0.01) at 8 weeks there was no statistical significant difference between the two	0	0	0	0	1-
				• When comparing THA vs BA at week 1 follow up THA had greater reduction of pain than BM (p<0.005) at the week 2 and 4 follow up there was no significant difference	0	0	0	0	1-
				• When comparing hydrocortisone acetate vs hydrocortisone tertiary butyl acetate at 2 weeks only hydrocortisone tertiary butyl acetate was statistically superior to placebo at 2 weeks (p< 0.02) and at 4 weeks both were non-significant	0	0	0	0	1-
				• When comparing intra-articular vs peripatella there was no significant difference between the two	0	0	0	0	1-
Hepper (2009) SR *Efficacy and preparations of IACI for knee osteoarthritis*	LQ (-)	5 RCTs	Pain	• 4 from 4 studies showed a statistically significant decrease in pain from baseline at week 1	0	0	1	1	1
				• Only one study reported a statistically significant decrease from baseline within the corticosteroid group at week 4	0	0	1	0	1-
				• At week 4-3, 6-8 and 12-24 no statistically significant differences were found between the steroid and the placebo group	0	0	1	0	1-
				• One study found at week 1 triamcinolone to be more effective than betamethasone however both groups had a statistically significant difference in pain scores	0	0	1	0	1-
				• One study found triamcinolone to be more efficacious than methylprednisolone at week 3	0	0	1	0	1-
				• Two of four studies failed to find any statistically significant difference between triamcinolone and methylprednisolone	0	0	1	0	1-
Godwin (2004) SR/MA *Intra-articular depo-corticosteroid preparation and knee osteoarthritis*	LQ (-)	5 RCTs	Pain	• At 1 week post injection 2 of 2 studies showed depo-corticosteroid statistically significantly reduced VAS compared to the control	1	0	1	0	1
				• At week 3 to 4 there was no significant difference in VAS score between the steroid group and the control group	1	0	1	0	1
				• At week 6 to 8 there was no significant difference in VAS score between the steroid group and the control group	1	0	1	0	1

Author and year	SIGN Score	Studies	Outcome	Conclusions	Evidence 1	2	3	4	Grade
Cheng (2012) SR *intra-articular corticosteroids for knee osteoarthritis*	LQ (-)	2 MAs	Pain	• One meta-analysis showed clinically and statistically significant reduction in knee pain 1 week after injection which could last for 3-4 weeks but is unlikely to continue beyond that	0	0	1	0	1-
				• Second meta-analysis showed that the improvement in symptoms after IACI only lasted up to 2 weeks	0	0	1	0	1-
Campbell (2015) SR *Intra-articular corticosteroids vs intra-hyaluronic acid for knee osteoarthritis*	LQ (-)	2 RCTs	Pain	• Corticosteroids are effective in controlling pain secondary to knee osteoarthritis in the short term (first four weeks)	0	0	0	0	1-
				• From the 5th to 13th week intra-articular hyaluronic acid was more effective and this relief lasted for up to 26 weeks in two studies	0	0	0	0	1-
Bjordal (2007) SR/MA *Short term effects of corticosteroids for knee OA*	LQ (-)	6 RCTs	Pain	• For steroid injections, the time point for maximum efficacy was at typically 1.5 weeks and corresponding to 14.5mm (95% CI 9.7 -19.2) on VAS decreasing to 6.7mm (95% CI 0.4 – 13.0) at week 4	1	0	1	0	1
				• During the first four weeks after treatment initiation intra-articular steroid injections offer limited pain relief over the placebo within 1-2 weeks	1	0	1	0	1
				• Intra-articular steroid injections don't offer meaningful pain relief beyond the first month	1	0	0	0	1
Bellamy (2006) SR/MA *Efficacy and safety of intra-articular corticosteroid for patients with knee OA*	HQ (++)	26 RCTs	Pain, physical function, patient global assessment, joint imaging	• Corticosteroids are effective at pain reduction in osteoarthritic knees in the short term (up to 4 weeks)	1	1	1	1	1++
				• Corticosteroids offer little to no effect on function	1	1	1	0	1+
Bannuru (2009) SR/MA *Comparing intra-articular corticosteroids with intra-articular hyaluronic acid for knee OA*	AQ (+)	RCTs	Pain	• Corticosteroids are effective at pain reduction in osteoarthritic knees in the short term (up to 4 weeks)	1	1	1	0	1+
				• The effect is largely absent by the 26 weeks time point	1	1	1	1	1++
Patellofemoral Pain Syndrome									
Heintjes (2008) SR *Steroid injections for patellofemoral pain syndrome*	HQ (++)	1 RCT	Clinical improvement of symptoms	• Significant difference were found in the number of participants that improved clinically; 20 out of 23 improved in the steroid group compared to 1 out of 20 in the placebo group	0	1	0	0	1-

Appendix 3: Quality scores for Systematic Reviews used in this Review

Quest	Reference (Author, year)	Wang and He 2015	Van Middelkoop et al., 2016	Maricar 2013	Juni 2015	Hirsch 2013	Hepper 2009	Heintjes 2008	Cheng 2012
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper. Does this study do it?	Y	Y	Y	Y	Y	Y	Y	Y
1.2	A comprehensive literature search is carried out?	Y	Y	Y	Y	Y	Y	Y	Y
1.3	At least two people should have selected studies	Y	Y	CS	Y	CS	CS	Y	Y
1.4	At least two people should have extracted the data	CS	Y	CS	Y	CS	CS	Y	Y
1.5	The status of publication was not used as an inclusion criterion	Y	N	N	N	N	N	N	N
1.6	The excluded studies are listed	N	N	N	Y	N	N	Y	N
1.7	The relevant characteristics of the included studies are provided	Y	Y	Y	Y	Y	Y	Y	Y
1.8	The scientific quality of the included studies was assessed and reported.	Y	Y	Y	Y	Y	N	Y	N
1.9	Was the scientific quality of the included studies used appropriately?	N	N	N	Y	N	N	Y	N
1.10	Appropriate methods are used to combine the individual study findings	Y	Y	NA	Y	NA	NA	NA	NA
1.11	The likelihood of publication bias was assessed appropriately	Y	N	N	Y	N	N	N	N
1.12	Conflicts of interest are declared	N	Y	Y	Y	N	Y	Y	Y
2.1	What is your overall assessment of the methodological quality of this review?	A	A	LQ	HQ	LQ	LQ	HQ	LQ
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y	Y	Y	Y	Y

Appendix 3: Quality scores for Systematic Reviews used in this Review (contd)

Quest	Reference (Author, year)	Campbell 2015	Bjordal 2007	Bellamy 2006	Bannuru 2009	Arroll and Goodyear-Smith 2005
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper. Does this study do it?	Y	Y	Y	Y	
1.2	A comprehensive literature search is carried out?	Y	Y	Y	Y	
1.3	At least two people should have selected studies	Y	CS	CS	Y	
1.4	At least two people should have extracted the data	CS	CS	Y	Y	
1.5	The status of publication was not used as an inclusion criterion	N	N	Y	Y	
1.6	The excluded studies are listed	N	N	Y	N	
1.7	The relevant characteristics of the included studies are provided	Y	Y	Y	Y	
1.8	The scientific quality of the included studies was assessed and reported.	Y	Y	Y	Y	
1.9	Was the scientific quality of the included studies used appropriately?	Y	Y	Y	Y	
1.10	Appropriate methods are used to combine the individual study findings	NA	NA	Y	Y	
1.11	The likelihood of publication bias was assessed appropriately	NA	N	N	N	
1.12	Conflicts of interest are declared	Y	Y	Y	N	
2.1	What is your overall assessment of the methodological quality of this review?	LQ	LQ	HQ	A	
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y	

Appendix 4: RCTs included in Systematic Reviews used in this Review

	Wang & He (2015)	van Middlekoop et al., 2016	Maricar 2013	Juni et al., (2015)	Hirsch, Kitas & Klocke 2013	Hepper et al., 2009	Heintjes 2008	Cheng at al 2012	Campbell et al., 2015	Bjordal et al., 2007	Bellamy et al., 2006	Bannuru 2009	Arroll and Goodyear-Smith 2005	
Antich 1986							1							1
Arden et al., 2008		1	1		1									3
Atchia et al., 2011		1												1
Beyaz 2012				1										1
Bias et al., 2001								1	1		1			3
Boon *et al.,* 2010		1												1
Caborn 2004	1								1		1	1		4
Campos 2013				1										1
Castro 2007				1										1
Cederlof 1966				1				1	1		1		1	5
Chao *et al.,* 2010		1	1	1	1									4
Chavez-Chiang 2011			1											1
de Campos et al., 2013		1												1
Di Sante 2012				1										1
Dieppe 1980			1	1	1	1		1	1	1	1		1	9
Dieppe 1993								1						1
Frias 2004				1										1
Friedman 1980				1				1	1	1	1		1	6
Friedman and Moore 1978					1	1								2
Frizziero 2002	1								1		1	1		4
Gaffney 1995			1	1	1	1		1	1	1	1		1	9
Grecomoro 1992				1										1
Henriksen 2015				1										1
Jones & Doherty 1996			1	1	1	1		1	1		1			7
Jones 1995	1							1	1	1	1	1	1	7
Lambert et al., 2007		1												1
Leardini 1987								1	1		1	1		4
Leardini 1991								1	1		1	1		4

Appendix 4: RCTs included in Systematic Reviews used in this Review (contd)

	Wang & He (2015)	van Middlekoop et al., 2016	Maricar 2013	Juni et al., (2015)	Hirsch, Kitas & Klocke 2013	Hepper et al., 2009	Heintjes 2008	Cheng at al 2012	Campbell et al., 2015	Bjordal et al., 2007	Bellamy et al., 2006	Bannuru 2009	Arroll and Goodyear-Smith 2005	
Leopold 2003					1			1	1		1			4
Lyons 2005				1										1
Miller 1958				1				1	1		1		1	5
Ozturk 2006				1										1
Pendleton 2008			1		1									2
Petrella 2015				1										1
Pietrogrande 1991								1	1		1	1		4
Popov 1989				1				1	1		1			4
Pyne 2004			1		1			1	1		1			5
Ravaud *et al.*, 1999		1		1		1		1	1	1	1		1	8
Reynauld 2003				1	1			1	1		1		1	6
Sambrook 1989														0
Schue 2011				1										1
Shah & Wright 1967			1											1
Shimizu 2010	1													1
Skwara 2009 (Durolane)	1													1
Skwara 2009 (Ostenil)	1													1
Smith 2003				1				1	1	1	1		1	6
Tasciotaoglu 2003	1							1	1		1	1		5
Tekeoglu et al., 1998								1	1		1			3
Thorpe 1985								1	1		1			3
Valtonen 1981					1			1	1		1			4
Wright 1960					1			1	1		1		1	5
Yavuz 2012				1										1
Young 2001				1				1	1		1			4
Zhilyayev 2012				1										1
	7	7	9	25	12	5	1	24	25	6	25	7	10	

Appendix 5: Quality Scores for Randomised Controlled Trials used in this Review

Quest	Reference (Author, year)	Wagner 2015	Soriano-Maldonado 2016	Skwara 2009	Sibbitt 2011
1.1	The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	Y	Y	CS	CS
1.3	An adequate concealment method is used.	Y	Y	CS	N
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	N	Y	CS	N
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y	Y	**CS**
1.6	The only difference between groups is the treatment under investigation.	Y	Y	Y	**Y**
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y	Y	**Y**
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	11% of all patients were withdrawn.	Case: 10% Control: 12%	**Not clear**	0%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y	Y	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	NA	NA	NA	NA
2.1	How well was the study done to minimise bias?	HQ	HQ	LQ	LQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y
2.4	Summary of the author's conclusion	All 3 knee injection sites studied have similar overall clinical benefit at 4-week follow-up.	Adding intra-articular corticosteroid injection 2 weeks prior to an exercise program does not provide additional benefits compared to placebo.	Single application of high-viscosity hyaluronan shows superior range of motion and pain reduction as well as improvement in clinical results	Sonographic needle guidance reduced procedural pain and improved the clinical outcomes and cost-effectiveness.

Appendix 5: Quality Scores for Randomised Controlled Trials used in this Review (contd)

Quest	Reference (Author, year)	Sari 2016	Pierce 2016	Parmigiani 2010	Tammachote 2016
1.1	The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	CS	CS	Y	Y
1.3	An adequate concealment method is used.	N	N	N	Y
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	N	N	Y	N
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y	Y	Y
1.6	The only difference between groups is the treatment under investigation.	Y	Y	Y	Y
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y	Y	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	0%	0%	0%	Hylan group:9.1% TA group: 11%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y	Y	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	NA	NA	NA	NA
2.1	How well was the study done to minimise bias?	LQ	AQ	HQ	HQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y
2.4	Summary of the author's conclusion	Genicular nerve radiofrequency neurotomy is a safe and efficient treatment modality and provides functional improvement along with an analgesia in patients with chronic knee OA.	Authors advocate for the use of infrapatellar injection whenever possible, with the degree and location of arthri¬tis guiding position of injection.	Joint lavage combined with triamcinolone hexacetonide does not present a greater benefit over intra-articular injection with triamcinolone hexacetonide alone for primary osteoarthritis of the knee.	TA provided similar improvement in knee pain, function, range of motion compared to hylan G-F 20 at 6-months, with better pain control in the 1st week & better knee functional improvement in 2nd week.

Appendix 5: Quality Scores for Randomised Controlled Trials used in this Review (contd)

Quest	Reference (Author, year)	Leighton 2014	Kongsgaard 2009	Housman 2014	Henriksen 2015
1.1	The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	Y	Y	Y	Y
1.3	An adequate concealment method is used.	Y	N	N	Y
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	Y	N (single blind)	N (injecting physician not blinded)	Y
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y	CS	Y
1.6	The only difference between groups is the treatment under investigation.	Y	Y	Y	Y
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y	Y	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	0%	CORT: 16% ECC: 31% HSR:16%	2x4 Hylastan: 17% 1x4 hylastan: 19% Steroid: 16%	Placebo: 12% Corticosteroid: 10%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y	Y	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	NA	NA	CS	NA
2.1	How well was the study done to minimise bias?	HQ	AQ	AQ	HQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y
2.4	Summary of the author's conclusion	Single-injection NASHA was well tolerated and non-inferior to MPA at 12 weeks. The benefit of NASHA was maintained to 26 weeks while that of MPA declined.	CORT has good short-term but poor long-term clinical effects, in patellar tendinopathy. HSR has good short- and long-term clinical effects.	Both IA hylastan injection regimens were effective in relieving pain with acceptable safety. IA hylastan was not superior to IA corticosteroid.	No additional benefit results from adding an intra-articular injection of 40mg of corticosteroid before exercise in patients with painful OA of the knee.

Appendix 5: Quality Scores for Randomised Controlled Trials used in this Review (contd)

Quest	Reference (Author, year)	Folman 2011	Dieu-Donne 2016	De Souza 2010	Davalillo 2015
1.1	The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	CS	N	N	Y
1.3	An adequate concealment method is used.	N	N	Y	Y
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	N	N	Y	N
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y	Y	N
1.6	The only difference between groups is the treatment under investigation.	Y	Y	Y	N
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y	Y	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Not clear	Not clear	Not clear, assume 0%	Hyal: 11% Beta: 9%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	CS	CS	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	CS	NA	NA	NA
2.1	How well was the study done to minimise bias?	LQ	LQ	LQ	LQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y
2.4	Summary of the author's conclusion	Peri-articular infiltration of corticosteroids is an alternative method of local administration in knee grade 1–3/4 osteoarthritis.	Corticosteroid injections have a short efficacy compared to NSAIDs. Prescribing NSAIDs should consider the cons-indications, comorbidities and their deleterious digestive, renal, and cardiovascular effect.	No difference in the analgesic effect was observed for the combined intra-articular administration of morphine (2mg) and methylprednisolone (80mg) in patients with knee osteoarthritis.	Both treatments effectively controlled OA symptoms. BM showed higher short-term effectiveness, while HA showed better long-term effectiveness.

Appendix 5: Quality Scores for Randomised Controlled Trials used in this Review (Contd)

Quest	Reference (Author, year)	Bodick 2015	Bellamy 2016
1.1	The study addresses an appropriate and clearly focused question.	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	Y	Y
1.3	An adequate concealment method is used.	Y	Y
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	Y	Y
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y
1.6	The only difference between groups is the treatment under investigation.	Y	Y
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	FX006 10mg: 3.5% FX006 40mg: 3% FX006 60mg: 2% TCA IR: 6%	Ketorolac: 6% Corticosteroid: 13%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	NA	NA
2.1	How well was the study done to minimise bias?	HQ	HQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y
2.4	Summary of the author's conclusion	Intra-articular injection of FX006, an extended-release formulation of triamcinolone acetonide, provided a clinically relevant improvement in pain relief in patients with knee osteoarthritis relative to immediate release triamcinolone acetonide.	Pain relief was similar between ketorolac and corticosteroid injections. Ketorolac knee injection is safe and effective with a cost savings percentage difference of 143% when compared with corticosteroid.

Appendix 6: Summary of Randomised Controlled Trial findings

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
Bodick et al., (2015)	United States of America (patients also recruited from Canada and Australia)	Either 10, 40 or 60mg of FX006 – an extended release formulation of triamcinolone acetonide 40mg Immediate – release triamcinolone acetonide	Mean daily pain on the 11-point numeric rating scale, WOMAC (pain, stiffness, functional), blood samples (hematology, chemistry and triamcinolone acetonide concentrations), electrocardiogram, vital signs, adverse events	Baseline and days 2,8,15,29,57 and 85	The 40mg dose of FX006 produced pain relief that was superior to immediate release triamcinolone acetonide at two through to twelve weeks (P=<0.05 at each time point, the mean pain reduction in comparison was -0.9) Also demonstrated significant imporvements (p<0.05) over immediate release triamcinolone acetonide at 8 weeks in key secondary outcomes that assessed pain, stiffness, function, patient global impression of change, clinician global impression of change and responder status	The 40mg dose of FX006 provided clinically meaningful improvement in analgesia relative to immediate –release acetonide while substantially reducing systemic exposure
Dieu-Donne et al., (2016)	Burkina Faso	Cortivazol 3 75mg or Betamethsone 2mg	Pain using VAS, algofunctional Lequesne index	Baseline, day 1,7,15,21,28, 35,42	Mean (SD) Spontaneous pain intensity in the NSAID at baseline was 50.46 (30.93) reducing to 6.72 (13.75) at 6 weeks compared to the SIAI group 63.92 (30.07) compared to 17.80 (21.78) at 6 weeks. Mean (SD) pain on walking for the NSAIDs group was 53.33 (22.31) at baseline and 19.11 (11.37) at 6 weeks and in the SIAI group 74.85 (17.55) at baseline and 35 (30.69) at 6 weeks Using the mean VAS the percentage of patients with pain (%) in the NSAIDs group at baseline was 50.5 reducing to 6.7 at 6 weeks and the SIAI at baseline was 63.9 reducing to 17.8 at 6 weeks	The number of patients with spontaneous pain in the NSAIDs group was significantly less than in patients who have received the steroid injection. The steroid injections seem to have a brief efficiency. The oral NSAIDs have the advantage of maintaining a relief in the period compared to steroid intra-articular injections
Davslillo et al., (2015)	Mexico	Betamethasone	Pain using VAS, function in the WOMAC (likert scale)	Baseline, 3,6,9 and 12 months	Raw value for pain showed significant reduction is both groups from early follow up, percentages of reduction were higher in the BM group at 3 months (66.3%, 95% CI 63.3 – 69.3) compared to the HA group (48.5%, 95% CI: 45.8 – 51.3) (P<0.0001). The 6 month visit, reduction in pain was significantly higher in the HA group and at 12 months the mean reduction in pain the HA group was 33.6% (95% CI: 31.1 – 36.1) compared to 8.2% (95% CI: 5.2-11.1) in patients treated with BM (P<0.0001) WOMAC function scores favoured the HA at all visits, at the end of the study HA participants had a mean improvement in function of 47.5% (95% CI: 45.6 – 49.3) compared to 13.2% (95% ci: 11.4-14.9) in the BM group (P<0.0001) The comparison between groups for WOMAC total scores, pain, stiffness subscales followed the same patterns	HA and BM showed remarkable long-term improvements in knee OA symptoms after treatment with both hyaluronic acid and betamethasone, in this study the statistical and clinical differences favoured HA from 3 month onwards, the efficacy of BM decreased in favour of HA, which continued to the end of the study.

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
Dieu-Donne et al., (2016)	Burkina Faso	Cortivazol 3 75mg or Betamethsone 2mg	Pain using VAS, algofunctional Lequesne index	Baseline, day 1,7,15,21,28, 35,42	Mean (SD) Spontaneous pain intensity in the NSAID at baseline was 50.46 (30.93) reducing to 6.72 (13.75) at 6 weeks compared to the SIAI group 63.92 (30.07) compared to 17.80 (21.78) at 6 weeks. Mean (SD) pain on walking for the NSAIDs group was 53.33 (22.31) at baseline and 19.11 (11.37) at 6 weeks and in the SIAI group 74.85 (17.55) at baseline and 35 (30.69) at 6 weeks Using the mean VAS the percentage of patients with pain (%) in the NSAIDs group at baseline was 50.5 reducing to 6.7 at 6 weeks and the SIAI at baseline was 63.9 reducing to 17.8 at 6 weeks	The number of patients with spontaneous pain in the NSAIDs group was significantly less than in patients who have received the steroid injection. The steroid injections seem to have a brief efficiency. The oral NSAIDs have the advantage of maintaining a relief in the period compared to steroid intra-articular injections
Folman and Shabot (2011)	Israel	2ml 80mg methylprednisolone acetate (Depo-Medrol)	WOMAC (5 categories) – pain while walking, pain while climbing stairs, nocturnal pain, pain during rest, pain from weight bearing	Baseline and 3/12	The pain intensity decreased in the IAI group from 56.6 (9.7) to 24.o (25.0) (P<0.001) The pain intensity decreased in the PAI group from 62.5 (19.0) to 27.0 (17.2) (P<0.001) 21.8% of the patients in the IAI group and 80.6% in the PAI group reported temporary (24-48 hour) intensification of the pain following the intervention All the patients reported immediate and considerable pain relief, the greatest relief reported by the PAI group	At the end of the 3 month follow up, most of the patients reported reduced pain compared to the pre-treatment intensity, peri-articular infiltration of inflamed tissue located by a TeP is simple and is an alternative to intra-articular infiltration of solution as it reduces the risk of infection in the joint space or systemic adverse events, however rare these are.
Housman et al., (2014)	USA, Canada, france, UK and Germany	Methlyprednisolone acetate 40mg	WOMAC, OMERACT-OARSI, patient global assessment, clinical observer global assessment	Baseline and week 4,8,12,16,20,26	For WOMAC pain score, estimated mean changes from baseline voer 26 weeks were similar in all three arms, 2 x 4ml Hyalstan -0.9 (95% CI -1.0, -0.7), 1 x 4ml hyalstan -0.8 (-0.9,-0.7) and the steroid group -0.9 (-1.0, -0.8) with no statistical difference between steroid and hyalstan Similar improvement from baseline in secondary clinical outcomes were also seen, but there was no significant differences between hyalstan and steroid Steroid group improved in PTGA for target knee Mean (SD) 2,4 (0.6) at baseline to 1.6 (0.9) at week 26 COGA target knee 2.3 (0.8) at baseline to 1.5 (1.1) at 26 weeks and WOMAC A1 walking pain from 2.3 (0.5) at baseline to 1.5 (0.8) at week 26	Within group changes from baseline over 26 weeks were statistically significant in all three arms and there was no difference between the arms. All three treatments were effective in the relief of OA associated knee pain as demonstrated by a reduction in WOMAC A pain score by 61pprox.. 1 point. The reduction in pain was evident in all first assessments (week 4) and was maintained to week 26

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
Konsgaard et al., (2009)	Denmark	1ml of 40mg methylprednisolone in 0.5ml lidocain	VISA –p and VAS for maximal tendon pain US patella tendon Muscle tendon structural properties Patella tendon biopsie Patella tendon structural properties Biochemical analysis of collagen, pyridinoline crosslink and pentosidine concentrations	Baseline, 12 and 26 weeks	VISA-p improved similarly and significantly form baseline to 12 weeks; Mean (SD) change from baseline to 12 weeks = 64 (14) to 82 (19) for steroid; 53 (13) to 75 (3) for eccentric and 56 (13) to 78 (18) for HSR. From 12 to 26 weeks; Mean (SD) = 82 (19) to 64 (22) for steroids; 75 (3) to 76 (16) for ECC and 78 (18) to 86 (12) for HSR. For VAS: Mean (SD) score at baseline, 12 and 24 weeks = 58 (17), 18 (21) 31 (29) for steroids; 59 (20), 31 (26), 22 (17) for ECC and 61 (15), 19 (15), 13 (16) for HSR Overall HSR had greatest % change on VAS of 70%, ECC had 55% and steroid s 47%	The three different treatment regimes had similar short-term effects and clinical patient satisfaction but different long term effects. The steroid half year follow up showed deteriorating effects while the eccentric exercises and heavy slow repetitions maintained clinical improvement
Leighton et al., (2014)	Canada, UK, Sweden	Methylprednisolone acetate (MPA)	WOMAC pain responder rate	Baseline, phone calls at 2 & 4 weeks, clinic visits at week 6, 12, 18 and 26	WOMAC pain responder rates at 12 weeks demonstrated NASHA to be non-inferiro to MPA (NASHA: 44.6%; MPA 46.2%; 95% CI of difference: 11.2%; +7.9%) WOMAC pain responder rate at week 6,12 and 18 remained comparable between NASHA and MPA Between weeks 18 and 26, the WOMAC pain responder rate remained stable in the NASHA group while there was a decrease in the MPA group over this period MPA provided early improvement in pain, reaching a maximum of 6 weeks and declining thereafter until 26 weeks	Both treatment modalities are able to reduce pain in osteoarthritic knees in the short-term but after week 6 the steroid efficacy started to deteriorate whereas the NASHA provided a longer lasting effect, with significantly improved pain response at 26 compared to MPA
Parmigiana et al., (2010)	Brazil	Triamcinolone hexacetonide (TH) 60mg	VAS for pain, VAS for improvement, range of movement of the knee, Lequesne's index, WOMAC index, five item likert scale for physician and patient assessment of improvement, timed 50 ft walk test	Baseline and week 1,4,8,12	Throughout the 12 week study, there were no statistically significant differences between groups for any of the variables studies During the course of the study, a maximum improvement of 80% (DP ± 18.84) by the JL/HT group and 73% (DP ±26.15) for the HT group Patients with the most severe osteoarthritis according to the KL scale achieved a statistically greater improvement over the other subgroup regarding WOMAC pain (p=0.01), Lequesne's index (p=0.021) and the likert improvement scale according to patient (p=0.013) and according to the physician (p=0.035) which were shown at week 8	Study demonstates that joint lavage in combination with triamcinolone hexacetonide does not present a greater benefit over intra-articular injection with TH alone for primary osteoarthritis of the knee

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
Tammachote et al., (2016)	Thailand	triamcinolone acetonide	VAS, WOMAC, Knee ROM	Baseline, day 1,2,3 and weeks 1 and 2 and months 1,2,3,4,5	The triamcinolone acetonide injection group had significantly better overall pain improvement than the hylan G-F 20 group (p= 0.02), especially in the first week after injection. The difference between groups for the mean VAS score for pain was approximately 11 points from immediately after injection to 1 week ($p < 0.05$), and then the mean differences became small and were not significant ($p > 0.05$) At 6 months, the mean change in VAS scores was approximately -30 points in both groups: -29 points (95% CI,-36.4 to -22.7 points) in the hylan G-F 20 group and -30 points (95% CI,-36.0 to -22.8 points) in the triamcinolone acetonide group ($p < 0.0001$) The triamcinolone acetonide group had better mean functional improvement than the hylan G-F 20 group only at 2 weeks after injection ($p = 0.029$) . At the end of 6 months, the mean modified WOMAC scores had significantly improved ($p < 0.0001$ for both) from 43 to 21 points (95% CI, 16.7 to 29.2 points) in the hylan G-F 20 group and from 39 to 21 points (95% CI, 11.0 to 24.3 points) in the triamcinolone acetonide group Active Knee Range of Motion The mean knee range of motion change was not differ- ent between the 2 groups at any time point ($p > 0.05$)	Patients who received a triamcinolone acetonide injection had similar pain improvement, functional improvement, and knee range of motion at 6 months compared with patients who received a hylan G-F 20 injection
Wagner et al., (2015)	USA	Depo-Medrol (Pfizer)	VAS for pain, WOMAC	Baseline, directly post injection, week 1 and 4	The mean (SD) VAS scores for procedural discomfort were 39.1 (28.5) for superolateral approach, 32.9 (31.5) for anteromedial approach and 33.1 (26.6) for anterolateral approach, (p=0.78) showing no statistical difference between groups WOMAC scores decreased at week 1 and 4 for all groups, with no significant differences between the 3 groups reductions. WOMAC scores for the SL, AM and AL groups were 701 (687), 593 (555) and 891 (714) @ 1 week follow up and 600 (610), 665 (683) and 954 (699) at 4 weeks respectively	Overall, clinical outcomes, as measured nu WOMAC scale, were not significantly different when injecting a dry knee using an SL, AL or AM portal with a 2 inch needle
Peirce et al., (2016)	USA	Corticosteroid – triamcinolone mixed with anaesthetic Xylocaine	VAS for pain	Baseline, 1 minute and 5 minutes post injection	Mean VAS scores at 1 minute for lateral suprapatellar, medial infrapatella and lateral infrapatella injections were 7, 4 and 2 points Infrapatella injections were associated with significantly less pain than suprapatellar injections (P=0.003)	Authors advocate for the use of infrapatella injection wherever possible, with the degree and location of arthritis guiding whether it would be inferomedial or inferolateral

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
Sari et al., (2016)	Turkey	Betamethasone with bupivacaine and 2.5mg morphine	VAS at rest, WOMAC	Baseline, 1 and 3 months	In the RF group, a significant reduction was observed in VAS pain at the first month (P<0.001) and the third month (P<0.001) in comparison with the steroid group. IN the RF group, a significant reduction was observed in WOMAC total scores at 1 month (P<0.001) in comparison to the steroid group. Steroid VAS: baseline = 8; 1/12 = 5 and 2/12 = 5.5. WOMAC; 47.19 (11.98) baseline, 37.53 (11.46) @ 1/12, 42.33 (10.95) @ 3/12 RF VAS: 8 @ baseline, 2 @ 1/12, 4 @ 2/12 WOMAC; 56.32 (9.13) @ baseline, 29.16 (8.66) @ 1/12, 39.70 (8.89) @ 3/12	The intensity of pain significantly reduced in the RF group following the procedure Significant short-term and long term clinical improvements were obsereved in patients from both groups (P<0.001) When compared to the IA group, the perception of pain significantly reduce in the GF, both in the short and long term (12 weeks)
Skwara et al., (2009)	Germany	Triamcinolone	VAS for pain, Knee Society Score, Lequesne Score	Baseline, 12 weeks	HA – group: Mean (SD) VAS @ baseline = 54.9 (15.2), 12/52 = 44.0 (22.3). Lequesne @baseline = 11.9 (1.5), 12/52 = 10.1 (1.1) TA-group: Mean (SD) Vas @ baseline = 52.9 (10.8), 12/52 = 45.8 (27.8). Lequesne @baseline = 11.6 (1.7), 12/52 = 9.7 (2.4) The clinical examination of the VAS for pain revealed a significant decrease in the HA group The mean values of the Lequesne score improved significantly in the HA group from 11.9 points in the screening visit to 10.1 in the follow up visit. The results in the VAS for pain declined from 52.9mm to 42.5mm without a significance. In the Lequesne score the TA group achieved a significant increase from 11.6 to 9.7 (P<0.0001)	The HA was able to produce a significant decrease in VAS for pain at the 12 week follow up compared to the TA group with decline from 52.9 to 42.55mm without a significane. There was a significant increase in the Lequesne score for both groups
Henrikson et al., (2015)	Denmark	Methylprednisolone acetate with lidocaine hydrochloride	KOOS – pain subscale, symptoms, function in daily living, function in sport and recreation, knee related quality of life, functional weight-bearing pain test muscle strength, 6-minute walking distance, plasma concentration of interleukin 6 measured from fasting morning blood samples and semiquant assessments of effusion and synovitis	Baseline, weeks 2,14,26	Mean (SD) KOOS pain scale from baseline @ week 14 Placebo 14.8 (1.8) to steroid 13.6 (1.8) with mean difference 1.2 (3.8 – 6.2) P=0.64 For all outcome measures considerable improvements were observed at every time point, no differences in the steroid and placebo groups were found Hamstring isometric strength was statistically significantly favoured the steroid group	No additional clinical benefit of adding 40mg methylprednisolone acetate to an intra-articular injection of saline and lidocaine before exercise in patients with OA of the knee

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
Bellamy et al., (2016)	USA	Triamcinolone Acetonide in 8cc of Bupivacaine Hydrochloride (0.5%)	VAS (pain), WOMAC, KSS, tegner/Lysholm knee scoring system, Short-form 36, University California Los Angeles activity score, price	Baseline, week 2, 6; Month 3 and 6	Mean VAS for both ketorolac and corticosteroid decreased significantly from baseline at 2 weeks, 6.3-4.6 (P=.003) and 5.2-3.6(P =.003), respectively and remained decreased throughout the 24 weeks. Data were normalized for VAS over time with no difference between the 2 treatments (P =0 .98) Mean WOMAC score for both ketorolac and corticosteroid increased from baseline at 2 weeks, 49-53 (P = .003) and 53-68 (P = .003), respectively. Corticosteroid appeared to have higher function scores than ketorolac at final follow-up. There was no significant difference in KS pain and function, Short Form-36, Tegner/Lysholm, and University California Los Angeles scores between ketorolac and corticosteroid throughout the 24 weeks (P > .05). The institutional costs per injection of triamcinolone and ketorolac are $12.28 and $2.01, respectively. The cost percentage difference is 143% between the 2 injections	Both treatments were able to decrease pain and improve the WOMAC scores, the only difference between the two that was shown to be statistically significant was that corticosteroids were able to produce a higher functional score at the final follow up. Ketorolac was the more cost-effective intervention
Sibbit et al., (2011)	USA	80mg triamcinolone acetonide suspension	VAS (pain), cost of procedure	Baseline, during insertion of needle, during injection of treatment, 2 weeks, 6 month	Anatomic palpation guidance = 69% reduction in absolute pain score @2/52 (baseline VAS: 7.8 (1.8); 2 week VAS: 2.4 (2.8) P<0.001) Duration of therapeutic effect was: mean (SD) 3.1 (2.1) Months Time to reinject: 6.0 (2.8) months Sonographically guided = 42% less pain than palpation method @2/52 (p<0.03) Absolute pain score @2/52 (baseline VAS 7.5 (2.0); 2/52 VAS: 1.4 (2.1) Pain @ 6/12 mean (SD) for palpation was 6.3 (2.9) and sonographically guided 6.3 (2.6) Time to next procedure mean (SD): Palpation = 6.0 (2.8) months and sonographically guided = 7.1 (3.2) months	Study demonstrated that intra-articular injection performed with sonographic image guidance can significantly and meaningfully improve pain outcomes.

Author	Country	Steroid	Pain			Conclusions
			Outcome measures	Outcome Assessment Timepoints	Results	
De souza, Issy & Sakata (2010)	Brazil	80 mg methylprednisolone with and without 2mg morphine	Time to first analgesic request recorded on a chart by the patient, pain intensity (0-10 numerical scale), most intense pain at rest and during movement, knee extension and flexion angle, quality of analgesia reported by the patient	Baseline, 30min, 60min, 1 week post injection	Two groups did not differ in term of the time for first analgesic supplementation = mean Hours (SD) Steroid and morphine group = 19.5 (4.2) Steroid group = 13.2 (6.5) p = 0.1274 Two groups did not differ in total paracetamol dose used over the 1 week; mean grams (SD); Steroid & Morphine = 3.6 (6.2), steroid = 3.4 (5.7) p = 0.4160 Intensity of pain during movement, Mean (SD); Steroid & Morphine @ baseline 7.9 (2.2); @ 30min 5.5 (2.8), @ 60min 3.5 (2.5). @ 1/52 3.3 (2.9); Steroid @ baseline 8.3 (1.4), @30min 4.8 (3.4, @60min 3.0 (3.92) @ 1 week 3.6 (2.9). A significant reduction in pain was observed in group 2 @ 1/52 p=0.0063 No difference in flexion and extension angle was observed @1/52 between the two groups Quality of analgesia was reported to be excellent or good by 78.5% of the patients of steroid and morphine group and 85.7% of patients in the steroid group – no significant difference was found between the two groups	Pain intensity was similar in the two groups at 1 week. No difference in the analgesic effect was observed with the added 2mg of morphine in knee osteoarthritis pain with intra-articular steroid injections
Soriano-Maldonado et al., (2016)	Denmark	Methylprednisolone acetate with lidocaine hydrochloride	Pressure pain sensitivity threshold (PPT) Temporal Summation (TS)	Baseline, 14,26	There was no significant group differences between changes in PPT or TS at week 14 or 26 There was no overall benefit to the pain sensitivity measures regardless of allocation	An intra-articular corticosteroid injection 2 weeks prior to an exercised based intervention program provides no additional benefits on pain sensitivity in comparison to placebo in patients with knee OA

Author	Imaging	Population Characteristics				
		N	Age (central tendency and variation)	Diagnostic Label	Diagnostic Tests	Duration of Pain
Bodick et al., (2015)	NR	N=229	Mean (SD) = 61.5 (8.48) for FX006 10mg, 60.9 (9.63) for 40mg, 61.9 (9.35) for60mg and 61.6 (10.09) for TCAIR	Unilateral or bilateral osteoarthritis of knee for at least 6 months	American College of Rheumatology Criteria for Classification of Idiopathic OA of the Knee A mean of ≥ 5 points and ≤ 9 points on the twenty-four-hour mean pain score (on the 0 to 10-pointNumeric Rating Scale) for at least five of the seven days prior to day 1 and a Kellgren-Lawrence grade of 2 or 3 were also required	Mean (days) SD =10mg FX006 = 28.3 (3.75), 40mg = 28.1 (4.07), 60mg = 29.0 (2.52), 40mg TCA IR = 28.3 (3.43)
Davslillo et al., (2015)	NR	N=195	Mean (SD) = 62.7 (0.6) for HA and 62.8 (0.6) for BM	Knee osteoarthritis	Radiographic OA grade II-III according to Kellgren and Lawrence (KL)	NA
Dieu-Donne	NR	N=70	Mean = 59.69 for NSAIDs and 46.40 for SIAI	Knee osteoarthritis	Not stated	Not stated
Folman and Shabot (2011)	Radiographic	N=63	Mean (SD) = 68.97 (11.72) for IAI group; 62.48 (11.88) for PAI group	Knee osteoarthritis	Antero-posterior xray in upright position, then Kellgren and Lawrence measure	Mean (SD) = 85.25 days (77.18)
Housman et al., (2014)	NR	N=391	Mean (SD) = 62.0 (9.7) Hyalstan 2x4ml, 60.6 (9.9) Hyalstan 1x4ml, 60.1 (9.3) steroid group	Knee Osteoarthritis	Score of 1.5-3.5 on the WOMAC LK 3.1 subscores WOMAC A and A1	Not Stated
Konsgaard et al., (2009)	Ultrasonography	N=37	Mean (SD) = 34.3 (10) steroid group, 31.3 (8.3) eccentric exercises, 31.7 (8.5) heavy slow reps	Patella tendinopathy	Ultrasonography requiring thickening of tendon	>3 months
Leighton et al., (2014)	Radiography	N= 442	Mean (SD) = 61.9 (9.6) NASHA group; 61.5 (9.9) Steroid group	Knee osteoarthritis	American College of Rheumatology Criteria for the diagnosis of OA Radiographically verified OA of the knee (Kellgren-Lawrence Grade II or III	Not Stated

Author	Imaging	Population Characteristics				
		N	Age (central tendency and variation)	Diagnostic Label	Diagnostic Tests	Duration of Pain
Tammachote et al., (2016)	Radiography	N=110	Mean = 62.6 Hylan GF 20 group; 61.0 Triamcinolone Acetonide Group	Knee Osteoarthritis	Clinical and radiographic evaluations in accordance with the American Rheumatism Association classification criteria for knee osteoarthritis	Not Stated
Parmigiana et al., (2010)	NA	N=60	Mean (SD) = 66.2 (9.07) JL/TH group; 61.2 (7.29) TH group	Knee Osteoarthritis	Painful OA base don the American College of Rheumatology criteria Classifiied radiographically as Kellgren Lawrence (KL) 2 and 3	Not stated
Pierce et al., (2016)	NA	N=69	Mean (range) = 62 (36-84) medial infrapatella, 61 (34 – 90) lateral infrapatella, 58 (32-82) lateral suprapatella	Knee Osteoarthritis	Not Listed	Not stated
Sari et al., (2016)	NA	N=73	Mean (SD) = 64 (8) in RF group; 64 (10) in IA group	Knee osteoarthritis	Criteria recommended by the American College of Rheumatology (ACR) Patients with stage 2 or higher Kellgren-Lawrence (K/L)	>3 months
Skwara et al., (2009)	Radiography	N = 60	Mean (SD) = 60.92 (10.43) for the HA group; 61.81 (10.53) for the TA group	Knee Osteoarthritis	Radiographically verified degenerative osteoarthritis of knee (grade II or III) according to the Kellgren and Lawrence classification	>6 months
Henrikson et al., (2015)	Radiographic	N= 100	Mean (SD) = 65.5 (8.3) for placebo group; 61.3 (9.9) for steroid group	Tibiofemoral osteoarthritis	Radiographic confirmation	Not stated
Wagner et al., (2015)	Radiographic	N= 53	Mean (SD) = 55.2 (10.8) for the AL group; 56.5 (11.5) for the AM group; 56.5 (9.0) for the SL group	Knee osteoarthritis	Radiographic confirmation grade I to III via the kellgren-lawrence (K-L) scale	Not Stated
Bellamy et al., (2016)	Radiographic	N=35 patients (36 knees)	Mean = 65 steroid group, 53 Ketorolac group	Knee Osteoarthritis	Radiographic confirmation of knee OA using the KellgreneLawrence (KL) grading scale	Not Stated

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		N	Age (central tendency and variation)	Diagnostic Label	Diagnostic Tests	Duration of Pain
Sibbit et al., (2011)	radiographic	N=92	Mean (SD) = 61.9 (9.9) palpation; 62.9 (9.9) sonograohic	Knee Osteoarthritis	Brandt grades 1 to 3 osteoarthritis as diagnosed by radiographs	Not Stated
De souza, Issy & Sakata (2010)		N=28	Mean (SD) = 67.3 (5.5) steroid and morphine group; steroid alone = 73.2 (8.6)	Knee osteoarthritis	Not stated	No stated
Soriano-Maldonado et al., (2016)	Radiographic	N= 100	Mean (SD) = 65.5 (8.3) for placebo group; 61.3 (9.9) for steroid group	Tibiofemoral osteoarthritis	Radiographic confirmation	Not stated