Washington State Health Care Authority

Hyaluronic Acid/Viscosupplementation and Platelet Rich Plasma for Knee or Hip Osteoarthritis

Final Evidence Report

June 26, 2023

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/about-hca/hta
shtap@hca.wa.gov

Hyaluronic Acid/Viscosupplementation and Platelet Rich Plasma for Knee or Hip Osteoarthritis

Provided by:

Aggregate Analytics, Inc.

Prepared by:

Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS
Mark Junge, BS
Dakota Riopelle, MPH
Shay Stabler-Morris, MSc
Asmaa Khariji Watson, PhD

June 26, 2023

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision-makers, clinicians, patients, and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

Aggregate Analytics, Inc. is a contract research organization whose team has over fifteen years of experience in performing health technology assessments, comparative effectiveness reviews, and systematic reviews for a variety of clients based on accepted methodologic standards for such research. AAI's mission is to assist healthcare professionals and organizations in the objective synthesis and generation of evidence to improve future healthcare delivery by providing timely, methodologically rigorous, transparent services and quality evidence synthesis products.

Contents

Tables

Figures

Abbreviations

ADL = Activities of daily living
AE = Adverse event
BMI = Body mass index
CI = Confidence interval
DB = Double blinded
EQ-5D = EuroQol 5-Dimension Questionnaire
EQ-VAS = EuroQol-visual analogue scales
FDA = United States Food and Drug Administration
F/U = Follow-up
HA = Hyaluronic acid
HHS = Harris hip score
HMW = High molecular weight
IA = Intra-articular
ICER = Incremental cost effectiveness ratio
IKDC = International Knee Documentation Committee
IM = Intramuscular injection
Inj. = Injection
KL = Kellgren-Lawrence
KOOS = Knee Injury and Osteoarthritis Outcome Score
KQ = Key question
KSS = Knee Society Score
LCD = Local Coverage Determination
LMW = Low molecular weight
LoE = Level of evidence
LP = Leukocyte poor
LR = Leukocyte rich
MA = Meta-analysis
MCID = Minimum clinically important difference
MCS = Mental component score
MD = Mean difference
N/A = Not available
NCD = National Coverage Determination
NR = Not reported
NRS = Numerical rating scale
NRSI = Nonrandomized study of intervention
NSAID = Nonsteroidal anti-inflammatory drug
OA = Osteoarthritis

OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative

OR = Odds ratio

PCS = Physical component score

PL = Profile likelihood

PRP = Platelet-rich plasma

PT = Physical therapy

QALY = Quality-adjusted life year

QHES = The Quality of Health Economic Studies

QoL = Quality of life

RCT = Randomized controlled trial

ROB = Risk of Bias

RR = Risk ratio

SAE = Serious adverse event

SB = Single blinded

SD = Standard deviation

SF-12 = Short form-12

SF-12 MCS = Short form-12 Mental component score

SF-12 PCS = Short form-12 Physical component score

SF-36 = Short form-36

SMD = Standardized mean difference

SOE = Strength of evidence

SR = Systematic review

S&R = Sport & Recreation

SSED = Summary of safety and effectiveness data

TENS = Transcutaneous electrical nerve stimulation

TKA = Total knee arthroplasty

U.S. = United States

US-FDA = United States Food and Drug Administration

VA/DoD = Veterans Affairs/Department of Defense

VAS = Visual analog scales

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

WTP = Willingness to pay

Executive Summary

Introduction

Osteoarthritis (OA), particularly of the knee and hip, is one of the most common disabilities affecting people in the United States, often causing pain, fatigue, disability, and general limitations to daily life activities that impact physical, mental, and emotional wellbeing.[57] There is no cure for this condition and, as such, it is imperative that treatment strategies are as effective and cost-effective as possible. Prior to joint replacement surgery, conservative management of osteoarthritis commonly includes exercise and physical therapy, use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, use of supportive devices, weight loss, corticosteroid injections and may include hyaluronic acid (HA, viscosupplementation) and intra-articular platelet-rich plasma (PRP).[17] Exercise and physical therapy are currently considered front-line treatments for knee and hip osteoarthritis and provide considerable benefit both for pain relief and maintenance of functionality, but may be difficult to begin for overweight or obese individuals and time commitments and costs may present challenges to some.[78] Pain medications such as NSAIDs and acetaminophen are commonly recommended or prescribed for relief of pain and inflammation caused by osteoarthritis. These medications are generally easy to access and carry relatively low cost, but long-term use increases risk of potentially serious adverse events such as stomach, kidney, and liver damage, heart attack, and stroke.[21]

Viscosupplementation is an increasingly popular treatment for knee and hip osteoarthritis over the last twenty years. Viscosupplementation with intra-articular hyaluronic acid (IAHA) is most commonly provided to individuals who are unable to utilize or do not respond well to other front-line or preferred treatments; it may provide anti-inflammatory, analgesic, and chondroprotective effects.[26] PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with a limited adverse event risk profile, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated.[9]

While IAHA and PRP are not curative, they may provide some longer-term relief compared with some primary treatment modalities and may be more acceptable to some patients. Previous reviews of the effectiveness of HA and PRP report mixed results on the effectiveness of these for pain reduction and/or functional improvement.

Policy Context/Reason for Selection

Health Technology Assessments (HTAs) on HA/viscosupplementation and PRP were performed in 2013 and 2016 respectively and reviewed by the Washington Health Technology Assessment Program (HTAP). The prior HA report (2013) focused on patients with knee OA. The prior PRP report (2016) included osteoarthritis as well as a range of other musculoskeletal conditions. The focus of this re-review will be on symptomatic adults with knee or hip OA who may be treated with HA or PRP as a primary form of treatment or in conjunction with conservative therapies. The HTAP is interested in re-evaluation of these treatments in patients with knee or hip osteoarthritis given that additional evidence has been published subsequent to the original reviews. Other musculoskeletal conditions will not be part of this re-review. Given the chronic and progressive nature of OA, the report will focus on RCTs that report on persistence of symptom relief or functional improvement one or more months post treatment.

The DRAFT Key Questions and Scope were published on the HTAP website in October 2022. Public comments were reviewed. None led to changes in the questions or scope. All citations suggested by commenters were evaluated for inclusion based on the final key questions and scope. The DRAFT report was also published on the HTAP website from May 12 to June 12, 2023.

Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the effectiveness and safety of HA and PRP for primary treatment of knee or hip osteoarthritis compared with placebo/sham, no treatment, common conventional treatment options, arthroscopic lavage and/or debridement, prolotherapy, corticosteroid injection in symptomatic adults. The differential effectiveness and safety of these therapies for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions and Scope

1. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with hyaluronic acid/viscosupplementation (HA)**
    a. What is the effectiveness of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment in the short and longer-term?
    b. What is the evidence regarding short- and longer-term harms and complications of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment?
    c. Is there evidence of differential efficacy, effectiveness, or safety of HA compared with placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), PRP, or no treatment by factors such as age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?
    d. What is the evidence of cost-effectiveness of HA compared with placebo/sham, PRP, common conservative treatments, or no treatment?
2. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with platelet-rich plasma (PRP)**
    a. What is the effectiveness of PRP compared with placebo/sham, common conservative treatments, treatments other than HA, or no treatment in the short and longer-term?
    b. What is the evidence regarding short- and longer-term harms and complications of PRP compared placebo/sham, common conservative treatments, treatments other than HA, or no treatment?
    c. Is there evidence of differential efficacy, effectiveness, or safety of PRP compared with, placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), treatments other than HA, or no treatment by factors such age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?
    d. What is the evidence of cost-effectiveness of PRP compared with placebo/sham, common conservative treatments, or no treatment?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Population	Adults with symptomatic knee or hip osteoarthritis Subpopulations based on patient characteristics, primary or secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options	• Conditions other than knee or hip OA • Patients <18 years old • Asymptomatic individuals
Intervention	Autologous PRP injection(s) or hyaluronic acid (HA) (viscosupplementation) injection(s) used as the primary intervention or in conjunction with common conservative care options	• Non-FDA-approved HA (viscosupplementation) formulations; products undergoing phase III trials may be considered • PRP or HA used in conjunction with another intervention not listed for inclusion (e.g., open, arthroscopic or minimally invasive surgery, invasive procedures are not included) • Combinations of HA with PRP together • Other biologics (growth factor injections [., plasma rich in growth factor], "stem cell" injections, etc.)
Comparator	• Common conservative treatment(s) (e.g., NSAIDs, oral pain medications, exercise, physical therapy, weight loss) which may be included in usual care • Arthroscopic lavage and/or debridement • Prolotherapy • Corticosteroid injection • Placebo or sham • No treatment	• Combinations of HA with PRP together • Other biologics (growth factor injections [e.g., plasma rich in growth factor], bone marrow aspirate/bone marrow aspirate concentrate, blood plasma, autologous blood products [e.g., autologous conditioned serum"] medicinal signaling cells, mesenchymal stem cells, "stem cell", adipose, fat, or microfat injections); peptide injections • Ozone treatment • Non-FDA approved treatments • Herbal treatments • Acupuncture • Nerve ablation
Outcomes	**<u>Primary</u>** • Function • Pain • Need for secondary invasive procedures (e.g., surgery) • Adverse events or harms **<u>Secondary</u>** • Symptom Recurrence (e.g., persistent or increased pain, reduced function) resulting in need for additional injection	• Non-clinical outcomes • Non-validated measures (e.g., for pain, function, QOL)

Study Component	Inclusion	Exclusion
	of HA or PRP within 2 months after protocol completion • Quality of life • Medication use • Return to normal activities (sports, work, or activity level) **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome	
Timing	Review will focus on persistence of relief 1 or more months post-treatment	
Study design	**Focus will be on studies with the least potential for bias with ≥ 1 month post treatment results** **Key Questions 1 and 2 parts a and b:** • High quality systematic reviews of RCTs will be considered if available and they address the key questions. • Randomized controlled trials (RCTs) • In the absence of RCTs, high quality non-randomized comparative studies will be considered in the absence of RCTs with a focus on comparative prospective studies **Key Question 1b and 2b:** • KQ2: In the absence of RCTs, high-quality non-randomized studies designed specifically to evaluate harms/adverse events that are rare or occur long-term **Key Question 1c and 2c:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest and test for interaction. **Key Question 1d and 2d:** Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Indirect comparisons • Comparisons with historical cohorts • Noncomparative studies (case series, single arm studies, pre-post) • Nonrandomized studies which do not control for confounding • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients per treatment group • Case reports • Studies in which <80% of patients have a condition of interest • Studies that do not report on primary outcomes or harms

Study Component	Inclusion	Exclusion
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)	• Abstracts, conference proceedings, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

FDA = United States Food and Drug Administration, HA = Hyaluronic acid, NSAID = non-steroidal anti-inflammatory drug, OA = Osteoarthritis, PRP = Platelet-rich plasma, QoL = Quality of life, SSED = Summary of safety and effectiveness data

Methods

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. Comments from clinical experts and peer-reviewers were considered for finalization of this report.

A formal, structured systematic search of the peer-reviewed literature was performed across multiple databases including PubMed and EMBASE to identify relevant peer reviewed literature as well as other sources (e.g., ECRI Guideline Trust) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews. Studies were selected for inclusion based on pre-specified criteria detailed in the full report.

All records were screened by two independent reviewers; discrepancies were resolved by consensus. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria.

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria[88] based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[40] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[1] In keeping with the AHRQ methods, each study was given a final rating of "good", "fair", or "poor" quality as described below. Discrepancies in ratings between reviewers were resolved through

discussion and consensus. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[56]

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[7,34,35] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[1] The SOE was based on the highest quality evidence available for the primary outcomes. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[11,75] Publication bias was unknown in all studies and thus this domain was eliminated from the SOE tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Methods for quantitative analysis are described in the full report. Briefly, meta-analyses were conducted using profile likelihood methods and focused on the primary outcomes. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed

statistical heterogeneity. Sensitivity analyses were considered excluding poor-quality trials, outlying data and related to clinical heterogeneity.

Results

From 2,014 unique citations identified from electronic database searches, hand searching and bibliography review of included studies, a total of 64 randomized controlled trials (RCTs) (in 67 publications) met our inclusion criteria: 61 RCTs (in 64 publications)[2-6,8,10,12,14,15,19,20,22-25,27-33,36,38,41,42,44-52,54,55,58-61,63-69,72,76,77,79-83,86,89-91,93-95] in knee osteoarthritis (OA) and three RCTs[13,62,87] in hip OA. The most common comparators for HA and PRP were placebo (saline), corticosteroids, oral analgesics, and exercise; in addition, several trials compared HA versus PRP. Over a third (37%) of the trials evaluating HA were funded by industry; none of the trials evaluating PRP received industry funding. In addition, eight formal cost-effectiveness analyses were included, four in U.S. settings[37,70,71,74] and four in non-U.S. settings[16,39,53,84]; all evaluated HA, with one comparing HA versus PRP, for primarily knee OA.

Key Question (KQ) 1: Hyaluronic Acid

Knee Osteoarthritis

KQ 1a. Key Points: Efficacy and Effectiveness of HA for Knee OA

HA versus Placebo

A total of nine RCTs (total N=2,696, N range 40 to 817),[2,5,8,25,31,32,36,45,59,79-81] five good, one fair and three poor quality, compared HA with placebo (saline) for treatment of knee OA (Table A).

- HA was associated with a small improvement in **function** short term versus saline placebo but there was no difference between treatments at intermediate term (SOE: moderate).
- There was no difference between HA and saline placebo at short or intermediate term on **pain** scores or likelihood of achieving a clinically meaningful threshold for pain improvement at either short or intermediate term (SOE: moderate for all).

Table A. Summary of evidence for HA vs. placebo (saline) for knee OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	Small improvement, 4 RCTs (SOE: Moderate)	No difference, 2 RCTs (SOE: Moderate)	No evidence
KOOS scores	INSUFFICIENT	INSUFFICIENT	No evidence
WOMAC pain Success (responders)	No difference, 2 RCTs (SOE: Moderate)	No difference, 2 RCTs (SOE: Moderate)	No evidence
WOMAC pain scores	No difference, 3 RCTs (SOE: Moderate)	No difference, 1 RCT (SOE: Moderate)	No evidence
VAS pain scores	No difference, 3 RCTs (SOE: Moderate)	No difference, 2 RCTs (SOE: Moderate)	INSUFFICIENT
OMERACT-OARSI criteria	INSUFFICIENT	INSUFFICIENT	No evidence
Invasive procedure	No evidence	No evidence	No evidence

HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Score; OA = osteoarthritis; OARSI = The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; OMERACT = Outcome

Measures in Rheumatology committee; PF = Physical Function; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

HA versus PRP

A total of eleven RCTs (total N=1,160, N range 56 to 189),[14,20,32,47,51,52,63,65,76,83,89] one good, five fair and five poor quality, compared HA versus PRP for treatment of knee OA (Table B).

- There were no differences between HA and PRP on either the likelihood of clinically meaningful **functional improvement** (response) or based on scores on measures of function at short term, but SOE was low. At intermediate and long term, PRP was favored over HA for the likelihood of clinically meaningful improvement based on the WOMAC Physical Function subscale (0-68) and for small improvement on scale scores for this measure. Other functional measures (IKDC and Lysholm scores, both 0-100) showed no difference between HA and PRP short term. PRP was associated with small functional improvements at intermediate and long term based on the IKDC. Strength of evidence was low for all function outcomes and time frames except for the Lysholm scores at intermediate and long term for which evidence was considered insufficient.
- There were no differences between HA and PRP on either the likelihood of clinically meaningful **improvement in pain** (response) or based on WOMAC Pain scores at short-term, however a small improvement favoring PRP over HA was seen. At intermediate term, PRP was associated with higher likelihood of treatment response and with small improvements in pain on both WOMAC and VAS pain scores. Improvement favoring PRP persisted into long term based on WOMAC Pain scores. SOE was low for all function outcomes and time frames.

Table B. Summary of evidence for HA vs. PRP for knee OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success (responders)	No difference, 4 RCTs (SOE: Low)	HA – lower likelihood, 1 RCT (SOE: Low)	HA – lower likelihood, 1 RCT (SOE: Low)
WOMAC PF scores	No difference, 4 RCTs (SOE: Low)	Small improvement (PRP Favored), 4 RCTs (SOE: Low)	Small improvement (PRP Favored), 4 RCTs (SOE: Low)
IKDC	No difference, 2 RCTs (SOE: Low)	Small improvement (PRP Favored), 3 RCTs (SOE: Low)	Small improvement (PRP Favored), 2 RCTs (SOE: Low)
Lysholm	No difference, 2 RCTs (SOE: Low)	INSUFFICIENT	INSUFFICIENT
WOMAC pain Success (responders)	No difference, 4 RCTs (SOE: Low)	Small improvement (PRP Favored), 1 RCT (SOE: Low)	No evidence
WOMAC pain scores	No difference, 6 RCTs (SOE: Low)	Small improvement (PRP Favored), 4 RCTs (SOE: Low)	Small improvement (PRP Favored), 5 RCTs (SOE: Low)
VAS pain scores	Small improvement (PRP Favored), 5 RCTs (SOE: Low)	Small improvement (PRP Favored), 6 RCTs (SOE: Low)	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

HA = hyaluronic acid; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

HA versus Steroid

A total of six RCTs (total N=1,044, N range 82 to 442),[6,12,15,48,82,86] one good, three fair, two poor quality, and one trial rated fair in the short term and poor quality in the intermediate and long term, compared HA with steroid for treatment of knee OA (Table C).

- There was no difference in **functional improvement** between HA and steroid injections across two measures of function (WOMAC Physical Function and KOOS ADL) at short term (SOE: low).
- Similarly, there was moderate evidence of no difference in **pain improvement** between HA and steroid injections at short or intermediate term on either the WOMAC Pain or VAS pain measures.

Table C. Summary of evidence for HA vs. steroids for knee OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF, KOOS ADL scores	No difference, 4 RCTs (SOE: Low)	No evidence	No evidence
KSS Function	INSUFFICIENT	INSUFFICIENT	No evidence
WOMAC Pain	No difference, 2 RCTs (SOE: Moderate)	No difference, 1 RCT (SOE: Moderate)	No evidence
VAS pain	No difference, 3 RCTs (SOE: Moderate)	No difference, 3 RCTs (SOE: Moderate)	INSUFFICIENT
Invasive procedures	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

ADL = activities of daily living; HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Score; KSS = Knee Society Score; OA = osteoarthritis; PF = Physical Function; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

HA versus NSAIDs

Two fair-quality RCTs (Total N=131, N range 62 to 69)[14,33] compared HA with NSAIDS for the treatment of knee OA. One trial[14] compared HA with oral etoricoxib and the other trial[33] compared HA with intramuscular (IM) injection of etofenamate (Flexo) (Table D).

- Two RCTs making this comparison reported on various measures at intermediate and long term; different NSAIDS and methods of delivery were used in these studies. One used oral etoricoxib, the other used IM injection of etofenamate (Flexo). For some outcomes, there was substantial heterogeneity in the results, making conclusions across the trials challenging; thus, they are considered separately.
- There was no difference in the likelihood of meeting clinically important **functional improvement** (WOMAC Physical Function) between HA and oral NSAID at intermediate or long term. Small functional improvement based on the scores was seen favoring HA at intermediate term, however long term, small improvement was associated with oral NSAID use. SOE was low for all functional outcomes.
- There was no difference between HA and oral NSAID in the likelihood of meeting clinically important **pain improvement** (WOMAC Pain or VAS Pain) at intermediate or long term.

Moderate improvement in WOMAC pain scores and small improvement in VAS pain scores was seen at intermediate term with HA versus oral NSAID, however this did not persist into long term. There was no difference between HA and IM NSAID in VAS pain scores at intermediate or long term in the other trial. SOE was low for all pain outcomes.

Table D. Summary of evidence for HA vs. NSAID* for knee OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success (responders)	No evidence	No difference, 1 RCT (oral NSAID) (SOE: Low)	No difference, 1 RCT (oral NSAID) (SOE: Low)
WOMAC PF scores	No evidence	Small improvement, 1 RCT (oral NSAID) (SOE: Low)	Small improvement – favored oral NSAID, 1 RCT (SOE: Low)
WOMAC pain VAS pain Success (responders)	No evidence	No difference, 1 RCT (oral NSAID) (SOE: Low)	No difference, 1 RCT (oral NSAID) (SOE: Low)
WOMAC pain scores	No evidence	Moderate, 1 RCT (oral NSAID) (SOE: Low)	No difference, 1 RCT (oral NSAID) (SOE: Low)
VAS pain scores	No evidence	Small improvement, 1 RCT (oral NSAID) (SOE: Low)	Small improvement – favored oral NSAID, 1 RCT (SOE: Low)
		No difference, 1 RCT (IM NSAID) (SOE: Low)	No difference, 1 RCT (IM NSAID) (SOE: Low)

HA = hyaluronic acid; IM= intramuscular; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PF = Physical Function; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

*Oral NSAID was used in Buendia-Lopez, IM NSAID was used in Guner.

HA versus other active comparators, usual care or different HA formulations

Three RCTs[38,69,72] compared HA to various comparators. One fair-quality RCT (N=90)[69] compared HA with both physical therapy (PT) and prolotherapy, one poor-quality RCT (N=156)[38] compared HA with usual care, and the third RCT (N=165),[72] also poor quality, compared HA with exercise (Table E and Table F). One fair-quality RCT (N=349)[94] compared animal-derived and a nonanimal-derived HA formulations (Table G).

- One fair quality trial compared HA with PT and with prolotherapy. Outcomes were only reported short term. Strength of evidence was low for all outcomes (Tables E and F).
    - For the comparison of **HA versus PT**, there was no difference between these on KOOS ADL function, but a small improvement favoring PT was seen. PT was associated with moderate **pain** improvement based on VAS scores, but a small improvement based on the KOOS pain. SOE was low for all outcomes.
    - For the comparison of **HA versus prolotherapy,** evidence for **function** was insufficient for KOOS ADL, however a small functional improvement **favoring prolotherapy** based on the KOOS Sport and Recreation (SOE: low)**.** Prolotherapy was associated with substantial **pain** improvement based on VAS scores, but a small improvement based on the KOOS pain (SOE: low).
- HA versus usual care: Evidence from one poor quality RCT was insufficient.
- HA versus exercise: Evidence from one poor quality RCT was insufficient.

- There was no difference in function or pain outcomes between an animal-derived and a nonanimal-derived HA formulation in one fair-quality RCT (SOE: low).

Table E. Summary of evidence for HA vs. physical therapy for knee OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
KOOS ADL scores	No difference, 1 RCT (SOE: Low)	No evidence	No evidence
KOOS S&R scores	Small improvement – favored PT, 1 RCT (SOE: Low)	No evidence	No evidence
VAS pain scores	Moderate improvement – favored PT, 1 RCT (SOE: Low)	No evidence	No evidence
KOOS pain scores	Small improvement – favored PT, 1 RCT (SOE: Low)	No evidence	No evidence

ADL = Activities of Daily Living; HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Score; KSS = Knee Society Score; OA = osteoarthritis; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation; VAS = visual analog scale.

Table F. Summary of evidence for HA vs. prolotherapy for knee OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
KOOS ADL scores	INSUFFICIENT	No evidence	No evidence
KOOS S&R scores	Small improvement – favored Prolo, 1 RCT (SOE: Low)	No evidence	No evidence
VAS pain scores	Large improvement – favored Prolo, 1 RCT (SOE: Low)	No evidence	No evidence
KOOS pain scores	Small improvement – favored Prolo, 1 RCT (SOE: Low)	No evidence	No evidence

ADL = Activities of Daily Living; HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Score; KSS = Knee Society Score; OA = osteoarthritis; Prolo = prolotherapy; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation (function); VAS = visual analog scale.

Table G. Summary of evidence for HA (animal derived) vs. HA (nonanimal derived) for knee OA

Improvement favors animal-derived HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	No evidence	No difference, 1 RCT (SOE: Low)	No evidence
WOMAC pain success (response)	No evidence	No difference, 1 RCT (SOE: Low)	No evidence
WOMAC pain scores	No evidence	No difference, 1 RCT (SOE: Low)	No evidence

HA = hyaluronic acid; OA = osteoarthritis; PF = Physical Function; RCT = randomized controlled trial; SOE = strength of evidence; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

KQ 1b. Key points: Adverse events and safety of HA for Knee OA

A total of 16 RCTs (18 publications)[2,5,8,12,25,31,33,36,38,45,48,59,79-82,86,94] provided information on safety and adverse events related to HA. Our focus was on those reported as treatment-related adverse events, particularly serious adverse events.

- There was substantial heterogeneity regarding how adverse events were categorized, reported and described.
- Based on authors' definitions, serious AEs seem to be uncommon following HA injection (0% to 4.3%); SAEs ranged from 0% to 3.2% in the saline placebo group and no statistical differences were reported between groups (SOE: insufficient).
- Serious HA treatment-related AEs ranged from 0% to 1.55%. All trials reporting these compared HA to saline placebo, reporting no events for that group (SOE: insufficient).
- Treatment-related AEs (variably defined, not specified as serious) were more common and generally there were no differences between HA and comparator groups (SOE: low).
    - For comparisons of HA with saline, events related to HA ranged from 0% to 26.9% compared with 0% to 25.8% following saline injection. Differences were statistically significant in one RCT (15.7% vs. 5.5%, RR 2.89, 95% CI 1.18 to 7.04).[5]
    - HA was associated with high risk of treatment related AEs compared with steroid in one RCT (21.7% vs. 6.8%, RR 3.20, 95% CI 1.85 to 5.54)[48] and compared with usual care in another RCT (45% vs. 18%, RR 2.56, 95% CI 1.50 to 4.38).[38]
    - For comparisons of HA with PRP, serious adverse events were poorly reported and were rare (<1%); there were no differences between HA and PRP across 4 RCTs[14,32,76,83] (SOE: insufficient).
- A wide range of other AEs (many not specified) were seen (SOE: low)
    - HA (0%–49.5%) vs. saline (0%–54%)
    - HA (0%–54.3%) vs. steroid (0%–64.3%)
- In one study comparing different two HA products found no differences between them in reported AEs.[94] Severe AEs (not specified) were seen in 4.6% vs. 3.4%, any treatment-related AEs were seen in 9.8% vs. 13.1% and the proportion patients reporting at least one event was 42.5% vs. 47.4% (SOE: low for all).

KQ 1c. Differential Efficacy and Safety

One fair-quality trial (N=162)[32] reported subgroup analyses for **HA versus placebo (saline) injections and versus PRP injections**, however no formal evaluation of differential efficacy via test for interaction was reported. Based on our calculations of effect sizes and evaluation of the extent to which subgroup confidence intervals overlapped, stage of OA may modify the effect of treatment, such that PRP patients with early OA reported better function as evaluated by the patient-reported IKDC measure as well as better quality of life as evaluated by the patient-reported EQ-VAS scale compared with those with advanced OA following PRP (for data see Table 20 of the full report). This is based on the observation that the MD estimates are different for the early and advanced OA groups and there is little or no overlap in the confidence intervals, suggesting that these groups may respond differently.

Evidence for differential efficacy was considered **insufficient** to draw conclusions. Future studies are needed to confirm and explore this further.

KQ 1d. Cost-effectiveness

Summary of studies and key points:

No full economic studies comparing PRP to conventional, conservative care were identified. One U.S. based study compared HA versus PRP.[74] One study compared HA with conservative care in patient with hip OA[53]; all others focused on HA use in knee OA.[16,37,39,70,71,74,84] The included studies ranged from poor to fair quality (QHES from 58 to 79 out of 100 points). Studies performed various levels of sensitivity analyses.

One systematic review of full economic studies comparing HA with usual care, placebo or NSAIDS for treatment of knee OA was identified.[73] It included a total of nine economic studies including four older studies[18,43,85,92] captured and described in the prior 2010 and 2013 HTA reports on HA as well as five economic studies published after that report.[16,37,39,71,84] Our search identified three additional recent studies[53,70,74] not included in the systematic review. This update report focuses on the US based studies published after the 2013 HTA report.

Eight cost-utility analyses (CUA)[16,37,39,53,70,71,74,84] and one systematic review[73] evaluating the cost-effectiveness of HA for treatment of knee OA and published subsequent to the prior reports were identified for this update. Four studies were conducted in the U.S.[37,70,71,74] and three were conducted in European countries[39,53,84] and one in Columbia.[16] The systematic review was conducted in France.[73] Six studies were industry funded[16,37,53,70,71,84]; one was funded by the Dutch Government[39] and one did not report funding.[74] Authors of the systematic review report that no funding was received.[73]

Key findings are summarized below.

- The systematic review reported a wide range of cost-effectiveness estimates; incremental cost effectiveness ratios (ICERs) ranged from between €240 and €53,225 per quality adjusted life year (QALY) gained. Authors state that conclusions regarding the cost-effectiveness of HA were difficult to assert given the substantial heterogeneity across studies regarding populations, interventions, comparators and modeling methods used in individual studies. They note that industry sponsored analyses found HA to be more favorable than academic studies.
- There was substantial heterogeneity related to populations, methods of modeling and health systems across included studies for this update.
- All included studies evaluated the cost-effectiveness of HA for knee OA; one non-US study evaluated the cost-effectiveness of HA for hip OA as well as knee OA.[53]
- Across four economic studies conducted in the U.S.:
    - The three compared HA with various forms of conservative care; all concluded that HA was cost-effective at a willingness to pay (WTP) of $50,000/QALY.
        - HA was reported to be the dominant strategy in two studies and ICER was not calculated. Base case ICERS ranged from $4499/QALY to 38,471/QALY.
        - Sensitivity analyses suggest a broad range of ICERS with a range of $77,500/QALY to $124,000/QALY at the higher end. Response rates for the different treatment groups generally had the most impact on ICERS.
        - One poor-study concluded that high molecular weight (HMW) HA was cost effective at this level in patients with early/mid stage knee OA compared with specific conservative management options (PT, braces, NSAIDS/analgesics) but

that its cost-effectiveness in late-stage knee OA was less apparent. Authors note uncertainty regarding the response of patients with late-stage knee OA to management options.[70]
        - General limitations across studies included no or little specification or modeling of adverse events, lack of specification regarding components and costs of conservative care options (most studies), methods of determining utilities based on WOMAC scores which may overpredict utility values in severe disease.
    - One poor-quality U.S.-based study which compared HA versus PRP reported an ICER of $12,628.15/QALY for PRP versus HA and concluded that PRP injections were not more cost-effective than HA. Cost-effectiveness was impacted by PRP costs and WOMAC scores used to determine utility values. Authors assumed that costs related to use of conservative measures would be equal in the HA and PRP groups. Limited sensitivity analyses were reported.
- Across four economic studies conducted outside of the U.S.:
    - Authors conclude that HA is more cost-effective than conventional conservative care for treatment of knee OA.
    - One study evaluating HA for hip OA also concluded that it was more cost-effective than conventional conservative care.
    - General limitations across studies included little no modeling of potential adverse events, use of data from non-randomized studies (some studies) and limited sensitivity analyses in two of the studies.
    - The applicability of these models is unclear given differences in health systems.

Key Question (KQ) 1: Hyaluronic Acid

Hip Osteoarthritis

KQ 1a and b: Effectiveness and Adverse Events and Safety of HA for Hip OA

HA versus Placebo

Two fair-quality RCTs (total N=426, range 69 to 357)[13,62] compared HA with a saline placebo for treatment of hip OA (Table H).

- There were no differences between HA and placebo on measures of function or pain across two RCTs short or intermediate term (SOE: low for all).
- One RCT reported that more HA recipients than placebo recipients met OARSI for response short term (53% vs. 44%) but do not provide sufficient information to calculate effect size.
- Arthroplasty was rare (1 small RCT); none occurred in the HA group and only one occurred in the placebo group (SOE: insufficient).
- NSAID use was similar between HA and placebo groups in the largest RCT.
- Harms and safety: The largest trial reported that while any treatment-related events were more common with placebo versus HA, similar proportions each group experienced treatment emergent events at the target hip. Authors report that only one serious SAE (arthralgia in the saline group) was considered treatment related. Withdrawal due to adverse events was similar between groups. SOE was low for all.

Table H. Summary of evidence for HA vs. placebo (saline) for hip OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF and Lequesne scores	No difference, 2 RCTs (SOE: low)	No difference, 1 RCT (SOE: low)	No evidence
WOMAC pain Success (responders)	No difference, 1 RCT (SOE: low)	No difference, 1 RCT (SOE: low)	No evidence
WOMAC pain and VAS pain scores	No difference, 2 RCTs (SOE: low)	No difference, 1 RCT (SOE: low)	No evidence
WOMAC Total scores	INSUFFICIENT	INSUFFICIENT	No evidence
OMERACT-OARSI criteria	INSUFFICIENT	INSUFFICIENT	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	No evidence
Serious AEs	INSUFFICIENT	INSUFFICIENT	No evidence
Treatment-Related* AEs	Any time; No difference, 1 RCT (SOE: low)		No evidence
Withdrawal due to AEs	Any time; No difference, 1 RCT (SOE: low)		No evidence

AEs = adverse events; HA = hyaluronic acid; OA = osteoarthritis; OARSI = The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; OMERACT = Outcome Measures in Rheumatology committee; PF = Physical Function; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
*Included arthralgia, injection site joint pain, injection site pain, groin pain and osteoarthritis.

HA versus PRP

One fair-quality RCT(N=74)[87] compared HA versus PRP or treatment of hip OA (Table I).

- There were no differences between HA versus PRP on patient-reported measures of function (**WOMAC**) or pain (**WOMAC, VAS**) at short and long term (SOE: low) or on the **Harris Hip Score** (HHS, 0-100 scale, clinician-based measure) short term, but long-term PRP may be associated with improved function on the HHS compared with HA (SOE: low); data were insufficient information to calculate effect size.
- There were consistently fewer HA recipients who met the criteria for response based on OMERACT-OARSI criteria at short (69% vs. 82%), intermediate (58% vs. 74%) and long term (44% vs. 65%), however authors indicate that differences were not statistically significant; data were insufficient to calculate effect size (SOE: low).
- There was no difference between groups in risk of arthroplasty (SOE: low).
- Harms and safety: Evidence was insufficient; one RCT reports that no events occurred; no further information provided.

Table I. Summary of evidence for HA vs. PRP for hip OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	No difference, 1 RCT (SOE: low)	No evidence	No difference, 1 RCT (SOE: low)
WOMAC pain and VAS pain scores	No difference, 1 RCT (SOE: low)	No evidence	No difference, 1 RCT (SOE: low)
WOMAC Total scores	No difference, 1 RCT (SOE: low)	No evidence	No difference, 1 RCT (SOE: low)
Harris Hip Score	No difference, 1 RCT (SOE: low)	No evidence	No difference, 1 RCT (SOE: low)
OMERACT-OARSI criteria	No difference, 1 RCT (SOE: low)	No difference, 1 RCT (SOE: low)	No difference, 1 RCT (SOE: low)
Arthroplasty	Any time: No difference, 1 RCT (SOE: low)		
Serious AEs	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

AEs = adverse events; HA = hyaluronic acid; OA = osteoarthritis; OARSI = The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; OMERACT = Outcome Measures in Rheumatology committee; PF = Physical Function; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

HA versus Steroid

One fair-quality RCT[62] compared HA with steroid for treatment of hip OA (Table J).

- There were no differences between HA and steroid use in on small RCT on measures of pain or function, however data were insufficient to calculate effect sizes (SOE: low).
- Evidence was insufficient for all other outcomes.
- Harms and safety: Insufficient evidence; one RCT states that no serious events occurred.

Table J. Summary of evidence for HA vs. steroid injection for hip OA

Improvement favors HA unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
Lequesne scores	No difference, 1 RCT (SOE: low)	No evidence	No evidence
VAS pain scores	INSUFFICIENT	No evidence	No evidence
WOMAC Total scores	INSUFFICIENT	No evidence	No evidence
OMERACT-OARSI criteria	INSUFFICIENT	No evidence	No evidence
Arthroplasty	INSUFFICIENT	No evidence	No evidence
Serious AEs	INSUFFICIENT	No evidence	No evidence

AEs = adverse events; HA = hyaluronic acid; OA = osteoarthritis; OARSI = The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; OMERACT = Outcome Measures in Rheumatology committee; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

KQ 1c: Differential Efficacy and Safety of HA for Hip OA

One fair-quality trial (N=101)[62] with three treatment arms (**HA, saline placebo and steroid**) explored the potential impact of hip OA severity on treatment effects by dichotomizing Kellgren-Lawrence grades (1 or 2 versus 3 or 4) and by presence of intra-articular effusion. At baseline 57% of participants had grade 1 or 2 and 21% had effusion. Evaluations were done to explore the impact of these factors on treatment effects with change in walking pain scores as the outcome of interest. Authors present data graphically and provide p-values for interaction, but no other data. All tests for interaction were not statistically significant. The study may not have been sufficiently powered to detect effect modification and **evidence is insufficient**.

KQ 1d: Cost-effectiveness of HA for Hip OA

One U.S.-based study compared HA with conservative care in patient with hip OA.[53] Results for this trial can be found under KQ 1d for Knee OA.

Key Question (KQ) 2: Platelet-Rich Plasma

Knee Osteoarthritis

KQ 2a. Key Points: Efficacy and Effectiveness of PRP for Knee OA

PRP vs. Placebo (Saline)

9 RCTs[10,19,22,23,32,49,55,58,93] (total N=1,683; N range, 33 to 644), two good quality and seven fair quality, and 3 fair-quality NRSIs[30,50,90] (self-described as RCTs but randomized knee within the same patients so are considered observational cohort studies for the purposes of this report) compared PRP with placebo (saline) for the treatment of knee OA; the RCTs provide the evidence base for SOE (Table K).

- Results varied based on the outcomes measure used; most trials reported WOMAC subscales and VAS pain scales.
- PRP was associated with improvement in ***function*** at all time points measured based on the WOMAC physical function and the IKDC scales (small effect short term to moderate/large effects at longer term), but there was no difference between PRP and placebo (saline) on the KOOS ADL and Sport and Recreation subscales. The SOE was low for all measures and timepoints except for WOMAC physical functions scores at short term for which the SOE was moderate.
- Similarly for ***pain***, PRP was associated with moderate improvement compared with placebo based on the WOMAC pain subscale at short and intermediate term (SOE: moderate), but there was no difference between groups at any time on the KOOS pain scale or at short and long term on the VAS pain scale (SOE: low); there was moderate improvement with PRP on the VAS scale intermediate term (SOE: low).
- Only one RCT reported ***OMERACT responder criteria*** and found a small increase in the likelihood of achieving response with PRP versus placebo but there was no difference at intermediate term (SOE: low).

- There was no difference in the frequency of ***additional invasive treatment*** between group over long term follow-up in one trial (SOE: low)

Table K. Summary of evidence for PRP vs. placebo (saline) for knee OA
Improvement favors PRP unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	Small improvement, 5 RCTs (SOE: moderate)	Moderate improvement, 4 RCTs (SOE: low)	Large improvement, 2 RCTs (SOE: low)
KOOS ADL and S&R scores	No difference, 4 RCTs (SOE: low)	No difference, 3 RCTs (SOE: low)	No difference, 3 RCTs (SOE: low)
IKDC scores	Small improvement, 1 RCT (SOE: low)	INSUFFICIENT	Moderate improvement, 1 RCT (SOE: low)
WOMAC pain scores	Moderate improvement, 5 RCTs (SOE: moderate)	Moderate improvement, 4 RCTs (SOE: moderate)	INSUFFICIENT
KOOS pain scores	No difference, 4 RCTs (SOE: low)	No difference, 3 RCTs (SOE: low)	No difference, 3 RCTs (SOE: low)
VAS pain scores	No difference, 7 RCTs (SOE: low)	Moderate improvement, 6 RCTs (SOE: low)	No difference, 5 RCTs (SOE: low)
OMERACT-OARSI criteria	Small increase, 1 RCT (SOE: low)	No difference, 1 RCT (SOE: low)	No evidence
Invasive procedures	No evidence	No evidence	No difference, 2 RCTs (SOE: low)

ADL = activities of daily living; AEs = adverse events; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; OA = osteoarthritis; OARSI = The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; OMERACT = Outcome Measures in Rheumatology committee; PF = Physical Function; PRP = platelet rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

PRP vs. Steroid

Nine RCTs (total N=598; N range 51 to 70),[24,27,28,41,42,46,54,55,60] three fair quality and six poor quality, compared PRP to steroids for the treatment of knee OA (Table L).

- For ***function***, except for KSS scores at intermediate term (moderate improvement with PRP), there was no difference between PRP and steroids at short (KSS, WOMAC physical function scores) or long term (WOMAC physical function scores) and SOE was low. Evidence from other functional measures was considered insufficient to draw conclusions. Point estimates varied substantially across the trials, both in direction and magnitudes of effect.
- For ***pain,*** PRP was associated with small improvements in VAS pain scores at short and long term compared with steroid (SOE: low) but there was no difference between groups across other pain measures (SOE: low) or the data was considered insufficient to draw conclusions.
- Evidence for ***additional invasive treatment*** was insufficient.
- Differences in study quality, injection regimens or patient characteristics may have contributed to the heterogeneity.

Table L. Summary of evidence for PRP vs. steroid for knee OA
Improvement favors PRP unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	No difference, 1 RCT (SOE: low)	INSUFFICIENT	No difference, 1 RCT (SOE: low)
KOOS ADL and S&R scores	INSUFFICIENT	INSUFFICIENT	No evidence
KSS scores	No difference, 2 RCTs (SOE: low)	Moderate improvement, 2 RCTs (SOE: low)	No evidence
IKDC scores	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT
KOOS pain scores	No difference, 2 RCTs (SOE: low)	INSUFFICIENT	No evidence
WOMAC pain scores	No difference, 1 RCT (SOE: low)	INSUFFICIENT	No difference, 1 RCT (SOE: low)
VAS pain scores	Small improvement, 5 RCTs (SOE: low)	INSUFFICIENT	Small improvement, 3 RCTs (SOE: low)
WOMAC total scores	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT
Invasive procedures	No evidence	No evidence	INSUFFICIENT

ADL = Activities of Daily Living; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KSS = Knee Society Score; OA = osteoarthritis; PF = Physical Function; PRP = platelet rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

PRP vs. Oral Analgesics

3 RCTs (total N=195; N range 60 to 70),[14,68,77] two fair quality and one poor quality, compared PRP with oral analgesics for the treatment of knee OA (Table M).

- In general, PRP was associated with improvement in ***function and pain*** (based on both responders and scores), but the magnitude of effect varied across different outcomes measures and timepoints (SOE: low for all).
- The evidence was insufficient evidence for ***additional invasive treatments.***

Table M. Summary of evidence for PRP vs. oral analgesics for knee OA
Improvement favors PRP unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success (responders)	No evidence	Large increase, 1 RCT (SOE: low)	Large increase, 1 RCT (SOE: low)
WOMAC PF scores	Moderate improvement, 2 RCTs (SOE: low)	Moderate improvement, 3 RCTs (SOE: low)	Small improvement, 2 RCTs (SOE: low)
WOMAC pain Success (responders)	No evidence	Large increase, 1 RCT (SOE: low)	Large increase, 1 RCT (SOE: low)
WOMAC pain scores	Moderate improvement, 2 RCTs (SOE: low)	Small improvement, 3 RCTs (SOE: low)	INSUFFICIENT
VAS pain scores	Moderate improvement, 2 RCTs (SOE: low)	Small improvement, 3 RCTs (SOE: low)	INSUFFICIENT

Invasive procedures	No evidence	No evidence	INSUFFICIENT

OA = osteoarthritis; PF = Physical Function; PRP = platelet rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

PRP vs. Exercise

Three fair-quality RCTs (total N=179, N range 52 to 65)[3,4,67] compared PRP with exercise for the treatment of knee OA (Table N).

- Except for ***WOMAC pain*** at intermediate term, for which there was *no difference* between PRP and exercise (SOE: low), evidence for all other measures of function and pain was considered insufficient to draw conclusions.
- The evidence was insufficient for ***additional invasive procedures***.

Table N. Summary of evidence for PRP (+ exercise) vs. exercise for knee OA
Improvement favors PRP unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	INSUFFICIENT	INSUFFICIENT	No evidence
KOOS ADL and S&R scores	INSUFFICIENT	No evidence	No evidence
WOMAC pain scores	INSUFFICIENT	No difference, 2 RCTs (SOE: low)	No evidence
KOOS pain scores	INSUFFICIENT	No evidence	No evidence
VAS pain scores	INSUFFICIENT	INSUFFICIENT	No evidence
Invasive procedures	No evidence	No evidence	INSUFFICIENT

ADL = activities of daily living; KOOS = Knee Injury and Osteoarthritis Outcome Score; OA = osteoarthritis; PF = Physical Function; PRP = platelet rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

PRP vs. PRP: Greater vs. Fewer Number of Injections

Six trials (total N=508; range, 52 to 133),[32,44,49,58,83,93] one good quality, four fair quality and one poor quality compared one versus three injections primarily followed by one versus two and two versus three injections (Table O).

- Except for ***KOOS Sport and Recreation subscale scores*** at short term, for which there was *no difference* between one (plus 2 placebo injections) versus three injections of PRP (SOE: low, 1 good quality RCT), evidence for all other measures of ***function and pain*** (WOMAC physical function success and scores; KOOS ADL; KOOS Sport and Recreation subscale at intermediate and long term; IKDC; WOMAC and VAS pain success and scores; KOOS pain) across injection regimens was considered insufficient to draw conclusions.
- There was no information on ***secondary invasive procedures***.

Table O. Summary of evidence for greater vs. fewer number of PRP injections for knee OA
Improvement favors greater number of PRP unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success (responders)	INSUFFICIENT	No evidence	No evidence
WOMAC PF scores	INSUFFICIENT	INSUFFICIENT	No evidence
KOOS ADL scores	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT
KOOS S&R scores	No difference, 2 RCTs (SOE: low)	INSUFFICIENT	INSUFFICIENT
IKDC	No evidence	INSUFFICIENT	No evidence
WOMAC pain and VAS pain Success (responders)	INSUFFICIENT	No evidence	No evidence
WOMAC pain and VAS pain scores	INSUFFICIENT	INSUFFICIENT	No evidence
KOOS pain scores	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT
Invasive procedures	No evidence	No evidence	No evidence

ADL = activities of daily living; IKDC = International Knee Documentation Committee score; KOOS = Knee Injury and Osteoarthritis Outcome Score; OA = osteoarthritis; PF = Physical Function; PRP = platelet rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; S&R = Sport and Recreation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

PRP vs. PRP: LP-PRP vs. LR-PRP

Two RCTs (N=130; N range 60 to 70),[91,95] one good quality and one fair quality, compared leukocyte-poor (LP)- with leukocyte-rich (LR)-PRP (Table P).

- There was *no difference* between LP- and LR-PRP injections in ***function*** based on the WOMAC physical functional scale at short, intermediate and long term (SOE: low).
- For ***pain,*** except for VAS pain scores short term which showed *no difference* between groups (SOE: low), evidence was insufficient for VAS scores at other timepoints, and for WOMAC pain scores at all timepoints.
- Evidence for ***secondary invasive procedures*** was considered insufficient to draw conclusions.

Table P. Summary of evidence for LP- vs. LR-PRP injections for knee OA
Improvement favors LP-PRP unless otherwise indicated

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF scores	No difference, 2 RCTs (SOE: low)	No difference, 2 RCTs (SOE: low)	No difference, 2 RCTs (SOE: low)
WOMAC pain scores	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT
VAS pain scores	No difference, 2 RCTs (SOE: low)	INSUFFICIENT	INSUFFICIENT
Invasive procedures	No evidence	INSUFFICIENT	No evidence

LP = leukocyte poor; LR = leukocyte rich; OA = osteoarthritis; PF = Physical Function; PRP = platelet rich plasma; RCT = randomized controlled trial; SOE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

All evidence for the following was considered **insufficient** to draw conclusions due to study quality:

- **PRP vs. PT:** 1 small (N=40) poor-quality RCT[29]: WOMAC physical function scores and VAS pain scores short term (3 months).
- **PRP vs. Prolotherapy:** 2 poor-quality RCTs (total N=102, N = 42 and 60)[61,66]: WOMAC physical function scores, WOMAC pain scores and VAS pain scores short (1-2 months) and intermediate term (6 months)

KQ 2b. Key points: Adverse events and safety of PRP for Knee OA

Nine RCTs[4,10,19,23,24,44,58,61,95] and one NRSI[30] evaluating PRP reported information on serious AEs. Comparators included placebo (4 RCTs, 1 NRSI),[10,19,23,30,58] steroids (1 RCT),[24] exercise (1 RCT),[4] and prolotherapy (1 RCT)[61]; two RCTs[44,58] compared number of PRP injections and one RCT[95] compared LP-PRP versus LR-PRP.

- Only two studies reported a serious adverse event as defined by the authors:
  - Three patients (11.5%) who received LR-PRP experienced severe swelling and mild fever (not beyond 37.5 C) compared with no patient who received LP-PRP; one of these patients required arthroscopic debridement to treat symptoms (1 RCT).[95]
  - There was one case of severe inflammation with swelling and stiffness immediately post-injection in a knee randomized to LP-PRP (5%; 1/20 knees) versus no events with saline injection; symptoms persisted for 2 weeks and then improved (1 NRSI).[30]
- Across the other eight RCTs, no serious treatment-related adverse events were reported to have occurred.
- Evidence on safety/harms was considered **insufficient** due to generally poor reporting of SAEs and small sample sizes. There was substantial heterogeneity regarding how AEs were categorized, reported and described (if described at all); many trials simply state that "no serious adverse events occurred".

KQ 2c Key points: Differential Effectiveness and Safety of PRP for Knee OA

One fair-quality trial (n=123)[32] reported subgroup analyses for **PRP versus placebo (saline) injections**, however no formal evaluation of differential efficacy via test for interaction was reported. Based on our calculations of effect sizes and evaluation of the extent to which subgroup confidence intervals overlapped, stage of OA may modify the effect of treatment, such that PRP patients with early OA reported better function as evaluated by the patient-reported IKDC measure as well as better quality of life as evaluated by the patient-reported EQ-VAS scale compared with those with advanced OA following PRP (for data see Table 35 of the full report). This is based on the observation that the MD estimates are different for the early and advanced OA groups and there is little or no overlap in the confidence intervals, suggesting that these groups may respond differently.

Evidence for differential efficacy was considered **insufficient** to draw conclusions. Future studies are needed to confirm and explore this further.

KQ 2d Key points: Cost-effectiveness of PRP for Knee OA

No full economic studies comparing PRP to conventional, conservative care were identified. One U.S. based study compared PRP vs. HA.[74] Results for this study can be found in **KQ 1d above** for the comparison of HA vs. PRP.

Key Question (KQ) 2: Platelet-Rich Plasma

Hip Osteoarthritis

One RCT[87] that evaluated PRP for treatment of hip OA met the inclusion criteria and compared PRP with HA. Results for this trial can be found above under **KQ 2a – efficacy** and **KQ 2b – Safety** for the comparison of HA vs. PRP for hip OA.

No studies were identified that evaluated **differential efficacy or safety** (**KQ 2c**) or conducted formal **cost-effectiveness** analyses (**KQ 2d**) of PRP for the treatment of hip OA.

Strength of Evidence Summaries

Detailed SOE tables, including reasons for downgrading, are found in section 7 of the report.

Executive Summary References

1. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
2. [No authors listed]. Summary of Safety and Effectiveness Data (SSED). Gel-One® (Gel-200). PMA No: P080020/S020. Approval Date: September 27, 2016. Accessed at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P080020S020.
3. Akan Ö, Sarıkaya NÖ, Koçyiğit H. Efficacy of platelet-rich plasma administration in patients with severe knee osteoarthritis: Can platelet-rich plasma administration delay arthroplasty in this patient population? International Journal of Clinical and Experimental Medicine 2018;11:9473-83.
4. Angoorani H, Mazaherinezhad A, Marjomaki O, Younespour S. Treatment of knee osteoarthritis with platelet-rich plasma in comparison with transcutaneous electrical nerve stimulation plus exercise: a randomized clinical trial. Med J Islam Repub Iran 2015;29:223.
5. Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. Curr Med Res Opin 2014;30:279-86.
6. Askari A, Gholami T, NaghiZadeh MM, Farjam M, Kouhpayeh SA, Shahabfard Z. Hyaluronic acid compared with corticosteroid injections for the treatment of osteoarthritis of the knee: a randomized control trail. Springerplus 2016;5:442.
7. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. Bmj 2004;328:1490.
8. Bao X, Tan JW, Flyzik M, Ma XC, Liu H, Liu HY. Effect of therapeutic exercise on knee osteoarthritis after intra-articular injection of botulinum toxin type A, hyaluronate or saline: A randomized controlled trial. J Rehabil Med 2018;50:534-41.
9. Bennell KL, Hunter DJ, Paterson KL. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. Curr Rheumatol Rep 2017;19:24.
10. Bennell KL, Paterson KL, Metcalf BR, et al. Effect of Intra-Articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients with Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. JAMA - Journal of the American Medical Association 2021;326:2021-30.
11. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD)2013.
12. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. Clin Exp Rheumatol 2016;34:857-63.
13. Brander V, Skrepnik N, Petrella RJ, Jiang GL, Accomando B, Vardanyan A. Evaluating the use of intra-articular injections as a treatment for painful hip osteoarthritis: a randomized, double-blind, multicenter, parallel-group study comparing a single 6-mL injection of hylan G-F 20 with saline. Osteoarthritis Cartilage 2019;27:59-70.
14. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín M. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. J Orthop Traumatol 2018;19:3.
15. Campos ALS, RSP EA, da Silva EB, et al. Viscosupplementation in patients with severe osteoarthritis of the knee: six month follow-up of a randomized, double-blind clinical trial. Int Orthop 2017;41:2273-80.

16. Castro JC, Daza AM, Misas JD. Cost-effectiveness Analysis of Viscosupplementation versus Conventional Supportive Therapy for Knee Osteoarthritis in Colombia. Value Health Reg Issues 2015;8:56-61.
17. Osteoarthritis. 2015. (Accessed September 21, 2022,
18. Chou CW, Lue KH, Lee HS, Lin RC, Lu KH. Hylan G-F 20 has better pain relief and cost-effectiveness than sodium hyaluronate in treating early osteoarthritic knees in Taiwan. J Formos Med Assoc 2009;108:663-72.
19. Chu J, Duan W, Yu Z, et al. Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2022;30:4063-71.
20. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. Am J Sports Med 2017;45:339-46.
21. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ 2021;375:n2321.
22. Dório M, Pereira RMR, Luz AGB, Deveza LA, de Oliveira RM, Fuller R. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. BMC Musculoskelet Disord 2021;22:822.
23. Elik H, Dogu B, Yilmaz F, Begoglu FA, Kuran B. The efficiency of platelet-rich plasma treatment in patients with knee osteoarthritis. J Back Musculoskelet Rehabil 2020;33:127-38.
24. Elksniņš-Finogejevs A, Vidal L, Peredistijs A. Intra-articular platelet-rich plasma vs corticosteroids in the treatment of moderate knee osteoarthritis: a single-center prospective randomized controlled study with a 1-year follow up. J Orthop Surg Res 2020;15:257.
25. Farr J, Gomoll AH, Yanke AB, Strauss EJ, Mowry KC. A Randomized Controlled Single-Blind Study Demonstrating Superiority of Amniotic Suspension Allograft Injection Over Hyaluronic Acid and Saline Control for Modification of Knee Osteoarthritis Symptoms. J Knee Surg 2019;32:1143-54.
26. Food and Drug Administration (FDA). Intent To Consider the Appropriate Classification of Hyaluronic Acid Intra-articular Products Intended for the Treatment of Pain in Osteoarthritis of the Knee Based on Scientific Evidence. 2018.
27. Forogh B, Mianehsaz E, Shoaee S, Ahadi T, Raissi GR, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness 2016;56:901-8.
28. Freire MRM, da Silva PMC, Azevedo AR, Silva DS, da Silva RBB, Cardoso JC. Comparative Effect between Infiltration of Platelet-rich Plasma and the Use of Corticosteroids in the Treatment of Knee Osteoarthritis: A Prospective and Randomized Clinical Trial. Rev Bras Ortop (Sao Paulo) 2020;55:551-6.
29. Gaballa NM, Mohammed YA, Kamel LM, Mahgoub HM. Therapeutic efficacy of intra-articular injection of platelet–rich plasma and ozone therapy in patients with primary knee osteoarthritis. Egyptian Rheumatologist 2019;41:183-7.
30. Ghai B, Gupta V, Jain A, Goel N, Chouhan D, Batra YK. Effectiveness of platelet rich plasma in pain management of osteoarthritis knee: double blind, randomized comparative study. Brazilian Journal of Anesthesiology 2019;69:439-47.
31. Gomoll AH, Farr J, Cole BJ, et al. Safety and Efficacy of an Amniotic Suspension Allograft Injection Over 12 Months in a Single-Blinded, Randomized Controlled Trial for Symptomatic Osteoarthritis of the Knee. Arthroscopy 2021;37:2246-57.

32. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2017;25:958-65.
33. Guner S, Gokalp MA, Gozen A, Unsal SS, Guner SI. Effectiveness of etofenamate for treatment of knee osteoarthritis: a randomized controlled trial. Ther Clin Risk Manag 2016;12:1693-9.
34. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
35. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380-2.
36. Hangody L, Szody R, Lukasik P, et al. Intraarticular Injection of a Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal) to Provide Symptomatic Relief of Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Trial. Cartilage 2018;9:276-83.
37. Hatoum HT, Fierlinger AL, Lin SJ, Altman RD. Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. J Med Econ 2014;17:326-37.
38. Hermans J, Bierma-Zeinstra SMA, Bos PK, Niesten DD, Verhaar JAN, Reijman M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: a randomised controlled trial. BMC Musculoskelet Disord 2019;20:196.
39. Hermans J, Reijman M, Goossens LMA, Verburg H, Bierma-Zeinstra SMA, Koopmanschap MA. Cost-Utility Analysis of High Molecular Weight Hyaluronic Acid for Knee Osteoarthritis in Everyday Clinical Care in Patients at a Working Age: An Economic Evaluation of a Randomized Clinical Trial. Arthritis Care Res (Hoboken) 2018;70:89-97.
40. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org2011.
41. Huang Y, Liu X, Xu X, Liu J. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis : A prospective randomized controlled study. Orthopade 2019;48:239-47.
42. Jubert NJ, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis: A prospective, randomized, double-blinded clinical trial. Orthopaedic Journal of Sports Medicine 2017;5.
43. Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine 2003;70:276-81.
44. Kavadar G, Demircioglu DT, Celik MY, Emre TY. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: a randomized prospective study. J Phys Ther Sci 2015;27:3863-7.
45. Ke Y, Jiang W, Xu Y, et al. Efficacy and safety of a single intra-articular injection of 6 ml Hylan G-F 20 compared to placebo in Chinese patients with symptomatic knee osteoarthritis : C-SOUND study, a 26-week multicenter double-blind randomized placebo-controlled trial in China. BMC Musculoskelet Disord 2021;22:428.
46. Khan AF, Gillani SFUHS, Khan AF. Role of intra-articular corticosteroid with xylocaine vs plate rich plasma for the treatment of early grade II knee osteoarthritis at Akhtar Saeed Teaching Hospital Lahore: A randomized controlled trail. Pakistan Journal of Medical and Health Sciences 2018;12:1432-5.
47. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. J Stem Cells Regen Med 2016;12:69-78.

48. Leighton R, Akermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. Osteoarthritis Cartilage 2014;22:17-25.
49. Lewis E, Merghani K, Robertson I, et al. The effectiveness of leucocyte-poor platelet-rich plasma injections on symptomatic early osteoarthritis of the knee: the PEAK randomized controlled trial. The bone & joint journal 2022;104-B:663-71.
50. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. Arthroscopy 2019;35:106-17.
51. Lisi C, Perotti C, Scudeller L, et al. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clin Rehabil 2018;32:330-9.
52. Louis ML, Magalon J, Jouve E, et al. Growth Factors Levels Determine Efficacy of Platelets Rich Plasma Injection in Knee Osteoarthritis: A Randomized Double Blind Noninferiority Trial Compared With Viscosupplementation. Arthroscopy 2018;34:1530-40 e2.
53. Migliore A, Integlia D, Pompilio G, Di Giuseppe F, Aru C, Brown T. Cost-effectiveness and budget impact analysis of viscosupplementation with hylan G-F 20 for knee and hip osteoarthritis. Clinicoecon Outcomes Res 2019;11:453-64.
54. Nabi BN, Sedighinejad A, Mardani-Kivi M, et al. Comparing the Effectiveness of Intra-articular Platelet-Rich Plasma and Corticosteroid Injection under Ultrasound Guidance on Pain Control of Knee Osteoarthritis. Iran Red Crescent Med J 2018;20:e62157.
55. Nunes-Tamashiro JC, Natour J, Ramuth FM, et al. Intra-articular injection with platelet-rich plasma compared to triamcinolone hexacetonide or saline solution in knee osteoarthritis: A double blinded randomized controlled trial with one year follow-up. Clinical rehabilitation 2022;36:900-15.
56. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
57. Osteoarthritis Action Alliance TARCatUoNC. OA Prevalence and Burden2021.
58. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. The American journal of sports medicine 2013;41:356-64.
59. Petterson SC, Plancher KD. Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: a multicenter, double-blind, randomized, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2019;27:1992-2002.
60. Phul SH, Mobushir M, Jilani RUA, Khan IS, Malik H, Jan G. Comparison of intra-articular steroids injection versus platelets rich plasma injection in patients with osteoarthritic knee joints. Pakistan Journal of Medical and Health Sciences 2018;12:931-4.
61. Pishgahi A, Abolhasan R, Shakouri SK, et al. Effect of dextrose prolotherapy, platelet rich plasma and autologous conditioned serum on knee osteoarthritis: A randomized clinical trial. Iranian Journal of Allergy, Asthma and Immunology 2020;19:243-52.
62. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006;14:163-70.
63. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, et al. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. BMC Musculoskelet Disord 2021;22:134.
64. Raeissadat SA, Ghorbani E, Taheri MS, et al. MRI changes after platelet rich plasma injection in knee osteoarthritis (Randomized clinical trial). Journal of Pain Research 2020;13:65-73.

65. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: Platelet-rich plasma (PRP) versus hyaluronic acid (A one-year randomized clinical trial). Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2015;8.
66. Rahimzadeh P, Imani F, Faiz SHR, Entezary SR, Zamanabadi MN, Alebouyeh MR. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clinical Interventions in Aging 2018;13:73-9.
67. Rayegani SM, Raeissadat SA, Taheri MS, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthopedic Reviews 2014;6:112-7.
68. Reyes-Sosa R, Lugo-Radillo A, Cruz-Santiago L, Garcia-Cruz CR, Mendoza-Cano O. Clinical comparison of platelet-rich plasma injection and daily celecoxib administration in the treatment of early knee osteoarthritis: A randomized clinical trial. J Appl Biomed 2020;18:41-5.
69. Rezasoltani Z, Azizi S, Najafi S, Sanati E, Dadarkhah A, Abdorrazaghi F. Physical therapy, intra-articular dextrose prolotherapy, botulinum neurotoxin, and hyaluronic acid for knee osteoarthritis: randomized clinical trial. Int J Rehabil Res 2020;43:219-27.
70. Rosen J, Niazi F, Dysart S. Cost-Effectiveness of Treating Early to Moderate Stage Knee Osteoarthritis with Intra-articular Hyaluronic Acid Compared to Conservative Interventions. Adv Ther 2020;37:344-52.
71. Rosen J, Sancheti P, Fierlinger A, Niazi F, Johal H, Bedi A. Cost-Effectiveness of Different Forms of Intra-Articular Injections for the Treatment of Osteoarthritis of the Knee. Adv Ther 2016;33:998-1011.
72. Saccomanno MF, Donati F, Careri S, Bartoli M, Severini G, Milano G. Efficacy of intra-articular hyaluronic acid injections and exercise-based rehabilitation programme, administered as isolated or integrated therapeutic regimens for the treatment of knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2016;24:1686-94.
73. Salmon JH, Rat AC, Charlot-Lambrecht I, Eschard JP, Jolly D, Fautrel B. Cost Effectiveness of Intra-Articular Hyaluronic Acid and Disease-Modifying Drugs in Knee Osteoarthritis. Pharmacoeconomics 2018;36:1321-31.
74. Samuelson EM, Ebel JA, Reynolds SB, Arnold RM, Brown DE. The Cost-Effectiveness of Platelet-Rich Plasma Compared With Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis. Arthroscopy - Journal of Arthroscopic and Related Surgery 2020;36:3072-8.
75. Schunemann HJ, Tugwell P, Reeves BC, et al. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. Res Synth Methods 2013;4:49-62.
76. Sdeek M, Sabry D, El-Sdeek H, Darweash A. Intra-articular injection of Platelet rich plasma versus Hyaluronic acid for moderate knee osteoarthritis. A prospective, double-blind randomized controlled trial on 189 patients with follow-up for three years. Acta Orthop Belg 2021;87:729-34.
77. Simental-Mendía M, Vílchez-Cavazos JF, Peña-Martínez VM, Said-Fernández S, Lara-Arias J, Martínez-Rodríguez HG. Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Archives of Orthopaedic and Trauma Surgery 2016;136:1723-32.
78. Skou ST, Roos EM. Physical therapy for patients with knee and hip osteoarthritis: supervised, active treatment is current best practice study. Clin Exp Rheumatol 2020;38:1036.
79. Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis Cartilage 2012;20:350-6.

80. Strand V, Lim S, Takamura J. Evidence for safety of retreatment with a single intra-articular injection of Gel-200 for treatment of osteoarthritis of the knee from the double-blind pivotal and open-label retreatment clinical trials. BMC Musculoskelet Disord 2016;17:240.
81. Takamura J, Seo T, Strand V. A Single Intra-Articular Injection of Gel-200 for Treatment of Symptomatic Osteoarthritis of the Knee Is More Effective than Phosphate Buffered Saline at 6 Months: A Subgroup Analysis of a Multicenter, Randomized Controlled Trial. Cartilage 2019;10:417-22.
82. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-Articular, Single-Shot Hylan G-F 20 Hyaluronic Acid Injection Compared with Corticosteroid in Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial. J Bone Joint Surg Am 2016;98:885-92.
83. Tavassoli M, Janmohammadi N, Hosseini A, Khafri S, Esmaeilnejad-Ganji SM. Single- and double-dose of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: A randomized controlled trial. World J Orthop 2019;10:310-26.
84. Thomas T, Amouroux F, Vincent P. Intra articular hyaluronic acid in the management of knee osteoarthritis: Pharmaco-economic study from the perspective of the national health insurance system. PLoS One 2017;12:e0173683.
85. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthritis Cartilage 2002;10:518-27.
86. Vaishya R, Pandit R, Agarwal AK, Vijay V. Intra-articular hyaluronic acid is superior to steroids in knee osteoarthritis: A comparative, randomized study. J Clin Orthop Trauma 2017;8:85-8.
87. Villanova-Lopez MM, Nunez-Nunez M, Fernandez-Prieto D, et al. Randomized, double-blind, controlled trial, phase III, to evaluate the use of platelet-rich plasma versus hyaluronic acid in hip coxarthrosis. Rev Esp Cir Ortop Traumatol (Engl Ed) 2020;64:134-42.
88. Viswanathan M, Ansari MT, Berkman ND, et al. Chapter 9: Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
89. Wang Z, Wang R, Xiang S, et al. Assessment of the effectiveness and satisfaction of platelet-rich plasma compared with hyaluronic acid in knee osteoarthritis at minimum 7-year follow-up: A post hoc analysis of a randomized controlled trial. Front Bioeng Biotechnol 2022;10:1062371.
90. Wu YT, Hsu KC, Li TY, Chang CK, Chen LC. Effects of Platelet-Rich Plasma on Pain and Muscle Strength in Patients With Knee Osteoarthritis. Am J Phys Med Rehabil 2018;97:248-54.
91. Yaradilmis YU, Demirkale I, Safa Tagral A, Caner Okkaoglu M, Ates A, Altay M. Comparison of two platelet rich plasma formulations with viscosupplementation in treatment of moderate grade gonarthrosis: A prospective randomized controlled study. J Orthop 2020;20:240-6.
92. Yen ZS, Lai MS, Wang CT, et al. Cost-effectiveness of treatment strategies for osteoarthritis of the knee in Taiwan. J Rheumatol 2004;31:1797-803.
93. Yurtbay A, Say F, Çinka H, Ersoy A. Multiple platelet-rich plasma injections are superior to single PRP injections or saline in osteoarthritis of the knee: the 2-year results of a randomized, double-blind, placebo-controlled clinical trial. Arch Orthop Trauma Surg 2022;142:2755-68.
94. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. Arthritis Res Ther 2015;17:51.
95. Zhou Y, Li H, Cao S, et al. Clinical Efficacy of Intra-Articular Injection with P-PRP Versus that of L-PRP in Treating Knee Cartilage Lesion: A Randomized Controlled Trial. Orthop Surg 2023;15:740-9.

1 Appraisal

1.1 Background and Rationale

Osteoarthritis (OA) is one of the most common disabilities affecting people in the United States, with roughly 32.5 million Americans currently affected.[98] This number is projected to grow in the coming years, with estimates as high as 29.5% of US adults over the age of 45 by 2032.[147] Osteoarthritis, which most commonly occurs in the knee and hip, often causes pain, fatigue, disability, and general limitations to daily life activities that impact physical, mental, and emotional wellbeing.[98] There is no cure for this condition and, as such, treatment can become considerably expensive long term. Healthcare cost due to osteoarthritis in the United States is estimated at $45.4 billion per year, with affected individuals paying an additional $1778 per year in healthcare costs on average.[3] Reduced ability to work results in additional wage loss of $1114 per year, more than double that of those without osteoarthritis ($517).[163]

Osteoarthritis is a progressive disease that may often lead to joint failure requiring total joint replacement. Given the generally slow rate of progression of the disease, however, care in the interim before eligibility or need for replacement surgery is of the utmost importance. Conservative management of osteoarthritis commonly includes exercise and physical therapy, use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, use of supportive devices, weight loss, corticosteroid injections and may include hyaluronic acid (HA, viscosupplementation) and intra-articular platelet-rich plasma (PRP).[28] Exercise and physical therapy are currently considered front-line treatments for knee and hip osteoarthritis and provide considerable benefit both for pain relief and maintenance of functionality, but may be difficult to begin for overweight or obese individuals and time commitments and costs may present challenges to some.[131] Pain medications such as NSAIDs and acetaminophen are commonly recommended or prescribed for relief of pain and inflammation caused by osteoarthritis. These medications are generally easy to access and carry relatively low cost, but long-term use increases risk of potentially serious adverse events such as stomach, kidney, and liver damage, heart attack, and stroke.[40]

Intra-articular corticosteroid injections may be effective at reducing pain in knee and hip osteoarthritis patients in short- and medium-term settings, but carry risk of adverse events such as pain flare and rapid destructive osteoarthritis of the joint[10,34] as well as increased risk of post-operative surgical infection months following injection, transient increases in blood sugar and hypertension and transient decrease in immune response. As corticosteroid injections are generally reserved for those not responding to other conservative treatment options, there are limited non-surgical options for individuals not responding to this treatment.[93] Viscosupplementation with intra-articular hyaluronic acid (IAHA) is most commonly provided to individuals who are unable to utilize or do not respond well to other front-line or preferred treatments and has become an increasingly popular treatment for knee and hip osteoarthritis over the last twenty years. It may provide anti-inflammatory, analgesic, and chondroprotective effects.[48] Hyaluronic acid products require approval from the Food and Drug Administration (FDA), which notes numerous mild to moderate adverse events such as swelling, pain, and edema at injection site and lack of sufficient evidence for non-knee indications.[2] PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with a similar adverse event risk profile, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated.[18]

While IAHA and PRP are not curative, they may provide longer-term relief compared with some primary treatment modalities and may be more acceptable to some patients. Previous reviews of the effectiveness of HA and PRP report mixed results on the effectiveness of these for pain reduction and/or functional improvement.

1.2 Policy Context

Health Technology Assessments (HTAs) on HA/viscosupplementation and PRP were performed in 2013 and 2016 respectively and reviewed by the Washington Health Technology Assessment Program (HTAP). The prior HA report (2013) focused on patients with knee OA. The prior PRP report (2016) included osteoarthritis as well as a range of other musculoskeletal conditions. The focus of this re-review was on symptomatic adults with knee or hip OA treated with HA or PRP as a primary form of treatment or in conjunction with conservative therapies. The HTAP is interested in re-evaluation of these treatments in patients with knee or hip osteoarthritis given that additional evidence has been published subsequent to the original reviews. Other musculoskeletal conditions were not part of this re-review. Given the chronic and progressive nature of OA, the report focused on RCTs that report on persistence of symptom relief or functional improvement one or more months post treatment.

The DRAFT Key Questions and Scope were published on the HTAP website in October 2022. Public comments were reviewed. None led to changes in the questions or scope. All citations suggested by commenters were evaluated for inclusion based on the final key questions and scope.

1.3 Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the effectiveness and safety of HA and PRP for primary treatment of knee or hip osteoarthritis compared with placebo/sham, no treatment, common conventional treatment options, arthroscopic lavage and/or debridement, prolotherapy, corticosteroid injection in symptomatic adults. The differential effectiveness and safety of these therapies for subpopulations was evaluated, as was the cost effectiveness.

1.4 Key Questions

1. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with hyaluronic acid/viscosupplementation (HA)**
    a. What is the effectiveness of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment in the short and longer-term?
    b. What is the evidence regarding short- and long-term harms and complications of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment?
    c. Is there evidence of differential efficacy, effectiveness, or safety of HA compared with placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), PRP, or no treatment by factors such as age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?

d. What is the evidence of cost-effectiveness of HA compared with placebo/sham, PRP, common conservative treatments, or no treatment?

2. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with platelet-rich plasma (PRP)**

a. What is the effectiveness of PRP compared with placebo/sham, common conservative treatments, treatments other than HA, or no treatment in the short and longer-term?

b. What is the evidence regarding short- and long-term harms and complications of PRP compared placebo/sham, common conservative treatments, treatments other than HA, or no treatment?

c. Is there evidence of differential efficacy, effectiveness, or safety of PRP compared with, placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), treatments other than HA, or no treatment by factors such age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?

d. What is the evidence of cost-effectiveness of PRP compared with placebo/sham, common conservative treatments, or no treatment?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Population	Adults with symptomatic knee or hip osteoarthritis Subpopulations based on patient characteristics, primary or secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options	• Conditions other than knee or hip OA • Patients <18 years old • Asymptomatic individuals
Intervention	Autologous PRP injection(s) or hyaluronic acid (HA) (viscosupplementation) injection(s) used as the primary intervention or in conjunction with common conservative care options	• Non-FDA-approved HA (viscosupplementation) formulations; products undergoing phase III trials may be considered • PRP or HA used in conjunction with another intervention not listed for inclusion (e.g., open, arthroscopic or minimally invasive surgery, invasive procedures, mannitol and similar combinations are not included) • Cellular matrix • Combinations of HA with PRP together • Other biologics (growth factor injections [., plasma rich in growth factor], “stem cell” injections, etc.)
Comparator	• Common conservative treatment(s) (e.g., NSAIDs, oral pain medications, exercise,	• Combinations of HA with PRP together

Study Component	Inclusion	Exclusion
	physical therapy, weight loss) which may be included in usual care • Arthroscopic lavage and/or debridement • Prolotherapy • Corticosteroid injection • Placebo or sham • No treatment	• Other biologics (growth factor injections [e.g., plasma rich in growth factor], bone marrow aspirate/bone marrow aspirate concentrate, blood plasma, autologous blood products [e.g., autologous conditioned serum"] medicinal signaling cells, mesenchymal stem cells, "stem cell", adipose, fat, or microfat injections); peptide injections • Ozone treatment • Non-FDA approved treatments • Herbal treatments • Acupuncture • Nerve ablation
Outcomes	**Primary** • Function • Pain • Need for secondary invasive procedures (e.g., surgery) • Adverse events or harms **Secondary** • Symptom Recurrence (e.g., persistent or increased pain, reduced function) resulting in need for additional injection of HA or PRP within 2 months after protocol completion • Quality of life • Medication use • Return to normal activities (sports, work, or activity level) **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome	• Non-clinical outcomes • Non-validated measures (e.g., for pain, function, QOL)
Timing	Review will focus on persistence of relief 1 or more months post-treatment	

Study Component	Inclusion	Exclusion
Study design	**Focus will be on studies with the least potential for bias with ≥ 1 month post treatment results** **Key Questions 1 and 2 parts a and b:** • High quality systematic reviews of RCTs will be considered if available and they address the key questions. • Randomized controlled trials (RCTs) • In the absence of RCTs, high quality non-randomized comparative studies will be considered in the absence of RCTs with a focus on comparative prospective studies **Key Question 1b and 2b:** • KQ2: In the absence of RCTs, high-quality non-randomized studies designed specifically to evaluate harms/adverse events that are rare or occur long-term **Key Question 1c and 2c:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest and test for interaction. **Key Question 1d and 2d:** Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Indirect comparisons • Comparisons with historical cohorts • Noncomparative studies (case series, single arm studies, pre-post) • Nonrandomized studies which do not control for confounding • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients per treatment group • Case reports • Studies in which <80% of patients have a condition of interest • Studies that do not report on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)	• Abstracts, conference proceedings, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

FDA = United States Food and Drug Administration, HA = Hyaluronic acid, ICER = Incremental cost effectiveness ratio, KQ = Key question, NSAID = Non-steroidal anti-inflammatory drug, OA = Osteoarthritis, PICOTS = Patients, Interventions, Comparators, Outcomes, Timing and Study Design, PRP = Platelet-rich plasma, QALY = Quality adjusted life year, QoL = Quality of life, RCT = Randomized controlled trial, SSED = Summary of safety and effectiveness data

1.5 Outcomes Assessed

This review focuses on the following primary effectiveness outcomes: validated measures of function and pain and need for secondary invasive procedures such as surgery. We focus on serious treatment-related adverse events, i.e., treatment-related events that may be life-threatening or required medical intervention. We also report on cost-effectiveness measures from full economic analyses. Table 1 provides a list of validated primary outcomes measures used in this review. We used definitions for the magnitude of effect size consistent with prior AHRQ reviews for treatment of pain,[31,129,130] Appendix J.

Table 1. Outcome measures used in included studies

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
PRIMARY					
Harris Hip Score (HHS)[61]	Clinician	Four subscales (16 items): Pain (44 points) Function (47 points) Deformity (4 points) Range of motion (5 points) Items scored on a 0 to variable maximum 1 to 44 point score	0 to 100 (total score)	The higher the score, the better the hip function. Score 100-90: excellent Score 89-80: good Score 79-70: fair Score <70: poor	For Hip OA: NR
International Knee Documentation Committee (IKDC) Subjective Knee Form[69]	Patient	3 subscales (45 items): Symptoms Sports activities Function	Scores summed and normalized to 100; total score ranges from 0 to 100.	The higher the score, the greater the knee function.	For Knee OA: NR
Knee Injury and Osteoarthritis Outcome Score (KOOS)[116]	Patient	5 subscales (42 items): Pain Symptoms Activities of daily living Sports and recreation Quality of life	Scores normalized to 100 for each subscale and each subscale scored separately	The higher the score, the greater the knee function.	For Knee OA: KOOS, KOOS PS, KOOS ADL: NR[38] KOOS PS: 2.2 KOOS QOL: 8.0[128]
Lequesne Index[79]	Patient	3 subscales (11 items): Pain Walking distance Activities of daily living Two indices available: hip and knee. Both scored the same,	0 to variable maximum (item score) 0 to 24 (total score)	The higher the score, the greater the impairment. Extremely severe: >14 Very severe: 11 to 13 Severe: 8 to 10 Moderate: 5 to 7 Minor: 1 to 4 No severity: 0	For knee OA: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		have identical subscales, etc. The 1997 update made minor changes to morning stiffness items and added "algofunctional index" to the name.			
Lysholm Knee Function Scoring Scale[88]	Patient	8 subscales (8 items): Instability (25 points) Pain (25 points) Catching, locking (15 points) Swelling (10 points) Stair climb (10 points) Squat (5 points) Limp (5 points) Support (5 points)	0 to 100 (total score)	The lower the score, the greater the disability. Score 100-95: excellent Score 94-84: good Score 83- 65: fair Score <65: poor	For general knee problems (Knee OA NR): Traumatic: 20.5 Non-traumatic: 13.0 Combined: 18.0
Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI) Responder Index[42,88]	Patient	3 subscales (item number variable by study)‡: Pain Function Patient's global assessment	Patient considered a "responder" if: experienced a high improvement in pain or function ≥50% and absolute change ≥20; OR improvement in 2 of the following Pain ≥20% and absolute change in ≥10 Function ≥20% and absolute change in ≥10 Patient's global assessment ≥20% and absolute change in ≥10 Failure to meet the above criteria indicates that the patient is a "non-responder".	If patient is considered a "responder", they have experienced high improvement in pain or function.	NR
Visual Analog Scale (VAS)§	Patient	Patients are asked to indicate on a scale line (100 mm in length) where they	0 to variable maximum typically of 10 or 100 (total score)	The higher the score, the greater the pain. No pain: 0 to 4 mm	For knee and hip OA: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		rate their pain level of the day. One variation of this measure includes changing the length of the line.		Mild pain: 5 to 44 mm Moderate pain: 45 to 74 mm Severe pain: 74 to 100 mm	
Western Ontario and McMaster OA index (WOMAC)[17]	Patient	3 subscales: Pain (5 items) Stiffness (2 items) Physical function (17 items)	Likert Scale: 0 to 68 (function) 0 to 20 (pain) 0 to 8 (stiffness) 0 to 96 (total score)	The higher the score, the greater the pain, stiffness, and functional limitations.	For Knee OA, 0-100 scale: Pain: 9.7 Stiffness: 9.3 Function: 10 (Babul 2004) Global: 17.13 Function: 17.02[97] Total WOMAC: 10.1 Pain: 2.1 Stiffness: 2.1 Function: 6.5[136] For hip OA: NR
SECONDARY					
EuroQol 5-Dimension Questionnaire (EQ5D)[45]	Patient	5 dimensions of health: Mobility Self-care Usual activities Pain/discomfort Anxiety depression Each dimension is rated on a scale from 1 (no problems) to 3 (extreme problems)	A 5-digit number is produced to represent level of problems in each dimension.	The higher the digit for each dimension, the greater the problems.	For knee and hip OA: NR
EuroQol Visual Analog Scale (EQ-VAS)[85]	Patient	One item asks the individual to select a number from a scale indicating their health state of the day.	0 to 100 (total score)	The higher the score, the lower the health impairment.	For Knee OA: MCID: NR
Short Form-12 (SF-12)[155]	Patient	8 subscales (12 items): Physical functioning Role-physical Bodily pain General health	0 to 100 (total score)	The higher the score, the lower the disability.	For knee and hip OA: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		Vitality Social functioning Role-emotional Mental health			
Short Form-36 (SF-36)[156,157]	Patient	8 subscales (36 items): Role-functioning Role limitations due to physical health problems Bodily pain General health Vitality Social functioning Role limitations due to emotional problems Mental health The Mental Component Score of the SF-36 (MCS-36) contains the subscales listed as 4-8 and includes 35 items. The Physical Component Score of the SF-36 (PCS-36) contains the subscales listed as 1-5 and includes 35 items.	0 to 100 (subscale score) 0 to 100 (component score) Total score not used	The higher the score, the greater the quality of life.	<u>For Knee OA</u>: 4.3 General health: -7.3 (-11.3 to -3.3) Vitality: 3.44 (-2.2 to 9.1) Social functioning: 6.15 (-1.7 to 14.0) Role emotional: 2.42 (-9.2 to 14.1) Mental health: 4.02 (-1.7 to 9.7)[136]

EQ-5D = EuroQol 5-Dimension Questionnaire, EQ-VAS = EuroQol visual analog scale IKDC = International knee documentation committee, KOOS = Knee injury and osteoarthritis outcome score, MCID = Minimum clinically important difference, MCS = Mental component score, mm = millimeter, NR = Not reported, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, PCS = Physical component score, SF-12 = Short form-12, SF-36 = Short form-36, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster OA index

*MCIDs were only found if an outcome was significant in any of the results of this report. Those that are significant in the results, but not found searching the literature, then the MCID is reported as NR.

‡The measures used for the three subscales vary depending on the study.

§ Multiple versions and modifications to this outcome measure were reported in the studies included in this report.

1.6 Washington State Utilization Data

Hyaluronic acid/viscosupplementation, platelet-rich plasma injections for knee or hip osteoarthritis

Washington State agency utilization data

Population

Administrative claims and encounter data for hyaluronic acid/platelet-rich plasma (HA/PRP) from the following Washington State health programs were assessed: the Public Employees Benefit Board (PEBB) and School Employees Benefit Board (SEBB) Uniform Medical Plan (UMP), Medicaid managed care (MC) and fee-for-service (FFS), and the Department of Labor and Industries (L&I) Workers' Compensation Plan.

The assessment includes final paid and adjudicated claims and encounters for all ages. Denied claims or rejected encounters are excluded. Individuals that were dually eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/SEBB UMP experience includes claims for non-Medicare services.

HA/PRP Procedures

The assessment includes only procedures and services specific to HA/PRP with a date of service between January 1, 2019, and December 31, 2022.

Claims and encounters for adults (>=18) with qualifying procedures or services according to current procedural terminology (CPT) codes during the period were extracted for analysis. Qualifying CPT codes included 0232T, G0460, P9020, J7318, J7320-J7329, J7331-J7332, for those with a diagnosis of knee or hip osteoarthritis (ICD-10 codes M17.0-M17.9 or M16.0-M16.9).

Table. Utilization of HA and related procedures and services, by state health program (2019-2022)

Medicaid	2019	2020	2021	2022	Total (unique)
Fee for service (FFS)					
Individuals with at least one HA-related procedure/service	64	28	31	30	**153**
Managed care (MC)					
Individuals with at least one HA-related procedure/service	650	599	637	749	2,635
Female, count	470	440	456	562	**1,928**
Male, count	179	159	181	187	**706**
Number of encounters with HA	1,538	1,519	1,663	1,998	**6,718**
Average encounters with HA/individual	2	3	3	3	**3**
Amount paid, HA	$451,802	$351,307	$293,614	$330,428	**$1,427,151**
Average payments per individual	$805	$751	$675	$657	**$726**
Amount paid, HA and related procedures	$1,011,570	$898,686	$923,260	$1,010,051	**$3,843,566**
Public Employees Benefit Board/School Employees Benefit Board Uniform Medical Plan (PEBB/SEBB UMP)					
Individuals with at least one HA-related procedure/service	951	774	950	953	3,628
Female, count	651	523	621	621	2,416
Male, count	300	251	329	332	1,212
Number of encounters with HA	2,741	2,113	2,751	2,581	**10,186**
Average encounters with HA/individual	3	3	3	3	**3**
Amount paid, HA	$176,318	$146,365	$186,803	$180,925	**$690,411**
Average payments per individual	$199	$208	$221	$215	**$211**
Amount paid, HA and related procedures	$639,530	$572,917	$704,313	$723,785	**$2,640,545**
Washington State Department of Labor and Industries (L&I)					
Individuals with at least one HA-related procedure/service	66	64	68	64	**262**
Female, count	22	22	25	28	97
Male, count	44	42	43	36	165

Number of encounters with HA	139	143	124	143	**549**
Average encounters with HA/individual	2	2	2	2	**2**
Amount paid, HA	$20,495	$29,601	$26,490	$22,098	**$98,683**
Average payments per individual	$477	$592	$491	$502	**$517**
Amount paid, HA and related procedures	$748,262	$630,536	$649,076	$590,806	**$2,618,681**
Washington State – Combined Medicaid, PEBB/SEBB UMP, L&I					
Individuals with at least one HA-related procedure/service	1,728	1,463	1,685	1,795	**6,671**
Female, count	1,184	1,005	1,120	1,228	**4,537**
Male, count	541	458	560	560	**2,119**
Number of encounters with HA	4,572	3,828	4,609	4,790	**17,799**
Amount paid, HA	$690,297	$547,793	$526,562	$553,669	**$2,318,321**
Amount paid, HA and related procedures	$2,513,854	$2,147,306	$2,325,811	$2,374,955	**$9,361,926**

Data notes: HA = hyaluronic acid; NR = not reported; small numbers suppressed to protect patient privacy. Claimant sex was not always reported. Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. Amount paid reflects all claims submitted with the procedure code for the same date of service, and includes professional, facility, and ancillary claims (such as arthrocentesis). Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than one year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations.

Table 2. Utilization of PRP and related procedures and services, by state health program (2019-2022)

Medicaid	2019	2020	2021	2022	Total (unique)
Fee for service (FFS)					
Individuals with at least one PRP-related procedure/service	0	0	0	0	**0**
Managed care (MC)					
Individuals with at least one PRP-related procedure/service	NR	NR	NR	NR	13
Female, count	NR	NR	NR	NR	**NR**
Male, count	NR	NR	NR	NR	**NR**
Number of encounters with PRP	NR	NR	NR	NR	**16**
Average encounters with PRP/individual	NR	NR	NR	NR	**1**
Amount paid, PRP	$0	$0	$0	$0	**$0**

Average payments per individual	$0	$0	$0	$0	**$0**
Amount paid, PRP and related procedures	$0	$0	$0	$0	**$0**
Public Employees Benefit Board/School Employees Benefit Board Uniform Medical Plan (PEBB/SEBB UMP)					
Individuals with at least one PRP-related procedure/service	NR	NR	NR	NR	71
Female, count	NR	NR	12	20	43
Male, count	NR	NR	NR	NR	28
Number of encounters with PRP	NR	13	21	27	**71**
Average encounters with PRP/individual	NR	2	2	1	**2**
Amount paid, PRP	$0	$0	$0	$77	**$77**
Average payments per individual	$0	$0	$0	$77	**$77**
Amount paid, PRP and related procedures	$0	$0	$0	$77	**$77**
Washington State Department of Labor and Industries (L&I)					
Individuals with at least one PRP-related procedure/service	15	15	27	24	**81**
Female, count	NR	NR	NR	NR	32
Male, count	NR	NR	18	15	49
Number of encounters with PRP	16	22	39	34	**111**
Average encounters with PRP/individual	1	1	1	1	**1**
Amount paid, PRP	$0	$1,009	$600	$0	**$1,609**
Average payments per individual	$0	$505	$600	$0	**$536**
Amount paid, PRP and related procedures	$0	$1,009	$600	$0	**$1,609**
Washington State – Combined Medicaid, PEBB/SEBB UMP, L&I					
Individuals with at least one PRP-related procedure/service	25	29	54	57	**165**
Female, count	14	11	25	31	**81**
Male, count	11	18	29	26	**84**
Number of encounters with PRP	27	53	86	77	**243**
Amount paid, PRP	$0	$1,009	$600	$77	**$1,686**

Amount paid, PRP and related procedures	$0	$1,009	$600	$77	**$1,686**

Data notes: PRP = platelet-rich plasma; NR = not reported; small numbers suppressed to protect patient privacy. Claimant sex was not always reported. Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. Amount paid reflects all claims submitted with the procedure code for the same date of service, and includes professional, facility, and ancillary claims (such as arthrocentesis). Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than one year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations.

Table 3. Demographics of Medicaid, UMP, & L&I beneficiaries with at least one HA/PRP procedure, SFY 2018-2022

Age	HA – Total individuals (unique)	PRP – Total individuals (unique)
18-64 years	3,174	135
65 years and above	3,503	30
Total	**6,671**	**165**

Table 4. HA/PRP breakdown by condition

Condition	HA – Total individuals/encounters	PRP – Total individuals/encounters
Knee OA	6,138/16,250	66/93
Hip OA	NR/15	18/35

Data notes: OA = osteoarthritis; NR = not reported; small numbers suppressed to protect patient privacy. ICD-10 category codes included: knee osteoarthritis – M17.0-M17.9; hip osteoarthritis – M16.0-M16.9.

Table 5. Codes and cost by HCPCS/CPT code (maximum allowable), by state health program and setting

Code	Description	Medicaid FFS		L&I	
CPT		Non-facility	Facility	Non-facility	Facility
0232T	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment	NC	NC	NC	NC
G0460	Platelet rich plasma, each unit	NC	NC	NC	NC
P9020	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed	AC	AC	BR	BR
20610	Arthrocentesis, aspiration and/or injection, major joint or bursa (e.g., shoulder, hip, knee, subacromial bursa); without ultrasound guidance	$37.49	$26.26	$111.75	$77.59
20611	Arthrocentesis, aspiration and/or injection, major joint or bursa (egg, shoulder, hip, knee, subacromial bursa); with ultrasound guidance, with permanent recording and reporting	$58.19	$34.56	$174.28	$101.90
J7318	Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg	NC	NC	BR	BR
J7320	Hyaluronan or derivative, genvisc 850, for intra-articular injection, 1 mg	NC	NC	BR	BR
J7321	Hyaluronan or derivative, hyalgan, supartz or visco-3, for intra-articular injection, per dose	NC	NC	$76.02	$76.02
J7322	Hyaluronan or derivative, hymovis, for intra-articular injection, 1 mg	NC	NC	BR	BR

J7323	Hyaluronan or derivative, euflexxa, for intra-articular injection, per dose	NC	NC	$138.53	$138.53
J7324	Hyaluronan or derivative, orthovisc, for intra-articular injection, per dose	NC	NC	$131.50	$131.50
J7325	Hyaluronan or derivative, synvisc or synvisc-one, for intra-articular injection, 1 mg	NC	NC	$10.16	$10.16
J7326	Hyaluronan or derivative, gel-one, for intra-articular injection, per dose	NC	NC	BR	BR
J7327	Hyaluronan or derivative, monovisc, for intra-articular injection, per dose	NC	NC	$709.05	$709.05
J7328	Hyaluronan or derivative, gelsyn-3, for intra-articular injection, 0.1 mg	NC	NC	BR	BR
J7329	Hyaluronan or derivative, trivisc, for intra-articular injection, 1 mg	NC	NC	BR	BR
J7331	Hyaluronan or derivative, synojoynt, for intra-articular injection, 1 mg	NC	NC	BR	BR
J7332	Hyaluronan or derivative, triluron, for intra-articular injection, 1 mg	NC	NC	BR	BR

Data notes: NC = not covered; AC = acquisition cost; BR = by report. Medicaid FFS from October 1, 2021 Physician-Related Services Fee Schedule (accessed May 18, 2023; webpage). L&I from 2021 provider fee schedule (accessed May 18, 2023). PEBB/UMP fees are confidential and not publicly available (proprietary).

2 Background

2.1 Epidemiology and Burden of Disease

Osteoarthritis (OA) is one of the most common disabilities affecting people in the United States, with roughly 32.5 million Americans currently affected.[98] This number is projected to grow in the coming years, with estimates as high as 29.5% of US adults over the age of 45 by 2032.[147] Osteoarthritis, which most commonly occurs in the knee and hip, often causes pain, fatigue, disability, and general limitations to daily life activities that impact physical, mental, and emotional wellbeing.[98] There is no cure for this condition and, as such, treatment can become considerably expensive long term. Healthcare cost due to osteoarthritis in the United States is estimated at $45.4 billion per year, with affected individuals paying an additional $1778 per year in healthcare costs on average.[163] Reduced ability to work results in additional wage loss of $1114 per year, more than double that of those without osteoarthritis ($517).[163]

2.2 Osteoarthritis

2.2.1 Osteoarthritis Pathogenesis

There are several changes within the joint that lead to osteoarthritis. Enzyme-driven degradation in response to physical loading begins in collagen within the extracellular matrix and makes its way into the and eventually causes cartilage delamination, thinning of the hyaline cartilage, and cartilage calcification. This leads to overall erosion of and formation of fissures within the cartilage. Subchondral bone also thickens and grows. Fissures develop within the bone marrow. These processes result in inflammation within the synovial fluid of the joint, known as synovitis, which disrupts production of hyaluronan and plasminogen activator production, causing thickening of synovial fluid. These effects seem to have a proliferative effect on each other and it is at this stage that osteoarthritis begins to become much more significant both clinically and radiologically.[105] Given the extent of the mechanisms in play, osteoarthritis can be considered not just a disease of the cartilage between joints, but a disease of the entire joint.

2.2.2 Osteoarthritis Classification

Osteoarthritis is frequently classified radiographically via verified scales. The scale used most frequently in trials included in this report is the Kellgren-Lawrence scale. This scale classifies OA based on joint space narrowing, presence of osteophytes, sclerosis, and bone-end deformity and is graded as follows: Grade 0 indicates no joint space narrowing or other changes; Grade 1 indicates possible osteophytic lipping and lack of joint space narrowing; Grade 2 indicates clear osteophytes and likely joint space narrowing; Grade 3 indicates a moderate osteophytes as well as clear joint space narrowing and sclerosis and possible bone-end deformity; Grade 4 indicates large osteophytes and severe joint space narrowing and sclerosis with clear bone-end deformity.[76] Additional scales used by trials included in this report include the Ahlbäck scale and the Shahriaree. The Ahlbäck scale primarily relied on joint space and bone defect and loss measures and is graded as follows: Grade 0 indicates absence of disease; Grade 1 indicates joint space narrowing less than three millimeters or 50 percent of the joint space; Grade 2 indicates obliteration of joint space; Grade 3 indicates bone defect or loss of less than five millimeters; grade 4 indicates bone defect or loss of five to ten millimeters.[76] The Shahriaree scale is an

MRI-based scale and is graded as follows: Grade 1 indicates softening and swelling of IA cartilage; Grade 2 indicates blistered cartilage with a still-intact surface; Grade 3 indicates surface irregularities, ulceration, or fibrillation that do not reach the bone; Grade 4 indicates surface irregularities, ulceration, or fibrillation extending into the bone with potential bony changes.[146]

2.2.3 Knee and Hip Osteoarthritis

Knee osteoarthritis is the most common form of osteoarthritis, with 40 percent of men and 47 percent of women at risk of developing the disease in their lifetimes and global age-standardized prevalence in 2010 was 3.8 percent.[39,94] Hip osteoarthritis is the third most common, with 18.5 percent of men and 28.6 percent of women at risk of developing the disease and an age-standardized prevalence of 0.85 percent in 2010.[39,80] In that same year, these two conditions were the eleventh-highest contributor to global disability and accounted for 17.1 million years lost to disability, an increase of nearly 7 million from 1990. Given the significance of disability caused by these conditions and the steady increase in prevalence, it is imperative that treatment options are consistently reviewed to ensure the highest quality care possible is available to individuals struggling with these conditions.[39]

2.3 Technologies & Interventions

2.3.1 Hyaluronic Acid/Viscosupplementation

Viscosupplementation with intra-articular hyaluronic acid (IAHA) is most commonly provided to individuals who are unable to utilize or do not respond well to other front-line or preferred treatments.[2,48] Hyaluronic acid occurs naturally in connective tissue, joints, and other places where extracellular matrix is present and, given its non-specificity to any tissue or species, theoretically carries no risk of immune response when injected. Most forms of hyaluronic acid used for injection today are made using either rooster combs (animal-derived) or via fermentation of bacteria (non-animal derived). Furthermore, hyaluronic acid can be particulate manufactured, in which particle size determines longevity, or non-particulate manufactured, in which density of cross-linkage determines longevity.[152] Within the joint, hyaluronic acid works via several mechanisms: While half-life within the joint is too short to achieve much clinical difference regarding increased joint cushioning and fluid retention (the function of native hyaluronic acid in joints), hyaluronic acid supplementation has shown an ability to inhibit inflammatory mechanisms and nociceptor firing (responsible for neurological pain sensation) within the joint as well as temporarily restore a portion of the joint's natural hyaluronan-producing mechanisms.[89] Through these mechanisms, hyaluronic acid is thought to improve osteoarthritis symptoms within the joint for a period much longer than its half-life would allow from a purely kinetic perspective. Hyaluronic acid products require approval from the Food and Drug Administration (FDA), which notes numerous mild to moderate adverse events such as swelling, pain, and edema at injection site and lack of sufficient evidence for non-knee indications.[11] There are currently 12 FDA-approved hyaluronic acid products available on the US market: Durolane, Euflexxa, Gel-One, Gelsyn-3, Hyalgan, Hymovis, Monovisc, Orthovisc High Molecular Weight Hyaluronan, Supartz-FX/Visco-3, Synvisc/Synvisc-One, Triluron, and TriVisc (see Appendix K). While the processes by which HA is made are standardized producing consistent products, the specific products themselves vary somewhat in their composition and there is no agreed upon threshold or range for molecular weight designations. Molecular weights are consistently reported as part of product formulation and are thought to impact the efficacy of HA, with higher molecular weight often associated with better efficacy.[68] HA has a wide range of possible

molecular weights, most commonly designated as “high”, “moderate” or “low”, but there is overlap and heterogeneity across these weight designations (given in kilodaltons [kDa])[68] that makes it difficult to assess the impact of HA molecular weight on clinical outcomes.

2.3.2 Platelet Rich Plasma

Platelet-rich plasma (PRP) has become increasingly popular for use in osteoarthritis management, though its mechanisms of action and effects are still not entirely clear. PRP is derived from a patient’s own blood by separating the plasma, platelets, and other cells and compounds including leukocytes and growth factors from red blood cells in a centrifuge or via filtration, sometimes activating the platelets via one of several processes, and injecting the resulting compound into the intra-articular space. Given its autologous nature, PRP is not regulated as a pharmaceutical product by the FDA and is not approved by the FDA for treatment of musculoskeletal conditions; therefore, it is used “off-label”.[70] However, a wide range of devices used to process PRP (i.e., centrifuge machines and PRP kits) have been cleared by the FDA through the 510(k) pathway.[70] Even so, PRP preparation still lacks the standardization that would create consistent enough products to obtain more conclusive results regarding its efficacy.[52] Current evidence suggests that PRP is able to lubricate the joint more effectively than similar treatments while also suppressing several inflammatory mechanisms and increasing cartilage production within the knee; thus, platelet-rich plasma not only helps reduce pain in the short term, but may be capable of repairing damage within osteoarthritic joints.[139] PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with a limited adverse event risk profile, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated.[18]

2.4 Comparator Treatments

Conservative management of osteoarthritis outside of HA and PRP commonly includes exercise and physical therapy, use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, use of supportive devices, weight loss, and corticosteroid injection.[28] Exercise and physical therapy are currently considered front-line treatments for knee and hip osteoarthritis and provide considerable benefit both for pain relief and maintenance of functionality, but may be difficult to begin for overweight or obese individuals and time commitments and costs may present challenges to some.[131] Pain medications such as NSAIDs and acetaminophen are commonly recommended or prescribed for relief of pain and inflammation caused by osteoarthritis. These medications are generally easy to access and carry relatively low cost, but long-term use increases risk of potentially serious adverse events such as stomach, kidney, and liver damage, heart attack, and stroke.[84] Supportive devices are commonly used by osteoarthritis patients, with between 40% and 76% of patients utilizing an assisted walking device such as a cane, walker, or crutches.[26] Evidence on the efficacy of these devices for pain reduction and slowing of disease progression, however, is limited and contradictory to professional consensus.[7,26] Weight loss has shown to be effective at reducing pain and increasing functionality in osteoarthritis patients, but this benefit is only available to overweight and obese individuals and there may be significant barriers to achieving weight loss, including pain and reduced functionality from the disease itself.[22] Less commonly, conservative care may include use of opiate medications, acupuncture, and supplements such as turmeric or glucosamine chondroitin.

Intra-articular corticosteroid injections may be effective at reducing pain in knee and hip osteoarthritis patients in short- and medium-term settings, but carry risk of adverse events such as pain flare and rapid destructive osteoarthritis of the joint as well as increased risk of post-operative surgical infection months following injection, transient increases in blood sugar and hypertension and transient decrease in immune response.[10,34] Viscosupplementation, particularly with hyaluronic acid, and platelet-rich plasma have become increasingly popular treatments for knee and hip osteoarthritis over the last twenty years.

2.5 Published Clinical Guidelines

PubMed and EMBASE databases were searched for clinical guidelines regarding intra-articular use of HA and PRP in the knee and hip using the same criteria and key words as the general literature search (Appendix B). A total of 30 guidelines fitting these criteria were found, many summarized in a review of clinical guidelines by Phillips et al. Of these guidelines, 14 were considered to be in populations comparable to the that of the United States and were included.

Guidelines from the following sources are summarized:

- American Academy of Orthopaedic Surgeons
- American College of Rheumatology
- Veterans Affairs/Department of Defense
- Phillips et al., 2021 (review of clinical guidelines)

Included recommendations as well as year of recommendation, evidence base, and rating and/or strength of recommendation are available in Table 2. A summary of the above sources is also provided below.

Hyaluronic Acid

American Academy of Orthopaedic Surgeons, 2022: *Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition*: Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee.

American College of Rheumatology (ACR), 2020: *Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee*: ACR Conditionally recommends against IAHA use in the knee and strongly recommends against its use in the hip.

Veterans Affairs/Department of Defense, 2020: *Clinical practice guideline for the non-surgical management of hip & knee osteoarthritis*: VA/DOD suggests offering intraarticular viscosupplementation injection(s) (HA) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions but suggests against its use in the hip.

Phillips et al., 2021: *A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis*: Of the 27 included clinical guidelines, 20 were in favor of use of IAHA for knee OA.

Platelet-Rich Plasma

American Academy of Orthopaedic Surgeons, 2022: *Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition*: Platelet-rich plasma may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

American College of Rheumatology (ACR), 2020: *Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee*: ACR strongly recommends against PRP use in both the knee and hip.

Veterans Affairs/Department of Defense, 2020: *Clinical practice guideline for the non-surgical management of hip & knee osteoarthritis*: VA/DOD does not have sufficient evidence to recommend for or against PRP injections in the knee or hip.

Phillips et al., 2021: *A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis*: Of the 27 included clinical guidelines, 9 indicated uncertainty or inability to make a recommendation for or against the use of PRP.

Table 2. Summary of Clinical Guidelines

Guideline	Year	Evidence Base	Recommendation	Rating/Strength of Recommendation
American Academy of Orthopaedic Surgeons (AAOS)	2022	• HA: 17 high quality studies, 11 moderate quality studies • PRP: 2 high quality studies, 1 moderate quality study	• Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee • Platelet-rich plasma may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee	• Moderate (3/5 stars) • Limited (2/5 stars)
Veterans Affairs/ Department of Defense (VA/DoD)	2020	• HA: 4 RCTs, 4 SRs	• HA: We suggest offering intraarticular viscosupplementation injection(s) (HA) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions • HA: We suggest against the use of intra-articular viscosupplementation injection(s) (HA) of the hip • PRP: There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee	• HA Knee: Weakly for • HA Hip: Weakly against • PRP: Insufficient
American College of Rheumatology (ACR)	2019	• HA: 1 moderate quality study, 3 low quality studies, 1 very low-quality study • PRP: 2 low quality studies	• HA: ACR Conditionally recommends against IAHA use in the knee and strongly recommends against its use in the hip	• NR

			• ACR strongly recommends against PRP use in both the knee and hip	
Osteoarthritis Research Society International (OARSI)	2019	• NR	• HA: OARSI conditionally recommends use of IAHA • PRP: OARSI strongly recommends against use of PRP	• HA: • PRP: Extremely low quality
Arthroscopy Association of Canada (AAC)	2019	• NR	• HA: Intra-articular injections of HMW HA provide improved pain relief and the restoration of function compared with placebo and can be considered in patients with mild to moderate knee OA • PRP: We cannot recommend for or against the use of PRP until further high-quality clinical studies become available	• HA: Good - A • PRP: Conflicting or poor-quality - C
EUROpean VIScosupplementation COnsensus Group (EUROVISCO)	2018	• NR	• HA: Recommended when NSAIDs are not effective	• NR
American Medical Society for Sports Medicine (AMSSM)	2016	• 11 studies	• AMSSM recommends the use of HA for the appropriate patients with knee OA (OMERACT-OARSI criteria)	• Over 60 years old: High quality • Under 60 years old: Moderate quality
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)	2016	• NR	• ESCEO task force recommends the use of IA HA in knee OA patients with mild-moderate disease, and for more severe patients who are either contraindicated to TKR surgery or wishing to delay the surgical procedure	• Good

National Institute for Health and Care Excellence (NICE)	2014	• 1 SR, 20 comparative studies	• Do not offer intra-articular hyaluronan injections for the management of osteoarthritis	• Moderate/Low (based on study grades, need to take closer look)
American Academy of Orthopaedic Surgeons (AAOS)	2013	• NR	• HA: We cannot recommend using HA for patients with symptomatic OA of the knee • PRP: We are unable to recommend for or against platelet rich plasma for patients with symptomatic OA of the knee.	• HA: Strong • PRP: Inconclusive
American Academy of Family Physicians (AAFP)	2012	• NR	• Compared with intra-articular corticosteroids, intra-articular hyaluronic acid injections of the knee are less effective in the short term, equivalent in the intermediate term (i.e., four to eight weeks), and superior in the long term.	• B
National Collaborating Centre for Chronic Conditions (NCC-CC)	2008	• 1 SR, 4 RCTs	• Not accessible	• Not accessible
Agency for Healthcare Research and Quality (AHRQ)	2007	• 5 MAs, 1 RCT	• Recommendation of HA is uncertain because of variability in the evidence	• NR
European League Against Rheumatism (EULAR)	2003	• 35 studies	• HA may have potential benefits	• 1B/B

HA = Hyaluronic acid, IAHA = Intra-articular hyaluronic acid, MA = Meta-analysis, NR = Not reported, NSAID = Non-steroidal anti-inflammatory drug, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, SR = Systematic review, TKR = Total knee replacement

2.6 Previous Systematic Reviews & Health Technology Assessments

Table 3. Selected Previous Systematic Reviews

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
PRP vs. HA							
Costa (2022) 1974 to January 2021 Medline, Embase, Scotus	Assess benefits and harms of PRP compared to other non-surgical methods for treatment of knee osteoarthritis	Knee osteoarthritis	Function* WOMAC Total IKDC KOOS ADL Pain* WOMAC Pain VAS KOOS pain	23 RCTs	Yes (Cochrane)	Yes	Function Very low to low quality evidence (GRADE) from pooled analyses showed a difference in function favoring PRP injection compared to HA at <3 (MD -0.31 (95% CI -0.53 to -0.08)), 6 (MD -0.88 (95% CI -1.29 to -0.46)), and >6 months (MD -1.67 (95% CI -2.40 to -0.93)). Pain Very low to low quality evidence (GRADE) from pooled analyses showed a difference in pain favoring PRP injection compared to HA at 6 (MD -0.47 (95% CI -0.79 to -0.15)) and >6 months (MD -0.88 (95% CI -1.43 to -0.34)), but not <3 months (MD -0.25 (95% CI -0.92 to 0.43)).
Filardo (2021) No limits (search January 17, 2020)	To evaluate effectiveness of PRP compared to placebo and other	Knee osteoarthritis	Function WOMAC (all scales) IKDC	21 RCTs	Yes (Cochrane)	Yes†	Function Very low to moderate quality evidence (GRADE) from pooled analyses showed a difference in overall WOMAC favoring PRP injection compared to HA at 1 (MD -2.62

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
PubMed, Cochrane Library, Scopus, Embase, Web of Science, and gray literature	intraarticular treatments for knee osteoarthritis		Pain WOMAC (all scales) VAS Averse events Complications Pain Swelling				(95% CI -3.47 to -1.77)), 3 (MD -4.59 (95% CI -8.91 to -0.26), 6 (MD -7.13 (95% CI -9.57 to -4.68)), and 12 months (MD -11.34 (95% CI -14.78 to -7.91)). Low to moderate quality evidence (GRADE) from pooled analyses showed a difference in WOMAC favoring PRP injection compared to HA at 3 (MD -0.39 (95% CI -0.64 to -0.15), 6 (MD -0.28 (95% CI -0.52 to -0.03)), and 12 months (MD -0.76 (95% CI -1.10 to -0.41)), but not 1 month (MD -0.08 (95% CI -0.33 to 0.17)). Very low to low quality evidence (GRADE) from pooled analyses showed a difference in WOMAC function favoring PRP injection compared to HA at 1 (MD -3.60 (95% CI -7.12 to -0.08)), 3 (MD -3.41 (95% CI -6.17 to -0.64)), 6 (MD -3.49 (95% CI -5.21 to -1.77), and 12 months (MD -8.89 (95% CI -11.87 to -5.91)). Very low to low quality evidence (GRADE) from pooled analyses showed no difference in IKDC between PRP injection and HA at 6 (MD 4.09 (95% CI -1.82 to

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							10.00)) or 12 months (MD 4.61 (95% CI -2.68 to 11.90)). <u>Pain</u> Low to moderate quality evidence (GRADE) from pooled analyses showed a difference in WOMAC pain favoring PRP injection compared to HA at 6 (MD -1.33 (95% CI -2.09 to -0.56)) and 12 months (-2.05 (95% CI -2.85 to -1.25)), but not 1 (MD -0.08 (95% CI -0.44 to 0.29)) or 3 months (-0.86 (95% CI -2.09 to 0.38)). Moderate quality evidence (GRADE) from pooled analyses showed a difference in VAS pain favoring PRP injection compared to HA at 6 (MD -0.59 (95% CI -1.07 to -0.12)) and 12 months (MD -1.21 (95% CI -1.91 to -0.50)), but not 1 (MD -0.21 (95% CI -0.67 to 0.26)) or 3 months (MD -0.17 (95% CI -0.70 to 0.35)). <u>Adverse Events</u> Pooled analyses (GRADE NR) showed no difference between PRP injection and HA for any complications (RR 1.32 (95% CI 0.84 to 2.07)), pain events (RR 1.23 (95% CI

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							0.72 to 2.12)), or swelling (RR 1.16 (95% CI 0.43 to 3.10)).
Tan (2021) 1950 to 2019 Medline, Allied and Complementary Medicine, Embase, CINHAL, Cochrane Library, China National Knowledge Infrastructure, Scopus, Biomed Central.	To compare effectiveness and safety of PRP and HA in patients with adult knee osteoarthritis.	Knee osteoarthritis	<u>Function</u> WOMAC (all scales) IKDC KOOS <u>Pain</u> WOMAC pain KOOS IKDC VAS EQ-VAS <u>QoL</u> KOOS <u>Adverse Events</u> Any AE	26 RCTs	Yes (Cochrane)	Yes	<u>Function</u> Pooled analyses (LoE NR‡) showed a difference in total WOMAC score favoring PRP injection compared to HA at 3 (MD -5.04 (95% CI -8.82 to -1.26)), 6 (MD -8.52 (95% CI -11.17 to -5.87)), and 12 months (MD -10.52 (95% CI -13.77 to -7.27)), but not at 1 month (MD -3.81 (95% CI -7.98 to 0.36)). Pooled analyses (LoE NR‡) showed a difference in WOMAC function favoring PRP injection compared to HA at 3 (MD -1.90 (95% CI -2.54 to -1.26)), 6 (MD -3.15 (95% CI -4.95 to -1.35)), and 12 months (MD -7.32 (95% CI -9.98 to -4.66)), but not at 1 month (MD -2.35 (95% CI -5.28 to 0.57)). Pooled analyses (LoE NR‡) showed a difference in IKDC scores favoring PRP injection compared to HA at 6 (MD 7.67 (95% CI 3.91 to 11.43)) and 12 months (MD

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							5.70 (95% CI 0.98 to 10.42)), but not at 1 (MD 0.04 (95% CI -7.70 to 7.78)) or 3 month (MD 3.727 (95% CI -0.21 to 6.75)). Pooled analyses (LoE NR‡) showed no difference in KOOS scores between PRP injection and HA at 1 (), 3 (), 6 (), or 12 months (). Pooled analyses (LoE NR‡) showed no difference in KOOS ADL scores between PRP injection and HA at 2 (MD -1.26 (95% CI -8.16 to 5.64)), 6 (MD 1.12 (95% CI -3.24 to 5.47)), or 12 months (MD 0.22 (95% CI -4.38 to 4.83)). Pooled analyses (LoE NR‡) showed no difference in KOOS sports scores between PRP injection and HA at 2 (MD -0.71 (95% CI -11.54 to 10.12)), 6 (MD 4.32 (95% CI -2.13 to 10.77)), or 12 months (MD 2.17 (95% CI -4.31 to 8.65)). <u>Pain</u> Pooled analyses (LoE NR‡) showed a difference in WOMAC pain favoring PRP injection compared to HA at 6 (MD -1.17 (95% CI -1.99 to -0.35)) and 12 months

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							(MD -1.62 (95% CI -2.26 to -0.98)), but not at 1 (MD -0.03 (95% CI -0.42 to 0.35)) or 3 months (MD 0.03 (95% CI -0.31 to 0.38)). Pooled analyses (LoE NR‡) showed a difference in VAS pain favoring PRP injection compared to HA at 3 (MD -0.54 (95% CI -1.03 to -0.05)), 6 (MD -0.77 (95% CI -1.24 to -0.29)), and 12 months (MD -0.99 (95% CI -1.54 to -0.45)), but not at 1 month (MD 0.01 (95% CI -0.13 to 0.15)). Pooled analyses (LoE NR‡) showed a difference in EQ-VAS scores favoring PRP injection compared to HA at 6 (MD 6.22 (95% CI 1.72 to 10.72)) and 12 months (MD 4.64 (95% CI 1.86 to 7.42)), but not at 2 months (MD 4.32 (95% CI -0.09 to 8.73)). Pooled analyses (LoE NR‡) showed no difference in KOOS pain scores between PRP injection and HA at 2 (MD -0.20 (95% CI -4.31 to 3.91)), 6 (MD 0.30 (95% CI -3.97 to 4.57)), or 12 months (MD -0.32 (95% CI -4.73 to 4.10)). <u>QoL</u>

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							Pooled analyses (LoE NR‡) showed no difference in KOOS QoL scores between PRP injection and HA at 2 (MD 0.06 (95% CI -4.97 to 5.09)), 6 (MD -0.63 (95% CI -6.02 to 4.76)), or 12 months (MD 0.42 (95% CI -5.15 to 5.99)). <u>Adverse Events</u> Pooled analyses (LoE NR‡) showed no difference between PRP injection and HA for any AE (RR 1.21 (95% CI 0.95 to 1.54)) <u>Subgroup analyses</u> Pooled analyses (LoE NR‡) showed no difference between PRP injection and HA when stratified by dose (<5 mL vs. ≥5 mL), type (fresh vs frozen), time (1 vs 2 vs 2+ times), and grade of OA. Data and further details were NR.
Kim (2022) Inception to March 2021 Medline, Embase	To provide clinical evidence regarding the efficacy and safety of intra-articular injection of PRPs in patients with knee	Knee osteoarthritis	<u>Function</u> WOMAC Total <u>Pain</u> VAS <u>Adverse events</u>	21 RCTs	Yes (Cochrane)	Yes	<u>Adverse events</u> Fair to good quality evidence (MCMS§) from pooled analyses showed no difference in procedure-related knee pain or swelling between PRP injection and HA (OR 1.68 (95% CI 0.93 to 3.09)). <u>Subgroup analyses</u> Function

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
	osteoarthritis based on leukocyte concentration the number of injection.		Procedure-related knee pain Swelling				Fair to good quality evidence (MCMS[§]) from pooled analyses showed a difference in function favoring LP-PRP injection compared to HA at 6 (MD 9.42 (95% CI 3.10 to 15.74)) and 12 months (MD 12.36 (95% CI 7.74 to 16.99)), but not at 3 months (MD 6.73 (95% CI -1.95 to 15.42)). Fair to good quality evidence (MCMS[§]) from pooled analyses showed a difference in function favoring LR-PRP injection compared to HA at 3 (MD 4.03 (95% CI 1.27 to 6.79)), 6 (MD 6.98 (95% CI 3.13 to 10.84)) and 12 months (MD 12.40 (95% CI 5.38 to 19.43)). Fair to good quality evidence (MCMS[§]) from pooled analyses showed a difference in pain favoring single PRP injection compared to HA at 3 (MD 4.38 (95% CI 0.14 to 8.62)), 6 (MD 4.57 (95% CI 0.42 to 8.73)) and 12 months (MD 9.52 (95% CI 1.33 to 17.70)). Fair to good quality evidence (MCMS[§]) from pooled analyses showed a difference in pain favoring multiple PRP injection compared to HA at 3 (MD 5.97 (95% CI

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							2.17 to 9.77)), 6 (MD 10.77 (95% CI 4.98 to 16.55)) and 12 months (MD 13.58 (95% CI 7.64 to 19.51)). VAS pain Fair to good quality evidence (MCMS§) from pooled analyses showed a difference in pain favoring LP-PRP injection compared to HA at 6 (MD 6.21 (95% CI 2.42 to 9.99)) and 12 months (MD 8.18 (95% CI 2.90 to 13.46)), but not at 3 months (MD 5.64 (-1.51 to 12.78)). Fair to good quality evidence (MCMS§) from pooled analyses showed a difference in pain favoring LR-PRP injection compared to HA at 6 (MD 8.14 (95% CI 3.00 to 13.29)) and 12 months (MD 17.49 (95% CI 7.20 to 27.78)), but not at 3 months (MD 5.85 (95% CI -0.89 to 12.58)). Fair to good quality evidence (MCMS§) from pooled analyses showed a difference in pain favoring single PRP injection compared to HA at 12 months (MD 20.79 (95% CI 4.30 to 37.29)), but not at 3 (MD

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							15.51 (95% CI -13.87 to 44.89)) or 6 months (MD 5.61 (95% CI -0.18 to 11.39)). Fair to good quality evidence (MCMS§) from pooled analyses showed a difference in pain favoring multiple PRP injection compared to HA at 6 (7.48 (95% CI 2.11 to 12.85)) and 12 months (MD 8.49 (95% CI 4.25 to 12.72)), but not at 3 months (MD 2.17 (95% CI -3.41 to 7.75)). Adverse events Fair to good quality evidence (MCMS§) from pooled analyses showed a difference in procedure-related knee pain or swelling between LR-PRP injection and HA (OR 3.32 (95% CI 1.07 to 10.25)), but not LP-PRP (OR 1.33 (95% CI 0.71 to 2.48)), single PRP injection (OR 1.63 (95% CI 0.53 to 5.00)), or multiple PRP injection (OR 1.82 (95% CI 0.81 to 4.07)).
PRP vs. placebo							
Costa (2022) 1974 to January 2021	Assess benefits and harms of PRP compared to other non-	Knee osteoarthritis	Function* WOMAC Total IKDC KOOS ADL	7 RCTs	Yes (Cochrane)	Yes	Function Very low to low quality evidence (GRADE) from pooled analyses showed a difference in function favoring PRP injection

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
Medline, Embase, Scopus	surgical methods for treatment of knee osteoarthritis.		Pain* WOMAC Pain VAS KOOS pain				compared to placebo at <3 (MD -0.37 (95% CI -0.66 to -0.09)), 6 (MD -1.57 (95% CI -2.40 to -0.74)), and >6 months (MD -1.11 (95% CI -1.67 to -0.56)). Pain Very low to low quality evidence (GRADE) from pooled analyses showed a difference in pain favoring PRP injection compared to placebo at 6 months (MD -1.54 (95% CI -2.22 to -0.86)), but not <3 months (MD -0.48 (95% CI -1.16 to 0.20)). Pain was not reported at >6 months. Subgroup analyses Very low to low quality evidence (GRADE) from pooled analyses showed a difference in function and pain favoring PRP injection compared to HA when grouped by molecular weight. All other subgroups showed no difference.
Filardo (2021) No limits (search January 17, 2020)	To evaluate effectiveness of PRP compared to placebo and other intraarticular treatments for	Knee osteoarthritis	Function WOMAC (all scales) Pain WOMAC pain VAS pain	8 RCTs	Yes (Cochrane)	Yes	Function Low quality evidence (GRADE) from pooled analyses a difference in overall WOMAC favoring PRP injection compared to placebo at 12 months (MD -19.4 (95% CI -36.0 to -2.72)), but not 1 (MD -6.50 (95% CI -14.40 to 1.50)), 3 (MD -10.70 (95% CI -

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
Medline, Cochrane Library, Scopus, Embase, Web of Science, and gray literature	knee osteoarthritis						23.70 to 2.30)), or 6 months (MD -12.5 (95% CI -25.70 to 0.69)). Low quality evidence (GRADE) from pooled analyses showed a difference in WOMAC stiffness favoring PRP injection compared to placebo at 3 (MD -0.90 (95% CI -1.30 to -0.50)) and 6 months (MD -1.30 (95% CI -2.60 to -0.10)), but not 1 month (MD -0.60 (95% CI -1.80 to 0.70)). Low quality evidence (GRADE) from pooled analyses showed no difference in WOMAC function between PRP injection and placebo at 1 (MD -4.40 (95% CI -11.50 to 2.60)) 3 (MD -6.80 (95% CI -16.90 to 3.30) or 6 months (MD -8.00 (95% CI -18.60 to 2.50)). <u>Pain</u> Low to moderate quality evidence (GRADE) from pooled analyses showed a difference in WOMAC pain favoring PRP injection compared to placebo at 3 (MD -3.00 (95% CI -5.70 to -0.30)) and 6 months (MD -3.10 (95% CI -5.50 to -0.70)), but not at 1 month (MD -1.70 (95% CI -3.90 to 0.60)).

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							Low quality evidence (GRADE) from pooled analyses showed a difference in VAS pain favoring PRP injection compared to placebo at 1 (MD -1.50 (95% CI -2.10 to -0.80)) and 6 months (MD -1.90 (95% CI -2.70 to -1.10)). Adverse Events Pooled analyses (GRADE NR) showed no difference between PRP injection and placebo for any AEs (RR 1.69 (95% CI 0.58 to 4.90)).
PRP vs. steroid							
Costa (2022) 1974 to January 2021 Medline, Embase, Scopus	Assess benefits and harms of PRP compared to other non-surgical methods for treatment of knee osteoarthritis	Knee osteoarthritis	Function* WOMAC Total IKDC KOOS ADL Pain* WOMAC Pain VAS KOOS pain	7 RCTs	Yes (Cochrane)	Yes	Function Very low to low quality evidence (GRADE) from pooled analyses showed a difference in function favoring PRP injection compared to corticosteroids at 6 (MD -1.37 (95% CI -2.10 to -0.63)) and >6 months (MD -1.84 (95% CI -2.72 to -0.97)), but not at <3 months (MD -0.25 (95% CI -1.19 to 0.69)). Pain Very low to low quality evidence (GRADE) from pooled analyses showed a difference

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							in pain favoring PRP injection compared to corticosteroids at 6 months (MD -1.34 (95% CI -1.93 to -0.75)), but not at <3 (MD 0.00 (95% CI -0.49 to 0.49)) or >6 months (MD -0.54 (95% CI -1.90 to 0.83)). <u>Subgroup analyses</u> Very low to low quality evidence (GRADE) showed a difference favoring PRP injection compared to HA for all subgroups (1 vs ≥2 injections, fresh vs frozen, concentration of platelets) other than LR-PRP on function.
Filardo (2021) No limits (search January 17, 2020) PubMed, Cochrane Library, Scopus, Embase, Web of Science, and gray literature	To evaluate effectiveness of PRP compared to placebo and other intraarticular treatments for knee osteoarthritis	Knee osteoarthritis	<u>Function</u> KOOS (all scales) <u>Pain</u> VAS KOOS (all scales) <u>QoL</u> KOOS QoL	6 RCTs	Yes (Cochrane)	Yes	<u>Function</u> Low quality evidence (GRADE) from pooled analyses showed a difference in KOOS ADL pain favoring PRP injection compared to steroids at 6 months (MD 15.51 (95% CI 9.71 to 21.31)). Low quality evidence (GRADE) from pooled analyses showed no difference in KOOS sports between PRP injection and steroid at 6 months (MD 5.86 (95% CI -4.77 to 16.49)). <u>Pain</u>

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							Moderate quality evidence (GRADE) from pooled analyses showed a difference in VAS pain favoring PRP injection compared to steroids at 6 months (MD -2.03 (95% CI -2.38 to -1.67)). Very low-quality evidence (GRADE) from pooled analyses showed a difference in KOOS pain favoring PRP injection compared to steroids at 6 months (MD 15.23 (95% CI 6.10 to 24.36)) <u>QoL</u> Low quality evidence (GRADE) from pooled analyses showed a difference in KOOS QoL favoring PRP injections compared to steroids at 6 months (MD 10.91 (95% CI 6.88 to 14.94)).
PRP vs. exercise							
Costa (2022) 1974 to January 2021 Medline, Embase, Scopus	Assess benefits and harms of PRP compared to other non-surgical methods for treatment of	Knee osteoarthritis	<u>Function*</u> WOMAC Total IKDC KOOS ADL <u>Pain*</u> WOMAC Pain VAS	5 RCTs	Yes (Cochrane)	Yes	<u>Function</u> Very low to low quality evidence (GRADE) from pooled analyses showed a difference in function favoring PRP injection compared to exercise at <3 months (MD -3.11 (95% CI -3.74 to -2.48)), but not at 6 (MD -2.07 (95% CI -4.37 to 0.24)) or >6 months (MD -0.25 (95% CI -0.85 to 0.36)).

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
	knee osteoarthritis		KOOS pain				Pain Very low to low quality evidence (GRADE) from pooled analyses showed a difference in pain favoring PRP injection compared to exercise at <3 (MD -1.96 (95% CI -2.47 to -1.44)), 6 (MD -1.60 (95% CI -2.73 to -0.46)), and >6 months (MD -0.06 (95% CI -0.67 to -0.54)).
PRP vs. pharm							
Costa (2022) 1974 to January 2021 Medline, Embase, Scopus	Assess benefits and harms of PRP compared to other non-surgical methods for treatment of knee osteoarthritis	Knee osteoarthritis	Function* WOMAC Total IKDC KOOS ADL Pain* WOMAC Pain VAS KOOS pain	2 RCTs	Yes (Cochrane)	Yes	Function Very low to low quality evidence (GRADE) from pooled analyses showed a difference in function favoring PRP injection to pharmacological agents at 6 (MD -9.05 (95% CI -9.58 to -8.51)) and >6 months (MD -8.27 (-8.81 to -7.73)). Function was not reported at <3 months. Pain Very low to low quality evidence (GRADE) from pooled analyses showed a difference in pain favoring PRP injection to pharmacological agents at 6 (MD -1.11 (95% CI -1.44 to -0.79)) and >6 months

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							(MD -0.88 (95% CI -1.16 to -0.60)). Pain was not reported at <3 months.
PRP vs. prolotherapy							
Filardo (2021) No limits (search January 17, 2020) PubMed, Cochrane Library, Scopus, Embase, Web of Science, and gray literature	To evaluate effectiveness of PRP compared to placebo and other intraarticular treatments for knee osteoarthritis	Knee osteoarthritis	<u>Function</u> NR <u>Pain</u> NR	1 RCT	Yes (Cochrane)	Yes	<u>Function</u> Low quality evidence (GRADE) from 1 RCT showed a difference in function favoring PRP injection compared to dextrose (MD NR). <u>Pain</u> Low quality evidence (GRADE) from 1 RCT showed a difference in pain favoring PRP injection compared to dextrose (MD NR).
PRP vs. multiple comparisons							
Vilchez-Cavazos[**] (2022) Inception to February to 2021	To evaluate whether PRP is as effective in patients with early-moderate knee osteoarthritis compared to	Knee osteoarthritis	<u>Function</u> WOMAC (all scores) IDK KOOS <u>Pain</u> VAS Pain	31 RCTs	Yes (Cochrane)	Yes	<u>Functions</u> Pooled analyses (LoE NR[††]) showed a difference in function favoring PRP injection to other intra-articular injections (MD -1.00 (95% CI -1.33 to -0.66)). <u>Pain</u>

SR, Search dates	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
Medline, Embase, Scopus, Web of Science	end-stage osteoarthritis subjects.						Pooled analyses (LoE NR^{++}) showed a difference in pain favoring PRP injection to other intra-articular injections (MD -1.05 (95% CI -1.41 to -0.68)). <u>Subgroup analyses</u> Function Pooled analyses (LoE NR^{++}) showed a difference in function favoring PRP injection compared to other intra-articular injections in patients with KL 1-2 (MD -0.83 (95% CI -2.35 to -0.14)), 1-3 (MD -0.83 (95% CI -1.19 to -0.47)), and 1-4 (MD -1.36 (95% CI -2.38 to -0.35) knee OA. Pain Pooled analyses (LoE NR^{++}) showed a difference in pain favoring PRP injection compared to other intra-articular injections in patients with KL 1-3 (MD -1.20 (95% CI -1.64 to -0.76)) and 1-4 knee OA (MD -1.15 (95% CI -1.55 to -0.75)), but not in patients with KL 1-2 (MD – 0.63 (95% CI -1.62 to 0.36)) knee OA.

ADL = activities of daily living; AE = adverse event; CI = confidence interval; EQ-VAS = EuroQol-visual analogue scales; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HA: hyaluronic acid; IKDC: International Knee Documentation Committee; KL = Kellgren-Lawrence; KOOS: Knee Injury and Osteoarthritis Outcome Score; LoE = level of evidence; LP-PRP = leukocyte poor platelet rich plasma; LR-PRP leukocyte rich platelet rich plasma; MCMS = Modified Coleman Methodology Score; MD = mean difference; NR = not reported; OA = osteoarthritis; OR = odds ratio; PRP: platelet-rich plasma; QoL = quality of life; RCT = randomized control trial; VAS: visual analog scales; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

* Costa 2022 reports that because not all studies used the same instrument, they used a hierarchy for assessing each outcome of interest for the purpose of pooling data. For pain: WOMAC pain, VAS, and then KOOS pain. For function: WOMAC total, IKDC, and then KOOS ADL.

† Meta-analyses only included double-blind RCTs.

‡ Authors evaluated individual studies using a modification of the generic evaluation tool used by the Cochrane Bone, Joint and Muscle Trauma Group, but do not provide level of evidence for each outcome or pooled analyses.

§ Authors used the Modified Coleman Methodology Score, where studies are graded from 0-100 with the grade as follows: >85: excellent; 70-84: good; 55-69: fair; ≤54: poor.

** Vilchez-Cavazos 2022 does not compare PRP to individual controls, but instead pools all comparisons (including bone marrow aspirate concentrate, HA, NSAIDs, ozone, steroids, placebo, different molecular weights of PRP, peptide, dextrose, and prolotherapy) in order to assess subgroups of Kellgren-Lawrence grade.

†† Authors did not assess quality of evidence.

2.7 Medicare and Representative Private Insurer Coverage Policies

Table 4. Coverage Policies for IAHA

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Centers for Medicare Services (CMS) via Novitas Solutions, Inc. LCD - Hyaluronan Acid Therapies for Osteoarthritis of the Knee (L35427) Last review: 10/1/2019 Next review: NR	NR	NR	Viscosupplementation therapy for the knee via intra-articular injections of hyaluronic preparations will be considered medically reasonable and necessary when ALL of the following conditions are met: The patient is symptomatic. Such symptoms may include pain which interferes with the activities of daily living such as ambulation and prolonged standing, or pain interrupting sleep, crepitus, and/or knee stiffness. The clinical diagnosis is supported by radiologic evidence of osteoarthritis of the knee such as joint space narrowing, subchondral sclerosis, osteophytes and sub-chondral cysts. If appropriate, other diagnoses have been excluded by appropriate evaluation and management services, laboratory and imaging studies (i.e., the pain and functional disability is not considered likely to be due to a diagnosis other than osteoarthritis of the knee). The patient has failed at least three months of conservative therapy. Conservative therapy is defined as: Nonpharmacologic therapy (such as but not limited to home exercise program, education, weight loss, physical therapy if indicated); and if not	NR

			contraindicated, simple analgesics and (e.g., acetaminophen) or NSAIDS per hyaluronan product prescribing information. The patient has failed to respond to aspiration of the knee when effusion is present and intra-articular corticosteroid injection therapy when inflammation is a significant component of the patient's symptoms and intra-articular corticosteroids are not contraindicated. A repeat series* of hyaluronan knee injection(s) for patients who have responded to a prior series is considered to be reasonable and necessary under the following circumstances: Symptoms have recurred and at least six months have elapsed since the prior series of injections and there was significant improvement in pain and functional capacity achieved with the prior series of injections using a standardized assessment tool or there is significant reduction in the doses of NSAID medications taken or reduction in the number of intra-articular steroid injections to the knees during the six-month period following the injection(s).	
Cigna Intraarticular Hyaluronic Acid Derivatives (IP0322) Last review: 1/1/2023 Next review: 1/1/2024	NR	Yes	Intraarticular Hyaluronic Acid products are considered medically necessary when the following are met: Intraarticular Hyaluronic Acid products are considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response, including the following: At least 6 months have lapsed since the completion of the prior treatment course	

United Healthcare Sodium Hyaluronate (2022D0081G) Last review: 7/1/2022 Next review: NR			Intra-articular injections of sodium hyaluronate are proven and medically necessary when all of the following are met: Diagnosis of knee osteoarthritis; and The member has not responded adequately to conservative therapy which may include physical therapy or pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen and/or topical capsaicin cream) or injection of intra-articular steroids and such therapy has not resulted in functional improvement after at least 3 months, or the member is unable to tolerate conservative therapy because of adverse side effects; and The member reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); and The pain is attributed to degenerative joint disease/primary osteoarthritis of the knee; and There are no contraindications to the injections (e.g., active joint infection, bleeding disorder); and Dosing is in accordance with the US FDA approved labeling as shown in the table below; and Initial authorization is for a single treatment course once per joint for 6 months (see table below) Repeated courses of intra-articular hyaluronan injections may be considered when all the following are met:	Gel-One, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz, Synojoynt, Synvisc or Synvisc-One, Triluron, TriVisc, and Visco-3 are typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan. Coverage for Durolane, Euflexxa, and Gelsyn-3 is contingent on criteria in the Diagnosis-Specific Criteria section. Prior authorization is not required.

			Diagnosis of knee osteoarthritis; and Documentation of positive clinical response to therapy (e.g., significant pain relief was achieved with the prior course of injections); and Pain has recurred; and At least 6 months have passed since the prior course of treatment for the respective joint; and Dosing is in accordance with the US FDA approved labeling as shown in the table below; and Continuing authorization is for a single treatment course once per joint for 6 months (see table below). Intra-articular injections of sodium hyaluronate are unproven and not medically necessary for treating any other indication due to insufficient evidence of efficacy including, but not limited to the following: Hip osteoarthritis, Temporomandibular joint osteoarthritis, Temporomandibular joint disc displacement	

LCD = Local coverage determination, NR = Not reported, NSAID = Non-steroidal anti-inflammatory drug, US FDA = United States Food and Drug Administration

Table 5. Coverage Policies for IA-PRP

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Centers for Medicare Services (CMS) National Coverage Determination (NCD) for Blood-Derived Products for Chronic Non-Healing Wounds (270.3) Last review: NR Next review: NR	NR	NR	The Centers for Medicare and Medicaid Services has determined that PRP – an autologous blood-derived product – will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when (certain) conditions are met.	NR
Centers for Medicare Services (CMS) via Noridian Healthcare Solutions Local Coverage Determination (LCD) for Platelet-Rich Plasma Injections for Non-Wound Injections (L39060) Last review: 02/15/2023 Next review: NR	NR	NR	Noridian Healthcare Solutions considers PRP injection and PRP combined with stem cells for musculoskeletal injuries and/or joint conditions, whether primary or adjunctive use, not medically reasonable and necessary	PRP is a general term describing a therapy with no gold standard of preparation or administration technique. This heterogeneity and the small number of controlled trials make it difficult to assess the efficacy of PRP for any disorder. There is a lack of standardization of the preparations of PRP amongst the trials, with varying concentrations of platelet, frozen vs. fresh preparations, and the filtration of white cells. While the body of evidence of utility for PRP is large, the overall quality of evidence is low. The studies are relatively small, observational studies, often confounded by lack of treatment control, precluding cause-and-effect conclusions. RCTs that compare outcomes in patients whose treatment is standardized are needed

				to determine definitive patient selection criteria and clinical utility.
Cigna Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP]) (0507) Last review: 10/15/2022 Next review: 10/15/2023	NR	Yes	The use of autologous platelet-derived growth factors (CPT® Code 0232T; HCPCS Codes G0460, S9055) for ANY condition or indication, including the following, is considered experimental, investigational, or unproven	There is insufficient evidence to support the use of PRP for any indication including in combination with other substances
United Healthcare Prolotherapy and Platelet Rich Plasma Therapies (2022T0498V) Last review: 1/1/2022 Next review: NR	NR	Yes	Due to insufficient evidence of efficacy, the following are unproven and not medically necessary for any condition or indication	While some available studies are promising, the majority of evidence on platelet-derived blood or plasma therapies compared to other standard treatment is highly variable with regard to efficacy or improved health outcomes for a wide range of conditions. Higher quality studies with longer follow up as well as standardization of best practices are needed to determine the benefit of this technology

NR = Not reported, PRP = Platelet-rich plasma, RCT = Randomized controlled trial

3 The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the effectiveness and safety of HA and PRP for primary treatment of knee or hip osteoarthritis compared with placebo/sham, no treatment, common conventional treatment options, arthroscopic lavage and/or debridement, prolotherapy, corticosteroid injection in symptomatic adults. The differential effectiveness and safety of these therapies for subpopulations was evaluated, as was the cost effectiveness.

3.1.2 Key Questions

1. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with hyaluronic acid/viscosupplementation (HA)**
    a. What is the effectiveness of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment in the short and longer-term?
    b. What is the evidence regarding short- and long-term harms and complications of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment?
    c. Is there evidence of differential efficacy, effectiveness, or safety of HA compared with placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), PRP, or no treatment by factors such as age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?
    d. What is the evidence of cost-effectiveness of HA compared with placebo/sham, PRP, common conservative treatments, or no treatment?
2. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with platelet-rich plasma (PRP)**
    a. What is the effectiveness of PRP compared with placebo/sham, common conservative treatments, treatments other than HA, or no treatment in the short and longer-term?
    b. What is the evidence regarding short- and longer-term harms and complications of PRP compared placebo/sham, common conservative treatments, treatments other than HA, or no treatment?
    c. Is there evidence of differential efficacy, effectiveness, or safety of PRP compared with, placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), treatments other than HA, or no treatment by factors such age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?
    d. What is the evidence of cost-effectiveness of PRP compared with placebo/sham, common conservative treatments, or no treatment?

3.1.3 Inclusion/Exclusion Criteria

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. Public comments as well as those from clinical experts and peer-reviewers were considered for finalization of this report. See Table 6 below for inclusion and exclusion criteria.

Table 6. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Adults with symptomatic knee or hip osteoarthritis Subpopulations based on patient characteristics, primary or secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options	• Conditions other than knee or hip OA • Patients <18 years old • Asymptomatic individuals
Intervention	Autologous PRP injection(s) or hyaluronic acid (HA) (viscosupplementation) injection(s) used as the primary intervention or in conjunction with common conservative care options	• Non-FDA-approved HA (viscosupplementation) formulations; products undergoing phase III trials may be considered • PRP or HA used in conjunction with another intervention not listed for inclusion (e.g., open, arthroscopic or minimally invasive surgery, invasive procedures, mannitol and similar combinations are not included) • Cellular matrix • Combinations of HA with PRP together • Other biologics (growth factor injections [., plasma rich in growth factor], "stem cell" injections, etc.)
Comparator	• Common conservative treatment(s) (e.g., NSAIDs, oral pain medications, exercise, physical therapy, weight loss) which may be included in usual care • Arthroscopic lavage and/or debridement • Prolotherapy • Corticosteroid injection • Placebo or sham • No treatment	• Combinations of HA with PRP together • Other biologics (growth factor injections [e.g., plasma rich in growth factor], bone marrow aspirate/bone marrow aspirate concentrate, blood plasma, autologous blood products [e.g., autologous conditioned serum"] medicinal signaling cells, mesenchymal stem cells, "stem cell", adipose, fat, or microfat injections); peptide injections • Ozone treatment • Non-FDA approved treatments • Herbal treatments • Acupuncture • Nerve ablation

Study Component	Inclusion	Exclusion
Outcomes	**Primary** • Function • Pain • Need for secondary invasive procedures (e.g., surgery) • Adverse events or harms **Secondary** • Symptom Recurrence (e.g., persistent or increased pain, reduced function) resulting in need for additional injection of HA or PRP within 2 months after protocol completion • Quality of life • Medication use • Return to normal activities (sports, work, or activity level) **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome	• Non-clinical outcomes • Non-validated measures (e.g., for pain, function, QOL)
Timing	Review will focus on persistence of relief 1 or more months post-treatment	
Study design	**Focus will be on studies with the least potential for bias with ≥ 1 month post treatment results** **Key Questions 1 and 2 parts a and b:** • High quality systematic reviews of RCTs will be considered if available and they address the key questions. • Randomized controlled trials (RCTs) • In the absence of RCTs, high quality non-randomized comparative studies will be considered in the absence of RCTs with a focus on comparative prospective studies **Key Question 1b and 2b:** • KQ2: In the absence of RCTs, high-quality non-randomized studies designed specifically to evaluate harms/adverse events that are rare or occur long-term **Key Question 1c and 2c:** • RCTs which present results for both intervention and comparator such that	• Indirect comparisons • Comparisons with historical cohorts • Noncomparative studies (case series, single arm studies, pre-post) • Nonrandomized studies which do not control for confounding • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients per treatment group • Case reports • Studies in which <80% of patients have a condition of interest • Studies that do not report on primary outcomes or harms

Study Component	Inclusion	Exclusion
	they are stratified on patient or other characteristics of interest and test for interaction. **Key Question 1d and 2d:** Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)	• Abstracts, conference proceedings, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

FDA = United States Food and Drug Administration, HA = Hyaluronic acid, NSAID = Non-steroidal anti-inflammatory drug, OA = Osteoarthritis, PRP = Platelet-rich plasma, QoL = Quality of life, RCT = Randomized controlled trial, SSED = Summary of safety and effectiveness data

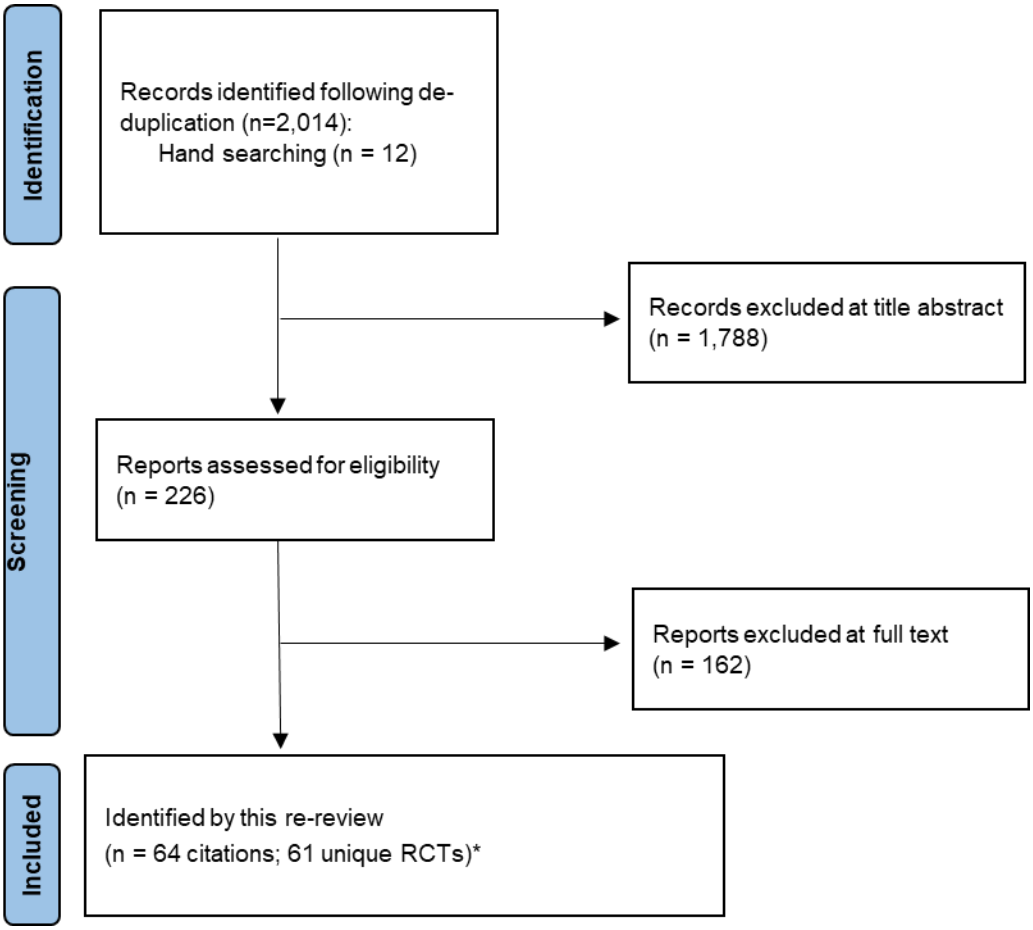
3.1.4 Data Sources and Search Strategy

We searched electronic databases from January 1, 2013 to December 31, 2022 for trials related to HA and from January 1, 2015 to December 31, 2022 for trials related to PRP to identify publications evaluating these treatments for knee and hip OA that had been published since the prior reports. The start dates of our searches overlapped by a few months with the end date of the searches in the prior reports. For Hip OA, since it was not part of the scope of the prior HA report, we re-ran the searches specific to hip OA without limitations. A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (see Appendix B for full search strategy) to identify relevant peer reviewed literature as well as other sources (ClinicalTrials.gov, ECRI Guidelines Trust, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The process involves four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography review. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic

evaluations. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the review and selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary, adjudicated by a third investigator. See Figure 1 below for a flow diagram of the search results. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report.

Figure 1. Flow of studies diagram



RCT = Randomized controlled trial

3.1.5 Data Extraction

Reviewers extracted the following data from the clinical studies: study design, setting, country, source of funding, sample size, inclusion and exclusion criteria, study population characteristics, follow-up time, PRP and HA injection regimens, doses, and preparation details, study outcomes and adverse events. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting data from the same study. Detailed study and patient characteristics and results are available in Appendix G.

3.1.6 Quality Assessment: Risk of Bias (RoB), Overall Strength of Evidence (SOE), and QHES evaluation

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria[151] based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[66] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[3] In keeping with the AHRQ methods, each study was given a final rating of "good", "fair", or "poor" quality as described below. Discrepancies in ratings between reviewers were resolved through discussion and consensus. Criteria are detailed in Appendix D.

Table 7. Criteria for grading the quality of individual studies

Rating	Description and Criteria
Good	• Low risk of bias; study results generally considered valid • Employed valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics/key risk factors for testing groups being compared; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinded outcomes assessment); and use appropriate analytic methods (e.g., intention-to-test analysis); full reporting on pre-specified outcomes. • For studies of testing, pre-specification of thresholds for a positive test,
Fair	• Study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention or test delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[96] Based on these quality criteria, each comparative study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating; details of each rating are available in Appendix E. Individual reliability studies were assessed as described in Appendix D. Individual studies for diagnostic accuracy were not assessed.

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[12,57,58] as outlined by the Agency for

Healthcare Research and Quality (AHRQ).[3] The strength of evidence was based on the highest quality evidence available for the primary outcomes.

In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[20,125] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Assessing the SOE for studies performing subgroup analysis for evaluation of differential effectiveness or safety requires additional considerations discussed below. Methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.7 Analysis

Evidence was summarized qualitatively and quantitatively. Risk ratio (RR) and 95% confidence intervals were used for dichotomous outcomes to evaluate the presence of an association between testing and the outcome. In the absence of adjusted effect size estimates, for dichotomous outcomes, crude risk ratios (RR) and 95% confidence intervals (CI) were calculated using either STATA 14.0[132] or Rothman Episheet.[1] For instances with fewer than five observations per cell, exact methods were employed. Where effect estimates that were adjusted for confounding were reported by study authors, they were preferred and reported. For continuous variables, mean differences (MD) and associated 95% CIs were calculated if the outcomes were reported using the same scale.

Meta-analyses were conducted as appropriate in order to summarize primary outcome data from multiple studies and to obtain more precise and accurate estimates using STATA 14.0.[132] Duration of follow up was categorized as short term (≤3 months), intermediate term (>3 to <12 months), and long term (≥12 months) and all meta-analyses were presented with data stratified by these timeframes. If a trial reported outcomes at multiple times within a follow-up category, the most common timeframe was used in the primary meta-analyses. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[65] To combine trials, we used a random effects model based on the profile likelihood method which provides a more conservative effect estimate; in the case of non-convergence with profile likelihood, the Der Simonian and Laird estimates were reported.[60] For continuous variables, differences in mean follow-up scores between treatments were analyzed to determine mean differences as an effect size. Methods for calculating the standard deviations and for imputing missing standard deviations followed the recommendations given in The Cochrane Handbook 7.7.[66] Where no events occurred in one arm of a study, a value of 0.50 was used for that arm in accordance with Cochrane methods. Studies in which no events occurred in either study arm did not contribute to effect estimates (0% weight) but were retained in some plots for visual effect and completeness. Sensitivity analyses were conducted excluding poor-quality studies, outlying data and clinically heterogeneous trials where there were sufficient data. We classified the magnitude of effects for continuous measures of pain and function using the same system as in prior AHRQ reviews on pain (Appendix J).[31-33,129,130] Effects below the threshold for small were categorized as no effect. Outcomes are detailed in the evidence tables in the appendices and/or the body of the report.

We did not conduct analyses to evaluate potential markers for publication bias given the substantial heterogeneity in study designs, treatment regimens and patient populations and small number of trials available for some analyses.[133]

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only RCTs that formally tested for interaction between subgroups were considered for Key Question 4. SOE for these studies is based on consideration of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, the hypothesized impact of a subgroup on the outcome/effect and sample size as evaluation of interaction requires greater sample size. Such analyses should be interpreted cautiously and consider the biologic plausibility of differential efficacy or safety. Such analyses are generally considered hypothesis generating, and additional confirmatory evidence should be sought.[99,138,153]

4 Results

4.1 Number of Studies Retained and Comparison with Prior Reports

From 2,014 unique citations identified from electronic database searches, hand searching and bibliography review of included studies, a total of 64 randomized controlled trials (RCTs) (in 67 publications) met our inclusion criteria: 61 RCTs (in 64 publications) in knee osteoarthritis (OA) and three RCTs in hip OA. Four studies (3 comparing PRP vs. placebo [saline][53,82,158] and one comparing PRP vs. exercise[108]) self-describe as RCTs; however, these trials randomized knee and for purposes of this report they are considered observational cohort studies (nonrandomized studies of interventions [NRSIs]) since the randomization was done to two knees within the same patient. Patient factors may influence outcomes for both treatments. Table 8 below provides an overview of trials by condition (knee or hip OA), intervention (hyaluronic acid [HA] or platelet rich plasma [PRP]) and comparator treatment and provides the funding source. The most common comparators for HA and PRP were placebo (saline), corticosteroids, oral analgesics, and exercise; in addition, several trials compared HA versus PRP. Over a third (37%) of the trials evaluating HA were funded by industry; none of the trials evaluating PRP received industry funding. In addition, eight formal cost-effectiveness analyses were included, four in U.S. settings[62,117,118,123] and four in non-U.S. settings[27,64,90,144]; all evaluated HA, with one comparing HA versus PRP, for primarily knee OA.

Comparison with 2016 Autologous Blood Injections (ABI) or PRP report

The evidence base for the prior PRP review included various musculoskeletal conditions that are not within the scope of this re-review. For the conditions of knee and hip OA only, a total of 11 RCTs were included (10 RCTs for knee OA and 1 RCT for hip OA). Of these 11 RCTs, six[8,49,55,100,109,111] in knee OA met the inclusion criteria for this re-review and were incorporated into the evidence (2 HA vs. PRP,[55,109] 1 HA vs. placebo [saline],[55] 2 PRP vs. placebo [saline],[55,100] 1 PRP vs. steroid,[49] 2 PRP vs. exercise[8,111] and 2 PRP single vs. PRP multiple injections[55,100]). The remaining four knee OA trials[29,47,124,149] and the sole hip OA trial[16] were excluded from this re-review because they used HA formulations/brands that are not FDA-approved or included interventions out of scope for this report (e.g., autologous conditioned serum, plasma rich in growth factors [PRGF]-Endorcet). Appendix C lists these (and all) studies excluded after full text review with reasons. No formal cost-effectiveness analyses that met inclusion criteria were identified.

Comparison with 2013 HA/Viscosupplementation re-review report

The 2013 report was a re-review of the original report published in 2010 and evaluated HA for knee OA only. The primary evidence base for the 2013 re-review included six systematic reviews (SRs) of RCTs or pseudo-randomized trials with meta-analyses (MAs), one of which was a review of six MAs.[13,14,37,113,119,122] In addition, four RCTs (5 publications) published after the SRs were included.[6,92,101,134,135] Most of the evidence evaluated the efficacy of HA (4 SRs representing a total of 81 generally placebo-controlled trials and >10,000 patients and 3 additional placebo-controlled RCTs); one SR compared HA with corticosteroid injections and one SR and one RCT compared different formulations of HA. Only one of the additional RCTs identified was included in this update report and compared HA with placebo (saline)[135]; reasons for exclusion of the other trials can be found in Appendix C. For cost effectiveness, four formal economic

evaluations summarized in the 2010 report were included and re-reviewed in the 2013 report; no new cost-effectiveness evaluations were identified for the 2013 report.

Table 8. Number of studies for each comparison of efficacy of HA and PRP for the treatment of Knee OA and Hip OA.

Comparisons	RCTs (publications)	Funding: No. RCTs (Publications)			
		Industry	Other*	None	NR
KNEE OA					
HA/Viscosupplementation					
HA vs. Placebo (Saline)	9 (12)[4,9,15,46,54,55,59,74,102,135,137,141]	7 (10)[4,9,46,54,59,74,102,135,137,141]	1[15]	1[55]	---
HA vs. PRP	11[24,36,55,77,83,87,107,109,126,143,154]	2[36,87]	4[83,107,143,154]	5[24,55,77,109,126]	---
HA vs. Corticosteroid	6[11,21,25,78,142,148]	1[78]	2[11,142]	3[21,25,148]	---
HA vs. NSAIDs	2[24,56]	---	---	2[24,56]	---
HA vs. Usual Care	1[63]	---	1[63]	---	---
HA vs. Exercise	1[120]	---	---	---	1[120]
HA vs. PT	1[115]	---	---	1[115]	---
HA vs. Prolotherapy	1[115]	---	---	1[115]	---
HA (HMW) vs. HA (LMW)	1[162]	1[162]	---	---	---
TOTAL: HA†	**30 (33)**[4,9,11,15,21,24,25,36,46,54-56,59,63,74,77,78,83,87,102,107,109,115,120,126,135,137,141-143,148,154,162]	**11 (14)**[4,9,36,46,54,59,74,78,87,102,135,137,141,162]	**8**[11,15,63,83,107,142,143,154]	**10**[21,24,25,55,56,77,109,115,126,148]	**1**[120]
PRP					
PRP vs. Placebo (Saline)‡	12[19,35,41,43,53,55,81,82,95,100,158,161]	---	6[19,35,81,82,100,158]	5[41,43,55,95,161]	1[53]
PRP vs. HA	See above	---			
PRP vs. Corticosteroid	9[44,49,50,67,71,75,91,95,103]	---	2[71,91]	3[44,49,95]	4[50,67,75,103]
PRP vs. Analgesics	3[24,114,127]	---	1[127]	1[24]	1[114]
PRP vs. Exercise‡	4[5,8,108,111]	---	1[8]	---	3[5,108,111]
PRP vs. Prolotherapy	2[104,110]	---	---	1[104]	1[110]
PRP vs. PT	1[51]	---	---	1[51]	0
PRP (single injection) vs. PRP (multiple injection)	6[55,73,81,100,143,161]	---	1[81,100]	2[55,161]	1[73]
PRP (LP) vs. PRP (LR)	2[159,164]	---	2[159,164]	---	---
TOTAL: PRP†‡	**34**[5,8,19,24,35,41,43,44,49-51,53,55,67,71,73,75,81,82,91,95,]	---	**13**[8,19,35,71,81,82,91,100,127,143,158,159,164]	**10**[24,41,43,44,49,51,55,95,104,161]	**11**[5,50,53,67,73,75,103,108,110,111,114]

Comparisons	RCTs (publications)	Funding: No. RCTs (Publications)			
		Industry	Other*	None	NR
	100,103,104,108,110,111,114,127,143,158,159,161,164				
TOTAL: KNEE OA†	**61 (64)**[4,5,8,9,11,15,19,21,24,25,35,36,41,43,44,46,49-51,53-56,59,63,67,71,73-75,77,78,81-83,87,91,95,100,102-104,107-111,114,115,120,126,127,135,137,141-143,148,154,158,159,161,162,164]	**11 (14)**[4,9,36,46,54,59,74,78,87,102,135,137,141,162]	**21**[8,11,15,19,35,63,71,81-83,91,100,107,127,142,143,154,158,159,164]	**17**[21,24,25,41,43,44,49,51,55,56,77,95,104,109,115,126,148,161]	**12**[5,50,53,67,73,75,103,108,110,111,114,120]
HIP OA					
HA/Viscosupplementation					
HA vs. Placebo (Saline)	2[23,106]	1[23]	1[106]	---	---
HA vs. PRP	1[150]	---	1[150]	---	---
HA vs. Corticosteroid	1[106]	---	1[106]	---	---
TOTAL: HIP OA	**3**[23,106,150]	**1**[23]	**2**[106,150]	---	---
TOTAL OVERALL	**64 (67)**[4,5,8,9,11,15,19,21,24,25,35,36,41,43,44,46,49-51,53-56,59,63,67,71,73-75,77,78,81-83,87,91,95,100,102-104,107-111,114,115,120,126,127,135,137,141-143,148,154,158,159,161,162,164]				

HA: hyaluronic acid; HMW = high molecular weight; LMW = low molecular weight; LP = leukocyte poor; LR = leukocyte rich; NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PRP: platelet-rich plasma; PT = physical therapy; RCT: randomized control trial; TENS: transcutaneous electrical nerve stimulation.
*Other = government, university, society, foundation.
†8 RCTs contributed to more than one comparison:

- Buendia-Lopez 2018 (HA vs. PRP, HA vs. NSAIDs, PRP vs. NSAIDs)[24]
- Gormeli 2017 (HA vs. Saline, HA vs. PRP, PRP vs. Saline, PRP vs. PRP)[55]
- Lewis 2022 (PRP vs. Saline, PRP vs. PRP [number of injections])[81]
- Nunes-Tamashiro 2022 (PRP vs. Saline, PRP vs. Corticosteroid)[95]
- Patel 2013 (PRP vs. Saline, PRP vs. PRP)[100]
- Rezasoltani 2020 (HA vs. PT, HA vs. Prolotherapy)[115]
- Tavassoli 2019 (HA vs. PRP, PRP vs. PRP [number of injections])[143]
- Yurtbay 2022 (PRP vs. Saline, PRP vs. PRP [number of injections])[161]

‡A total of 4 trials (3 PRP vs. placebo [saline][53,82,158] and 1 PRP vs. exercise[108]) of primarily bilateral knee OA randomized by knees (as opposed to patients). While they self-describe as RCTs, for purposes of this report they are considered observational cohort studies (nonrandomized studies of interventions [NRSIs]) since the randomization was done to two knees within the same patient. Patient factors may influence outcomes for both treatments.

4.2 Comparison with the 2013 and 2016 reports

Hyaluronic Acid/Viscosupplementation

Comparison of key results from the 2013 HTA Report on HA

The findings from this updated review appear to be generally consistent with findings from the 2013 review and more recent systematic reviews published since the 2013 review.

Comparison of findings between this update and the prior report are challenging. The methodology for this update differs in several important ways. The update focuses on primary RCTs published since the 2013 review and includes information on HA use in hip OA. This update also includes evaluation of PRP for knee and hip OA as an update to our 2016 report. Based on input from a clinical expert, the key questions and PICOTS were revised for this combined update. We evaluated the impact treatments at short, intermediate, and long term to assess the persistence of effects beyond the short-term, given the chronic and progressive nature of knee and hip OA. The prior report did not.

The 2013 HTA report on HA updated a prior report from 2010 on use of HA specifically for knee OA only. The 2013 review largely summarized evidence from published systematic reviews and incorporated new RCTs published subsequent to those reviews into the report. Meta-analyses in the SRs summarized in that report included between 18 and 68 RCTs comparing HA with various placebo and non-placebo controls.

Summary of main findings from the 2013 review:

- Pain: Results across four SRs and one RCT published after the SRs suggest that HA was associated with a small mean improvement in pain short term (~3 months) versus comparators; evidence was listed as moderate.
- Function: Similarly, across three SRs and one RCT published after the SRs suggest that HA was associated with a small mean improvement in function short term (~3 months) versus comparators; evidence was listed as moderate.
- Likelihood of clinically important benefit for pain or function (specific measures not described)
    - HA versus placebo (based on 11 RCTs): Low quality evidence some studies favored HA and others favored placebo.
    - HA as an add on to usual care alone: Moderate evidence indicates that differences are statistically significant. The report does not state the direction of effect; presumably HA was favored.
    - HA versus intra articular corticosteroids: Low evidence from pooled estimates that steroid injection may be favored initially, but HA was significantly favored at 11-16 weeks, but that there was no difference at 17 to 26 weeks.
    - HA versus NSAIDs; No quality assessment was reported; HA and NSAIDs were considered to have comparable efficacy based on 4 RCTs included in one systematic review.
- No definitive statement can be made regarding the cost-effectiveness of viscosupplementation.

Although methods between the prior report and this update differ, as seen below, results of this re-review are generally consistent with the prior report and provide additional insight into the durability of findings from more recent RCTs.

Platelet Rich Plasma

Comparison of key results from the 2016 HTA Report on PRP

Table 9. Comparison of key results from the 2016 PRP report and this re-review

	Key Results From 2016 HTA Report: Autologous Blood or PRP Injections	Results From This 2023 Updated Report:
Knee OA		
Key Question 1a: Efficacy		
PRP vs. Placebo (Saline)		
Evidence base	2 fair-quality RCTs (N=78, 136)	• 9 RCTs (2 good and 7 fair quality; total N=1,683, N range 33 to 644) • 3 NRSIs* (fair quality; 20 knees in 40 patients [2 NRSIs], 58 knees [patients unclear, 1 NRSI])
Short term	• Function (1 RCT) and pain (1 RCT) scores better with PRP vs. saline (Low SOE)	• Results varied based on the outcomes measure used. • **Function**: small improvement with PRP vs. saline for WOMAC physical function (5 RCTs, Moderate SOE) and IKDC (1 RCT, Low SOE) scores; no difference for KOOS ADL and Sport and Recreation scores (Low SOE) • Pain: moderate improvement with PRP vs. saline for WOMAC pain scores (5 RCTs, Moderate SOE); no difference for KOOS pain (4 RCTs) and VAS pain (7 RCTs) (Low SOE) • Small increase in the likelihood of achieving response with PRP vs. saline based on OMERACT-OARSI criteria (1 RCT, Low SOE)
Intermediate term	• Function (2 RCTs) and pain (1 RCT) scores better with PRP vs. saline (Low SOE)	• Results varied based on the outcomes measure used. • Function: moderate improvement with PRP vs. saline for WOMAC physical function (4 RCTs, Low SOE) but no difference for KOOS ADL and Sport and Recreation scores (3 RCTs, Low SOE); evidence insufficient for IKDC • Pain: moderate improvement with PRP vs. saline for WOMAC pain (4 RCTs, Moderate SOE) and VAS pain (6 RCTs, Low SOE) scores; no difference for KOOS pain (3 RCTs) or OMERACT-OARSI responders (1 RCT) (Low SOE for both)
Long term	• No evidence	• Results varied based on the outcomes measure used. • Function: large improvement with PRP vs. saline for WOMAC physical function (2 RCTs, Low SOE) and moderate improvement in IKDC scores (1 RCT, Low SOE), but no difference for KOOS ADL and Sport and Recreation scores (3 RCTs, Low SOE) • Pain: No difference in pain improvement between PRP and placebo for KOOS pain (3 RCTs) and VAS pain (5 RCTs) (Low SOE for both); evidence for WOMAC pain was insufficient and there was no evidence for OMERACT-OARSI criteria
PRP vs. Steroid		

	Key Results From 2016 HTA Report: Autologous Blood or PRP Injections	Results From This 2023 Updated Report:
Evidence base	1 fair-quality RCT (N=48)	9 RCTs (3 fair and 6 poor quality; total N=598, N range 51 to 70)
Short term	• Insufficient evidence for function and pain scores	• Results varied based on the outcomes measure used • Function: no difference between PRP and steroid for WOMAC physical function (1 RCT) and KSS (2 RCTs) scales (Low SOE); insufficient evidence for KOOS ADL and Sport and Recreation and IKDC scales. • Pain: small improvement in VAS pain scores (5 RCTs, Low SOE) with PRP vs. steroid but no difference in WOMAC pain (1 RCT) or KOOS pain (2 RCTs) scores (Low SOE).
Intermediate Term	• Insufficient evidence for function and pain scores	• Except for KSS scores which were moderately improved after PRP vs. steroid (2 RCTs, Low SOE), the evidence was considered insufficient for all other function (WOMAC physical function, KOOS ADL and Sport and Recreation, IKDC) and pain (WOMAC pain, KOOS pain, VAS pain) measures.
Long term	• No evidence	• Function: no difference between PRP and steroid for WOMAC physical function (1 RCT, Low SOE); insufficient evidence for IKDC • Pain: Small improvement in VAS pain scores with PRP vs. steroid (3 RCTs) but no difference in WOMAC pain scores (1 RCT) (Low SOE for both)
PRP vs. Exercise ± TENS		
Evidence base	2 fair-quality RCTs (N=54, 65)	3 fair-quality RCTs (total N=179, N=52 to 65)
Short term	• Insufficient evidence for function and pain scores	• Insufficient evidence for function and pain scores
Intermediate Term	• Insufficient evidence for function and pain scores	• No difference between PRP vs. exercise for WOMAC pain (2 RCTs, low SOE) • All other evidence was insufficient (WOMAC physical function and pain subscales; KOOS ADL, Sport and Recreation and Pain subscales; KOOS pain; VAS pain)
Long term	• No evidence	• Insufficient evidence for function and pain scores
PRP vs. Analgesics		
Evidence base	No evidence	3 RCTs (2 fair and 1 poor quality; total N=195, N range 60 to 70)
Short term	-----	• Moderate improvement with PRP versus oral analgesics for WOMAC physical function, WOMAC pain, and VAS pain scores (2 RCTs, Low SOE)
Intermediate Term	-----	• Function: large increase in likelihood of response using ≥20% decrease on WOMAC function scale (1 RCT) and moderate improvement in WOMAC function scores (3 RCTs) with PRP vs. analgesics • Pain: large increase in likelihood of response using ≥20% decrease on WOMAC pain scale (1 RCT) and small

	Key Results From 2016 HTA Report: Autologous Blood or PRP Injections	Results From This 2023 Updated Report:
		improvements in WOMAC and VAS pain scores (3 RCTs) with PRP vs. analgesics • All Low SOE
Long term	-----	• Function: large increase in likelihood of response using ≥20% decrease on WOMAC function scale (1 RCT) and small improvement in WOMAC function scores (2 RCTs) with PRP vs. analgesics • Pain: large increase in likelihood of response using ≥20% decrease on WOMAC pain scale (1 RCT) with PRP vs. analgesics • All Low SOE
PRP vs. Prolotherapy		
Evidence base	No evidence	2 poor-quality RCTs (total N=102, N=42 and 60)
Short term	-----	• Insufficient evidence for function and pain scores
Intermediate Term	-----	• Insufficient evidence for function and pain scores
Long term	-----	• No evidence
PRP vs. PT		
Evidence base	No evidence	1 poor-quality RCT (N=40)
Short term	-----	• Insufficient evidence for function and pain scores
Intermediate Term	-----	• No evidence
Long term	-----	• No evidence
PRP: fewer vs. greater number of injections		
Evidence base	No evidence	6 RCTs (1 good, 4 fair, 1 poor quality; total N=508, range 52 to 133)
Short term	-----	• No difference between 1 (plus 2 placebo injections) versus 3 injections of PRP on the KOOS Sport and Recreation subscales (1 good quality RCT, low SOE) • Insufficient evidence for all other function and pain measures
Intermediate Term	-----	• Insufficient evidence for all function and pain measures
Long term	-----	• Insufficient evidence for all function and pain measures
PRP: leukocyte poor vs. leukocyte rich		
Evidence base	No evidence	2 RCTs (1 good and 1 fair quality; total N=130; N range 60 to 70)
Short term	-----	• Function: no difference between LP- and LR- PRP for WOMAC physical function (2 RCTs, low SOE) • Pain: no difference between LP- and LR- PRP for VAS pain scores (2 RCTs, low SOE); insufficient evidence for WOMAC pain scores

	Key Results From 2016 HTA Report: Autologous Blood or PRP Injections	Results From This 2023 Updated Report:
Intermediate Term	-----	• Function: no difference between LP- and LR- PRP for WOMAC physical function (2 RCTs, low SOE) • Pain: insufficient evidence
Long term	-----	• Function: no difference between LP- and LR- PRP for WOMAC physical function (2 RCTs, low SOE) • Pain: insufficient evidence
Key Question 2: Safety		
Evidence base	4 RCTs (N=584), 3 cohort studies (N=320), primarily PRP vs. HA	9 RCTs, 1 NRSI*
Any time	• No serious treatment-related adverse events were reported to have occurred (Low SOE)	• Three patients (11.5%) who received LR-PRP experienced severe swelling and mild fever (not beyond 37.5 C) compared with no patient in the LP-PRP arm; one patient required arthroscopic debridement (1 RCT) • One case of severe inflammation with swelling and stiffness immediately post-injection in the knee randomized to LP-PRP (5%; 1/20 knees) vs. no events with saline injection; symptoms persisted for 2 weeks and then improved. • Across 8 RCTs, no serious treatment-related adverse events were reported to have occurred • Data was considered insufficient due to generally poor reporting of SAEs. There was substantial heterogeneity regarding how AEs were categorized, reported and described (if described at all).
Key Question 3: Differential Efficacy and Safety		
	Insufficient evidence from one RCT comparing PRP and HA that reported subgroup analyses stratified by OA grade (early vs. advanced).	• No new evidence
Key Question 4: Cost-effectiveness		
	No evidence	

ADL = Function in daily living, AE = Adverse event, HTA = Health technology assessment, IKDC = International knee documentation committee, KOOS = Knee injury and osteoarthritis outcome score, KSS = Knee society score, LP = Leukocyte poor, LR = Leukocyte rich, NRSI = Non-randomized study of intervention, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, PRP = Platelet-rich plasma, PT = Physical therapy, RCT = Randomized controlled trial, SAE = Serious adverse event, SOE = Strength of evidence, TENS = Transcutaneous electrical nerve stimulation, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*While these studies self-describe as RCTs, for purposes of this report they are considered observational cohort studies (nonrandomized studies of interventions [NRSIs]) since the randomization was done to two knees within the same patient. Patient factors may influence outcomes for both treatments.

5 Knee Osteoarthritis

5.1 Key Question 1: Hyaluronic Acid (HA)/Viscosupplementation for Knee OA

5.1.1 Key Question 1a: Efficacy and Effectiveness of HA for Knee OA

5.1.1.1 HA vs. Placebo

Nine RCTs (in twelve publications)[4,9,15,46,54,55,59,74,102,135,137,141] compared HA with placebo (saline) for the treatment of knee OA (Appendix G). Sample sizes ranged from 40 to 817 (total N=2,696). The average age of participants was 59.8 years (range, 53.1 to 62.0), 60.3 percent were female (range, 45.0% to 77.8%) and the average BMI was 28.2 (range, 25.5 to 30.2). The severity of OA was classified as Kellgren-Lawrence grade 1 in 13.6 percent of participants (range, 0% to 27.7%), grade 2 in 45.3 percent (range, 35.8% to 62.1%) and grade 3 in 40.8 percent (range, 18.7% to 58.4%), across eight trials;[4,9,15,46,54,59,74,102,135,137,141] One trial[55] did not report OA grade. Most trials excluded participants with grade 4 (severe) OA; however, one trial[59] included a small number of participants (0.5%) with grade 4. Symptom duration was 2.7 years in one trial.[9] One trial[135,137] required participants to be symptomatic for 4 weeks, one trial[4,141] for 30 days, one trial[55] for 4 months, and one trial[102] for 6 months for inclusion; Five trials[9,15,46,54,59,74] did not report a minimum duration required for inclusion.

Single injection (7 trials)[4,15,46,54,59,74,102,135,137,141], three-injection (1 trial),[55] and five-injection (1 trial)[9] regimens were used for HA therapy; Injections were given weekly in both the three-injection[55] and five-injection trials.[9] Eight trials used high molecular weight formulations (Durolane, 1 trial[9]; Gel-One, 1 trial[4,141]; Hylan GF-20, 1 trial[74]; Monovisc, 3 trials[46,54,59,102]; Orthovisc, 1 trial[55]; Supartz, 1 trial[15]) and one trial[135,137] used Gel-200 but did not report molecular weight; Doses ranged from 30mg to 88mg per injection where reported. Single (8 trials)[4,9,15,46,54,59,74,102,135,137,141] and three-injection (1 trial)[55] regimens were used for placebo therapy; Injections were given weekly in the three-injection trial.[55] Only one trial[15] reported using ultrasound guidance. Reporting of cointerventions varied but acetaminophen (4 trials),[9,55,59,102] glucosamine (2 trials),[102,135,137] chondroitin sulfate (2 trials),[102,135,137] minocycline (1 trial),[135,137] NSAIDs (1 trial),[135,137] non-prescription herbal supplements (1 trial),[135,137] short-acting opiates (2 trials),[74,135,137] acetaminophen with tramadol (1 trial),[74] and exercise therapy (1 trial)[15] were most commonly permitted. It should be noted that one trial[135,137] was much more lenient, allowing all three chondroprotective agents, NSAIDs, herbal supplements, and opiates whereas other trials did not allow most of these. In general, patients were required to stop using non-acetaminophen pain relievers and steroids before trials entry and were not allowed to use them until the trial was complete. Follow-up ranged from 6 weeks (short term) to 6 months years (intermediate term) with most trials reporting intermediate term results; two trials[9,15] reported short term results only and one trial reported long-term results.[46,54] Seven trials[4,9,46,54,59,74,102,135,137,141] received industry funding, one[15] received funding from non-industry sources (e.g., governments, university, etc.), and one[55] reported no funding. Four trials[4,46,54,102,135,137,141] were located in the United States, two in China,[15,74] and one each in Turkey,[55] Poland and Hungary,[59] and Sweden, Germany, and the United Kingdom.[9]

Five trials[9,59,102,135,137] were considered good quality, two fair[4,55,141] and two poor quality.[15,46,54] Primary methodological shortcomings in fair trials included lack of care provider blinding and lack of clarity

regarding randomization; in addition, the poor quality trials also had high attrition and lack of clarity regarding outcome assessor blinding.

For the Gel-200 HA, two RCTs were identified (registry numbers NCT00449696 and NCT00450112). Three publications[134,135,137] for one 13-week trial were identified, two of which focused on an open label observational extension of the trial[135,137] in addition to the primary report of the trial[135]. Results for effectiveness reported here are based on this primary trial. A primary journal publication of the full population of the other trial was not identified and we used data from the FDA SSED. A journal publication analyzing a subset of the full population for this 26-week RCT was identified.[141] A publication pooling results across the two RCTs was also identified.[140] The results below focus on data across the individual primary RCTS (across HA products evaluated) identified for this review. The subset and pooled analyses are mentioned for completeness at the end of this section following description of secondary outcomes.

5.1.1.1.1 Function

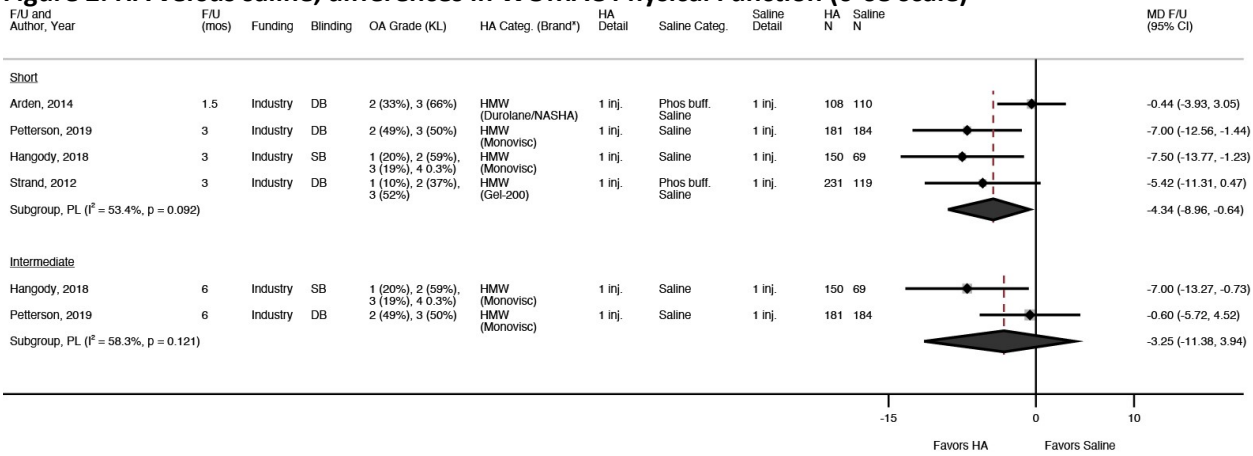
Function "Success"

No studies reported on this.

Function: scores

Four RCTs comparing single injections of HA with saline as a placebo reported **WOMAC Physical Function** Scores (0-68 scale).[9,59,102,135] All were considered good quality and reported industry funding or author association with industry. HA was associated with small functional improvement versus saline placebo (4 RCTs, MD -4.34, 95% CI -8.96 to -0.64, I^2=53.4%) however estimates are imprecise. No difference between HA and saline was seen at intermediated term (2 RCTs, MD -3.25, 95% CI -11.38 to 3.94, I^2=58.3%).[59,102]

Figure 2. HA versus saline, differences in WOMAC Physical Function (0-68 scale)*



CI = Confidence interval, COI = Conflict of interest, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, MD = Mean difference, OA = Osteoarthritis, Phos. buff. saline = Phosphate-buffered saline, SB = Single blinded

*Hangody only reported change scores.

One poor quality RCT[46,54] (2 publications) comparing HA with saline reported on KOOS ADL (0-100) and KOOS Sport and Recreation (0-100) as measures of function. There was no difference in KOOS ADL scores between HA and saline at short term (MD -0.98, 95% CI -0.51 to 3.14), intermediate term (MD -5.19, 95% CI -13.24 to 2.86) or long term (MD -2.1, 95% CI -10.71 to 6.51). Similarly, there were no differences between groups on the KOOS Sport and Recreation subscale short term (MD 1.16, 95% CI -4.59 to 6.61) intermediate term (MD -7.18, 95% CI -18.41 to 4.05) or long term (MD 1.33, 95% CI -0.69 to 13.35). In contrast, one fair quality trial reported that HA was associated with moderate functional improvement versus placebo at intermediate term on the International Knee Documentation Committee (IKDC, 0-100 scale); MD 11.9, 95% CI 9.5 to 14.35.[55]

5.1.1.1.2 Pain

Pain "Success" (response)

Three good-quality RCTs comparing HA with a saline placebo reported pain "success" (responders) i.e., on the proportion of patients in each group that met various clinically meaningful thresholds of pain relief on the **WOMAC Pain** score[9,102] or the WOMAC pain while walking question (WOMAC A1).[74] There were no differences between HA and saline at short-term or intermediate term (Table 10).

Table 10. Summary of pain success: HA versus saline placebo

Author, year	Time	Scale	Threshold	HA	Saline	RR (95% CI)
Arden, 2014	1.5 mos.	WOMAC Pain (0-20)	40% reduction from baseline w/ absolute improvement >=5 points	30.6% (33/108)	26.4% (29/110)	1.16 (0.76 to 1.77)
Petterson, 2019	3 mos.	WOMAC Pain (0-20)	> 50% improvement from baseline and > 20 mm absolute improvement from baseline	52.5% (95/181)	52.7% (97/184)	1.00 (0.82 to 1.21)
Ke, 2021	6 mos.	WOMAC A1 Pain (0-4)	>2-point improvement from baseline in WOMAC A1 NRS (clinically important reductions in pain)	67.0% (146/218)	68.2% (150/220)	0.98 (0.86 to 1.12)
Petterson, 2019	6 mos.	WOMAC Pain (0-20)	> 50% improvement from baseline and > 20 mm absolute improvement from baseline	51.4% (93/181)	48.9% (90/184)	1.04 (0.85 to 1.28)

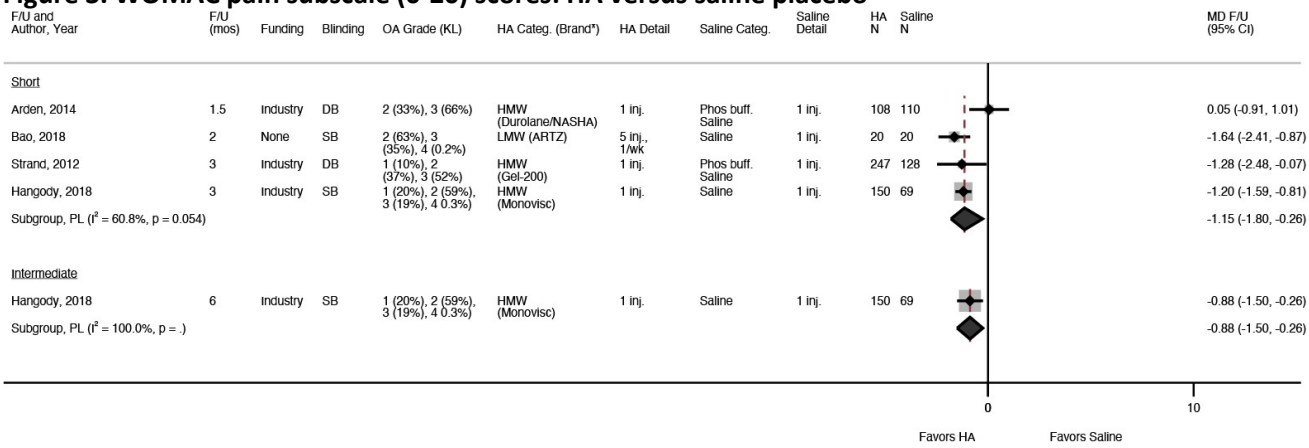
HA = Hyaluronic acid, mm = millimeter, mos. = months, NRS = Numerical rating scale, RR = Risk ratio, WOMAC = Western Ontario and McMaster osteoarthritis index

Pain scores

WOMAC Pain subscale scores (0-20 scale) were reported in four RCTs at short term[9,15,59,135] (3 good[9,59,135] and one poor[15] quality). HA was associated with a small improvement in pain versus saline at short term across them (4 RCTs, MD -1.15, 95% CI -1.80 to -0.26, I^2=60.8%); clinical importance of this difference is unclear (Figure 3). Exclusion of the small, poor-quality trial decreased the effect size below the threshold for a small effect and results were no longer statistically significant (3 RCTs MD -0.90, 95% CI -1.75 to 0.11, I^2=65.2%). There was no difference between HA and saline placebo in one trial at intermediate term (MD -0.88, 95% CI -1.05 to -0.26, on 0-20 scale) as the effect estimate did not meet the threshold for a small effect.

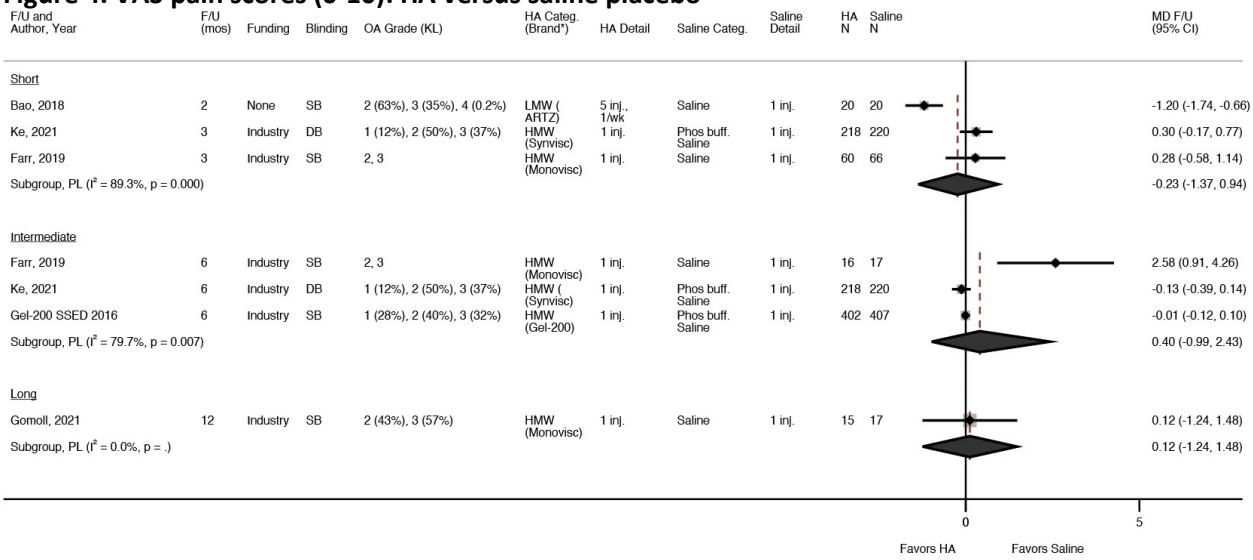
VAS pain scores (0-10 scale) reported in reported in four RCTs (five publications)[4,15,46,54,74]; two were rated as poor quality.[15,46,54] No difference in pain improvement was seen at short-term (3 RCTs MD -0.23, 95%CI -1.37 to 0.94, I^2=89.3%).[15,46,74] Exclusion of a poor-quality outlier trial[15] reduced heterogeneity (2 RCTs MD 0.29, 95% CI -0.21 to 0.80, I^2=0%)[46,74]; the large, good-quality trial found no difference. (Figure 4) At intermediate term, there was no difference between HA and saline (3 RCTs, MD 0.40, 95% CI -0.99 to 2.43, I^2=79.7%). Exclusion of one poor-quality outlier RCT,[46] which suggested a large effect at intermediate term, removed the heterogeneity and improved precision (2 RCTs, N=1247, MD -0.03, 95% CI -0.20 to 0.09, I^2=0%). This RCT excluded patients reporting unacceptable pain at 3 months who had requested unblinding. The same trial reported no difference in VAS pain scores between interventions at longer term (MD 0.12, 95% CI -1.24 to 1.48).[54] This poor-quality RCT also reported KOOS pain scores, finding no difference between HA and saline short term or long term and a small effect at intermediate term, however estimates were imprecise. (Appendix F).

Figure 3. WOMAC pain subscale (0-20) scores: HA versus saline placebo



CI = Confidence interval, COI = Conflict of interest, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, MD = Mean difference, OA = Osteoarthritis, Phos. buff. saline = Phosphate-buffered saline, SB = Single blinded.

Figure 4. VAS pain scores (0-10): HA versus saline placebo



CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, MD = Mean difference, OA = Osteoarthritis, Phos. buff. saline = Phosphate-buffered saline, SB = Single blinded, SSED = Summary of safety and effectiveness data.

5.1.1.1.3 Outcomes assessing multiple domains

WOMAC total Score and OMERACT-OARSI response criteria

One of the RCTs reported no difference in **WOMAC Total score**s between HA and saline short term (MD -5.64, 95% CI -0.2 to 11.47).[135]

Two RCTs (3 publications) reported treatment response based on **OMERACT-OARSI** criteria. This is a composite outcome which combines thresholds for improvement in pain and function to describe treatment response and was variably defined across the studies. There was no difference between HA and saline placebo in the likelihood of improvement from one good quality study[135] short term or from one poor quality trial at intermediate or long term (Table 11).[46,54]

Table 11. Summary of OMERACT-OARSI Responders: HA versus saline

Outcome Author Quality	Time	Definition	HA	Saline	RR (95% CI)
Responders (OMERACT-OARSI) **Strand, 2012 Good**	3 mos.	Improvements from baseline in WOMAC pain or physical function subscores >20% with absolute changes >10 mm in two of three measures: WOMAC pain/physical function, patient global assessments of disease activity	61% (141/247)	54.6% (65/128)	1.12, 95% CI 0.92 to 1.38
OMERACT-OARSI simplified **Farr, 2019**	6 mos. 12 mos.	>=50%decrease in pain or increase in function and absolute change of >=20 points OR at least two of the following: (1) improvement in pain >=20% and absolute change >=10, (2)	37.5% (6/16) 33.3% (5/15)	41.2% (7/17) 42.9% (6/14)	0.92, 95% CI 0.40 to 2.09 0.84, 95% CI 0.34 to 2.09

Gomoll, 2021 **Poor**		improvement in function >=20% and absolute change >=10, (3) improvement in patients' global assessment >=20% and absolute change >=10			

CI = Confidence interval, HA = Hyaluronic acid, mm = Millimeter, Mos. = Months, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, RR = Risk ratio, WOMAC = Western Ontario and McMaster osteoarthritis index

Additional invasive procedures

None of the included trials described the need for additional invasive procedures such as joint-replacement surgery.

5.1.1.1.4 Secondary Outcomes

Symptom recurrence

Persistent, or increased pain, reduced function resulting in need for additional injection of HA or PRP within 2 months after protocol completion was not reported by included RCTs. One poor quality RCT[46] excluded patients who reported unacceptable pain at 3 months and requested unblinding (68% from HA, 75% from placebo group) from analyses and note that most missing data were due to inadequate response to assigned injection.

Quality of Life

One fair-quality RCT reported that HMW HA was associated a moderate improvement in health status versus saline placebo at intermediate term as measured by the EuroQoL VAS (0-100 scale lower score worse, MD 12.8, 95% CI 10.04 to 15.56).[55] One poor quality RCTs (2 publications) found no difference between HA and saline at short term (MD 2.89, 95% CI -1.34 to 7.12) or long term (3.21, 95% CI -5.63 to 12.05) based on KOOS QoL (0-100 scale).[46,54] While they report a moderate improvement with HA versus saline at intermediate term (MD -12.11, 95% CI -20.38 to -3.84), authors had excluded patients reporting unacceptable pain at 3 months who had requested unblinding. All estimates from this trial are imprecise. One small (N=40) poor-quality RCT reported that HA was associated with improved SF-36 MCS (MD 7.2, 95% CI 1.80 to 12.60) and PCS (MD 10.9, 95% CI 5.98 to 15.82) versus saline.[15]

Medication use

None of the included trials described the need for additional invasive procedures.

Return to normal activities

None of the included trials described the need for additional invasive procedures.

5.1.1.1.5 Outcomes from subset and pooled analyses of NCT00449696 and NCT00450112 trials.

Analysis of a subset of patients from one 26-week RCT of single Gel-200 injection versus placebo was identified (NTC 01934218).[141] The subgroup analyses focused on a subset of patients that authors feel was more consistent with populations evaluated in other trials of HA. Namely, patients who had didn't have posttraumatic OA, had K-L grades 2 or 3 with ≥3-month pain duration and WOMAC pain on walking and WOMAC pain sub-scores of 40 to 80 mm were included (N=311 of the 809 enrolled as reported in the SSED). The WOMAC pain score is generally described on a 0 to 20 scale. Based on differences in change scores from baseline and repeated measures analysis over 26 weeks, authors report a difference of -4.5 (95% CI -8.7 to -0.4) favoring HA versus placebo. HA was also favored over placebo (small improvement) based on WOMAC function (difference -5.0, 95% CI -10.1 to 0.1, 0-68 scale) and WOMAC total scores (difference -5.4, 95% CI 10.4to -0.4, 0-96 scale). All estimates are imprecise.

A pooled analysis across the two GEL-200 trials (N=1184) was identified.[140] Follow-up time was 13 weeks for one trial[135] and 26 weeks for the other[4] data collection occurred at somewhat different time frames in the two trials. Given lack of data from the end of the 13-week trial to 26 weeks, authors report treating the missing visits "similar to those for subjects who withdrew" or had missing data for the 26-week trial. Using this methodology, based on differences in change scores from baseline and repeated measures analysis over the 26 weeks, authors report improvement in WOMAC Pain sub-scores (difference -3.0, 95% CI -5.4 to 0.5) with HA versus placebo, however there was no statistically significant difference between treatments at the 26 week time point (-3.0, 95% CI -6.2 to 0.2). Across the 26 weeks, there was no difference between HA and placebo in WOMAC Function (difference -2.1, 95% CI -4.6 to 0 .4, 0-68 scale) or in WOMAC Total Scores (-2.1, 95% CI -4.5 to 0.3). All estimates are imprecise. At individual time frames, the proportions of OMERACT-OARSI strict responders appear to be somewhat similar for HA and placebo (e.g., 42.3% versus 40.9% at 12 weeks); authors report an odds ratio of 1.2 (95% CI 1.0 to 1.5), presumably across the 26 weeks.

5.1.1.2 HA vs. PRP

Eleven RCTs (in eleven publications)[24,36,55,77,83,87,107,109,126,143,154] compared HA versus PRP for the treatment of knee OA (Appendix G). Sample sizes ranged from 56 to 189 (total N=1,160). The average age of participants was 58.3 years (range, 53.6 to 65.1), 69.8 percent were female (range, 37.8% to 83.6%) and the average BMI was 27.2 (range, 22.8 to 29.0). The severity of OA was classified as Kellgren-Lawrence grade 2 in 46.0 percent of participants (range, 0% to 100%) and grade 3 in 43.8 percent (range, 0% to 100%), across eight trials[24,36,77,87,107,109,126,154]; one trial[143] reported OA severity using the Ahlback scale (grade 2: 36.3%, grade 3: 63.7%); one trial[83] included only patients with grade 2 or 3 OA on the Shahriaree scale but did not provide more information; and one trial[55] did not report OA grade. Most trials excluded participants with grade 1 (minor) and grade 4 (severe) OA; however, three trials[24,36,77] included participants with grade 1 (2.9% to 55.4%) and two trials[36,109] included participants with grade 4 OA (range, 1.1% to 13.8%). Symptom duration was 5.5 years (range, 4.2 to 8.3) in two trials[87,107] reporting duration. Two trials[107,109] required participants to be symptomatic for 3 months, 2 trials[55,77] for four months, and one trial[126] for 6 months for inclusion; no other trials reported a minimum duration required for inclusion.

Single injection (2 trials)[24,87] and three-injection (9 trials)[36,55,77,83,107,109,126,143,154] regimens were used for HA therapy; Injection intervals in the three-injection trials ranged from weekly to monthly. Five

trials[83,107,109,126,143] used low molecular weight formulations (Hyalgan) and six trials used high molecular weight formulations (Durolane, 2 trials[24,87]; Orthovisc, 1 trial[55]; Synvisc, 1 trial[36]; Supartz, 1 trial[154]). Doses ranged from 16mg to 60mg per injection where reported. Single (4 trials),[24,55,87,143] two-injection (3 trials),[107,109,143] and three-injection (6 trials)[36,55,77,83,126,154] regimens were used for PRP therapy; injection intervals ranged from weekly to monthly. Five trials[55,107,109,143,154] used leukocyte-rich PRP, five trials[24,36,77,87,126] used leukocyte-poor, and one[83] did not report which it used. Platelet counts varied amongst studies but were most frequently two to five times normal blood platelet count and activating agents used included calcium chloride (4 trials),[24,55,107,154] calcium gluconate (1 trial),[83] and serum (1 trial).[77] Three trials[36,77,83] reported using ultrasound guidance, one[87] reported using echographic guidance, and seven[24,55,107,109,126,143,154] did not report using any imaging guidance. Reporting of cointerventions varied but acetaminophen (6 trials),[55,87,107,109,126,143] exercise therapy (2 trials),[107,109] and Tylenol with codeine (1 trial)[109] were most commonly permitted. In general, patients were required to stop using non-acetaminophen pain relievers and steroids before trials entry and were not allowed to use them until the trial was complete. Follow-up ranged from 6 weeks (short term) to 7 years (long term) with most trials reporting intermediate term results; one trial[143] reported short term results only and eight[24,36,77,83,107,109,126,154] reported long term results. Two trials[36,87] received industry funding, four trials[83,107,143,154] received funding from non-industry sources (e.g., governments, university, etc.), and five trials[24,55,77,109,126] reported no funding. Three trials[107,109,143] were located in Iran and one each in Spain,[24] Turkey,[55] Italy,[83] the United States,[36] Brazil,[77] France,[87] Egypt[126] and China.[154]

One trial[87] was considered good quality, five[24,36,55,77,83] fair, and five[107,109,126,143,154] poor. Primarily methodological shortcomings in fair trials included lack of care provider blinding, and lack of clarity regarding concealed allocation and intention to treat; in addition, the poor-quality trials also had lack of outcome assessor and patient blinding.

5.1.1.2.1 Function

Function "Success" (Responders)

Two RCTs reported on the proportions of participants meeting different thresholds for a clinically important decrease **WOMAC Physical Function scores**. One fair-quality trial[24] comparing single injections of HA and PRP reported a substantially lower likelihood of a 20% decrease in WOMAC Physical function score with HA compared with PRP (N=65, 14.2% vs. 45%, RR 0.34, 95% CI 0.14 to 0.84) at intermediate term. At long term, none of the HA recipient knees and 24% of the PRP recipients maintained the threshold ($p < 0.05$) but effect estimates are imprecise. The poor-quality trial[143] compared three HA injections given at 3-week intervals with two PRP injection protocols (single PRP injection and 2 injections at 3-week intervals). The two PRP arms were combined for these analyses. The trial reported results for two response thresholds, a 30% decrease in WOMAC Physical Function and a 50% decrease at short term. No HA recipients met either a 30% or 50% decrease in scores from baseline. The proportion of responders following PRP using the 30% threshold was 62.5%; 10.7% of PRP recipients met the 50% response threshold.

Function: scores

Five of the 11 RCTs comparing HA versus PRP assessed function based on the **WOMAC Physical Function** subscale (0-68 scale).[77,83,87,107,143] Two of the five studies reporting WOMAC Physical Function also

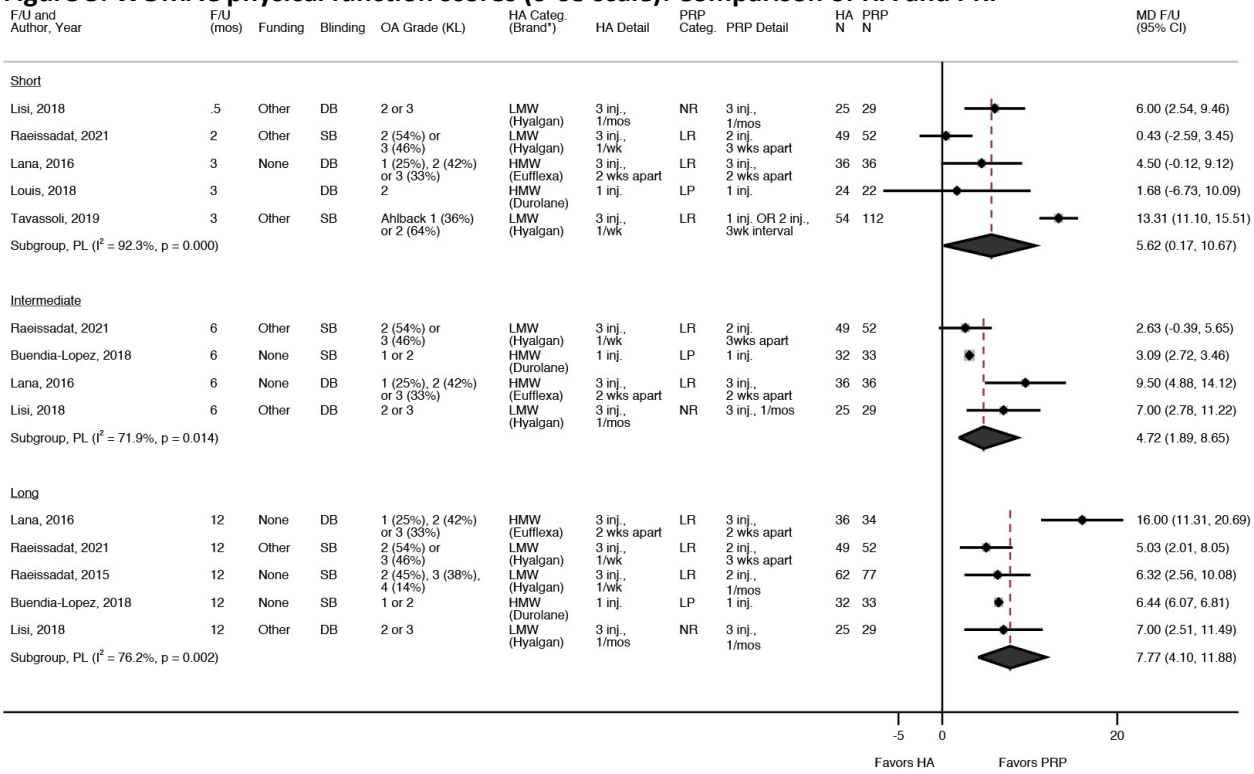
reported Lysholm **Knee Function Scoring scale (0-100 scale)**. Three studies evaluated function based on the **IKDC (0 to 100 scale)** but not WOMAC Physical function. Across meta-analyses, effect estimates were imprecise and heterogeneity in estimates was common. It is unclear to what extent differences in preparations or injection protocols may contribute to heterogeneity.

PRP was associated with a small improvement in function versus HA on the **WOMAC Physical Function** subscale (0-68) at short term (5 RCTs, MD 5.62, 95% CI 0.17 to 10.67, I^2=92.3%),[77,83,87,107,143] (Figure 5) however substantial heterogeneity is noted. Exclusion of one poor-quality outlier RCT[143] which reported results based on numbers of knees, not patients, decreased the effect size and the heterogeneity; results were no longer statistically significant (4 RCTs, MD 3.24, 95% CI -0.18 to 6.72 I^2=51.3%)[77,83,87,107] (Appendix H, Figure H1) and was below the threshold for a small effect. Exclusion of this trial and the other poor-quality trial slightly decreased the effect estimate and eliminated statistical heterogeneity; PRP was associated with small improvement in function (3 RCTs, MD 5.09, 95% CI 1.67 to 7.70, I^2=0%) Heterogeneity may have been in part due to study quality.

PRP was associated with small improvement in function versus HA the WOMAC Physical Function subscale (0-68) at intermediate term (4 RCTs, MD 4.72, 95% CI 1.89 to 8.65, I^2=71.9%),[24,77,83,107] however substantial heterogeneity is noted. Analysis confined to the highest quality trials slightly increased the effect size but it remained small favoring PRP over HA and heterogeneity increased slightly (3 RCTs, MD 5.67, 95% CI 1.76 to 10.84, I^2=81%).[24,77,83]

Long-term, PRP was associated with a moderate improvement in function versus HA on the WOMAC Physical Function subscale (0-68) (5 RCTs, MD 7.77, 95% CI 4.01 to 11.88, I^2=76.2%), however substantial heterogeneity is noted.[24,77 Raeissadat, 2015 #10,83,107] Exclusion of one outlier trial[77] removed heterogeneity and decreased effect size consistent with a small effect (4 RCTS, MD 6.42, 95% CI 5.68 to 6.95, I^2=0%).[24,83,107,109] Exclusion of two poorest quality RCTs[107,109] suggests that PRP is associated with a moderate functional improvement, however there was an increase in heterogeneity (3 RCTs, MD 9.39, 95% CI 2.87 to 16.54, I^2=84.4%).[24,77,83]

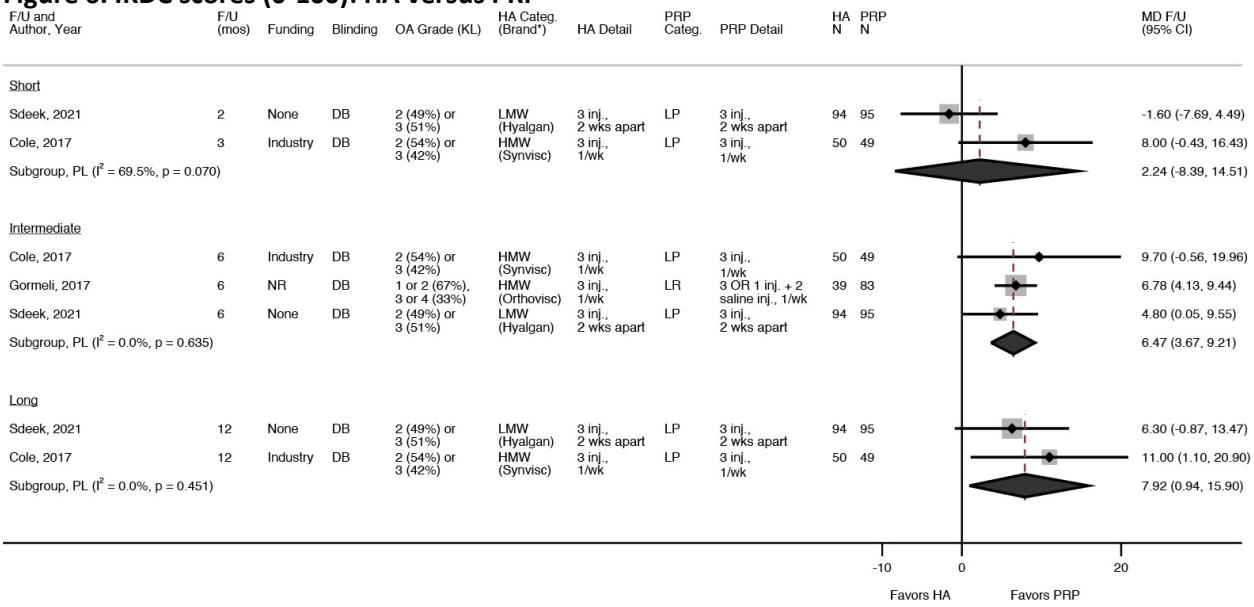
Figure 5. WOMAC physical function scores (0-68 scale): Comparison of HA and PRP



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SB = Single blinded

Other measures reported in some trials were the IKDC (0-100 scale) and the Lysholm Knee Function score. Three RCTs, reported function based on the **IKDC (0 to 100 scale);** they did not report WOMAC function.[36,55,126] Short term, there was no difference between HA and PRP (2 RCTs MD 2.24, 95% CI -8.39 to 14.51, I^2= 69.5%). PRP was associated with small functional improvement at intermediate term (3 RCTs, MD 6.47, 95% CI 3.67 to 9.21, I^2= 0%). Figure 6. One of the trials used two different PRP protocols (one PRP injection followed by two saline injections weekly and 3 weekly PRP injections; these arms were combined for these analyses.[55] At long term, PRP was also associated with a small functional improvement vs. HA (2 RCTS 9.75, 95% CI 3.05 to 16.81, I^2=0%). Sensitivity analysis using the 12-month instead of the 36-month follow up for one RCT[126] was also consistent with a small effect but the estimate was slightly smaller (2 RCTs, MD 7.92, 95% CI 0.94 to 15.90, I^2=0%).

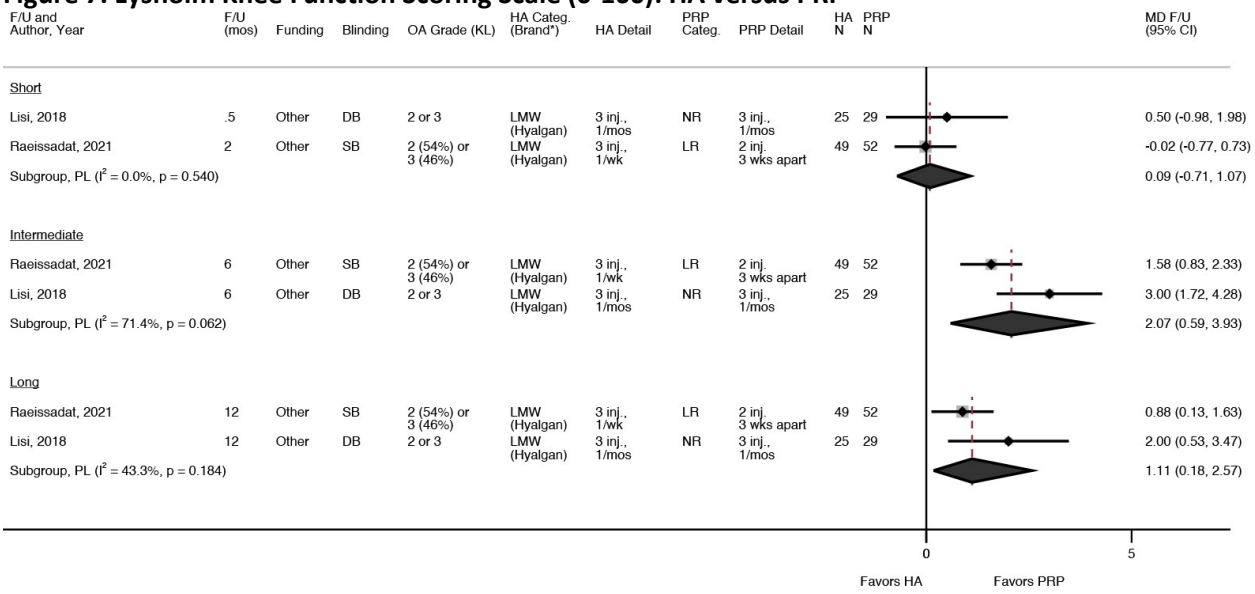
Figure 6. IKDC scores (0-100): HA versus PRP



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, LP = Leukocyte poor, MD = Mean difference, OA = Osteoarthritis, PRP = Platelet-rich plasma

Two RCTs assessed function using the Lysholm Knee Function Scoring Scale (0-100 scale).[83,107] They also contributed data to the WOMAC Function meta-analysis. Short term, there was no difference between HA and PRP (2 RCTs, MD 0.09, 95% CI -0.71 to 1.07, I^2=0%). Although statistically significant, we considered there to be no difference at intermediate term (MD 2.07, 95% CI 0.59 to 3.93 I^2=0%) and long term (2 RCTs, MD 1.11, 95% CI 0.18 to 2.57, I^2=43.3%) at the effect sizes were below the threshold for a small effect and the clinical importance is unclear.

Figure 7. Lysholm Knee Function Scoring Scale (0-100): HA versus PRP



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, LR = Leukocyte rich, MD = Mean difference, OA = Osteoarthritis, PRP = Platelet-rich plasma, SB = Single blinded

5.1.1.2.2 Pain

Pain "Success" (response)

Two RCTs (one fair, one poor quality) reported on the proportions of participants meeting different thresholds for a clinically important decrease **WOMAC Pain scores** (0-20 scale). One fair-quality trial comparing single injections of HA and PRP reported a substantially lower likelihood of a 20% decrease in WOMAC Pain score with HA compared with PRP (N=65, 21.9% vs. 48.5% RR 0.45, 95% CI 0.21 to 0.95) at intermediate term.[24] At long term, none of the HA recipients and 30.3% of the PRP recipients maintained the threshold. Estimates are imprecise. The poor-quality trial compared three HA injections given at 3-week intervals with two PRP injection protocols (single PRP injection and 2 injections at 3-week intervals).[143] The two PRP arms were combined for these analyses. The trial reported results for two response thresholds, a 30% decrease in WOMAC Pain Score and a 50% decrease at short term. No HA recipients met either a 30% or 50% decrease in scores from baseline. The proportion of responders following PRP using the 30% threshold was 92.8% and 39.3% of PRP recipients met the 50% response threshold.

The same two RCTs (one fair, one poor quality) reported on the proportions of participants meeting different thresholds for a clinically important decrease **VAS Pain scores** (0-10 scale). One fair-quality trial comparing single injections of HA and PRP reported a substantially lower likelihood of a 20% decrease in VAS Pain score with HA compared with PRP (N=65, 25% vs. 48.5% RR 0.52, 95% CI 0.26 to 1.03) at intermediate term.[24] At long term, none of the HA recipients and 15.2% of the PRP recipients maintained the threshold. Estimates are imprecise. The poor-quality trial compared three HA injections given at 3-week intervals with two PRP injection protocols (single PRP injection and 2 injections at 3-week intervals).[143] The two PRP arms were combined for these analyses. The trial used a 50% decrease

from baseline in VAS Pain scores as a threshold. No HA recipients met the threshold compared with 33.9% of PRP recipients.

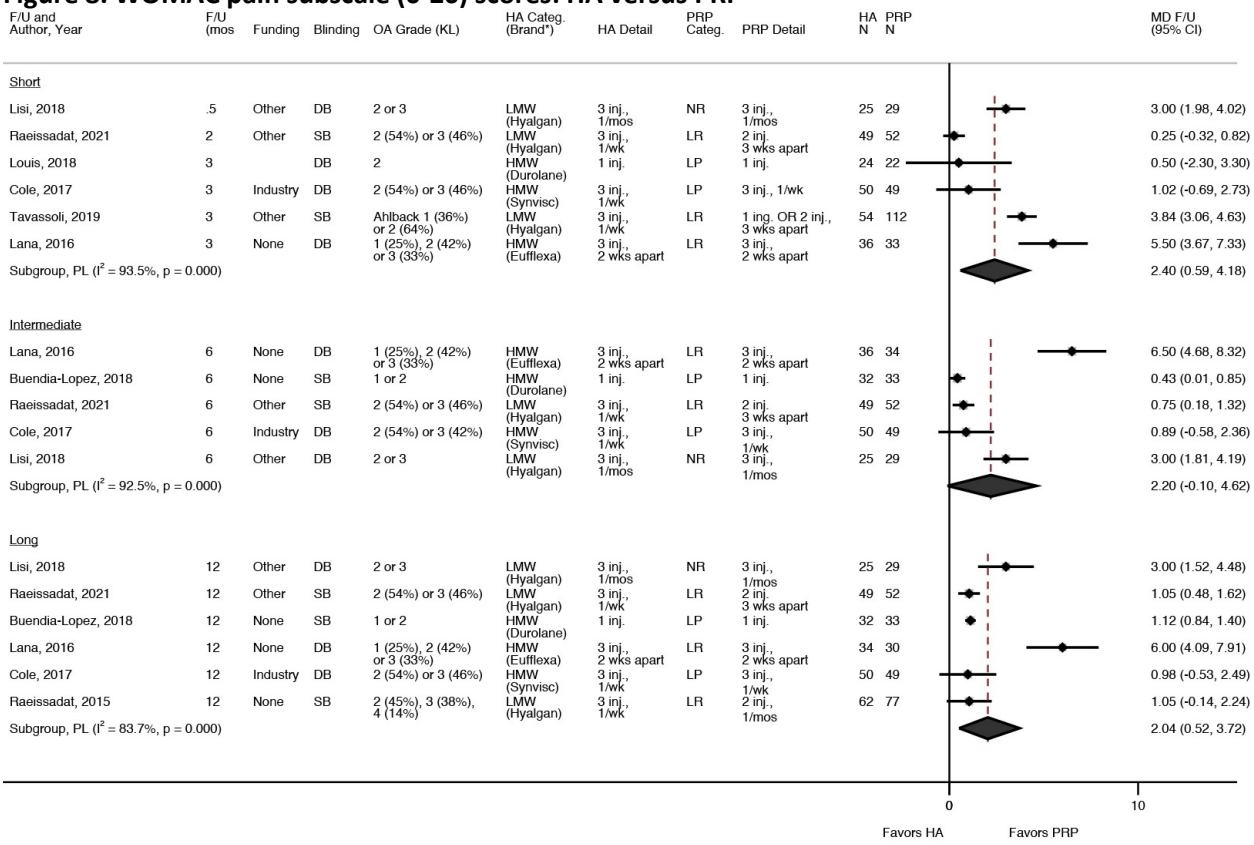
Pain scores

WOMAC Pain subscale scores (0-20 scale) were reported in seven RCTs[36,77,83,87,107,109,143]. Across six RCTs at short term, PRP was associated with moderate pain improvement versus HA (6 RCTs, MD 2.40, 95% CI 0.59 to 4.18, I^2=93.5%),[36,77,83,87,107,143] (Figure 8). Substantial heterogeneity was noted due to one extreme outlier estimate (MD of 5.50 versus other MDs of 0.5 to 3.8). There was a significant difference in baseline WOMAC pain scores between HA and PRP in the outlier trial and medians and ranges were reported (instead of means and standard deviations); although we used standard conservative methods for calculating estimates for meta-analyses, the confidence in the estimate for this trial is very low.[77] Following exclusion of the extreme outlier,[77] PRP was associated with small improvement in pain versus HA at short term (5 RCTs, N=480, MD 1.87, 95% CI 0.16 to 3.45, I^2=93.4%)[36,83,87,107,143] (Appendix H, Figure H2) however, substantial heterogeneity remained, likely due to other, but less extreme outlying values. One such outlier was a poor-quality RCT which reported results based on numbers of knees, not patients.[143] The extent to which different HA agents (e.g., high versus low molecular weight or formulation) and/or PRP preparation or injection protocols) may contribute to the heterogeneity. Further sensitivity analyses excluding poor quality studies as well as the outlier slightly increased the effect estimates but results were no longer statistically significant (3 RCTs, MD 1.94, 95% CI -0.24 to 3.52, I^2=63.9%).[36,83,87]

Similarly at intermediate term, PRP was associated with moderate pain improvement versus HA on the WOMAC Pain scale (5 RCTs, MD 2.20, 95% CI 0.10 to 4.62, I^2= 92.5%)[24,36,77,83,107]; however, the same extreme outlier trial (MD of 6.5 versus other ranging from 0.43 to 3.0) and substantial heterogeneity were again noted (Figure 8). Following exclusion of the extreme outlier,[77] a small improvement in pain was seen with PRP versus HA and heterogeneity was reduced (4 RCTs, N=319, MD 1.16, 95% CI -0.01 to 2.47, I^2= 81.3%),[24,36,83,107] Appendix H, Figure H2. Another outlier was a poor-quality RCT which reported results based on numbers of knees, not patients.[143] Further sensitivity analyses excluding high risk of bias studies as well as the outlier resulted in a conclusion of no difference between HA and PRP and slightly increased heterogeneity (3 RCTs, MD 1.36, 95% CI -0.41 to 3.25, I^2=87.5%).[24,36,83]

Similarly at long term PRP was associated with small pain improvement versus HA on the WOMAC Pain scale (6 RCTs MD 2.04, 95% CI 0.52 to 3.72, I^2= 83.7%)[24,36,77,83,107,109] and the same extreme outlier trial[77] and substantial heterogeneous are noted (Figure 8). Exclusion of the extreme outlier again reduced the magnitude of effect and there was substantial reduction in heterogeneity (5 RCTs, N=458, MD 1.15, 95% CI 0.90 to 1.57 I^2=36.2%)[24,36,83,107,109] (Appendix H, Figure H2). Further sensitivity analyses excluding high risk of bias studies as well as the outlier did not substantially impact effect size and increased heterogeneity (3 RCTs, MD 1.18, 95% CI 0.60 to 2.68).[24,36,83]

Figure 8. WOMAC pain subscale (0-20) scores: HA versus PRP



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SB = Single blinded

VAS pain scores

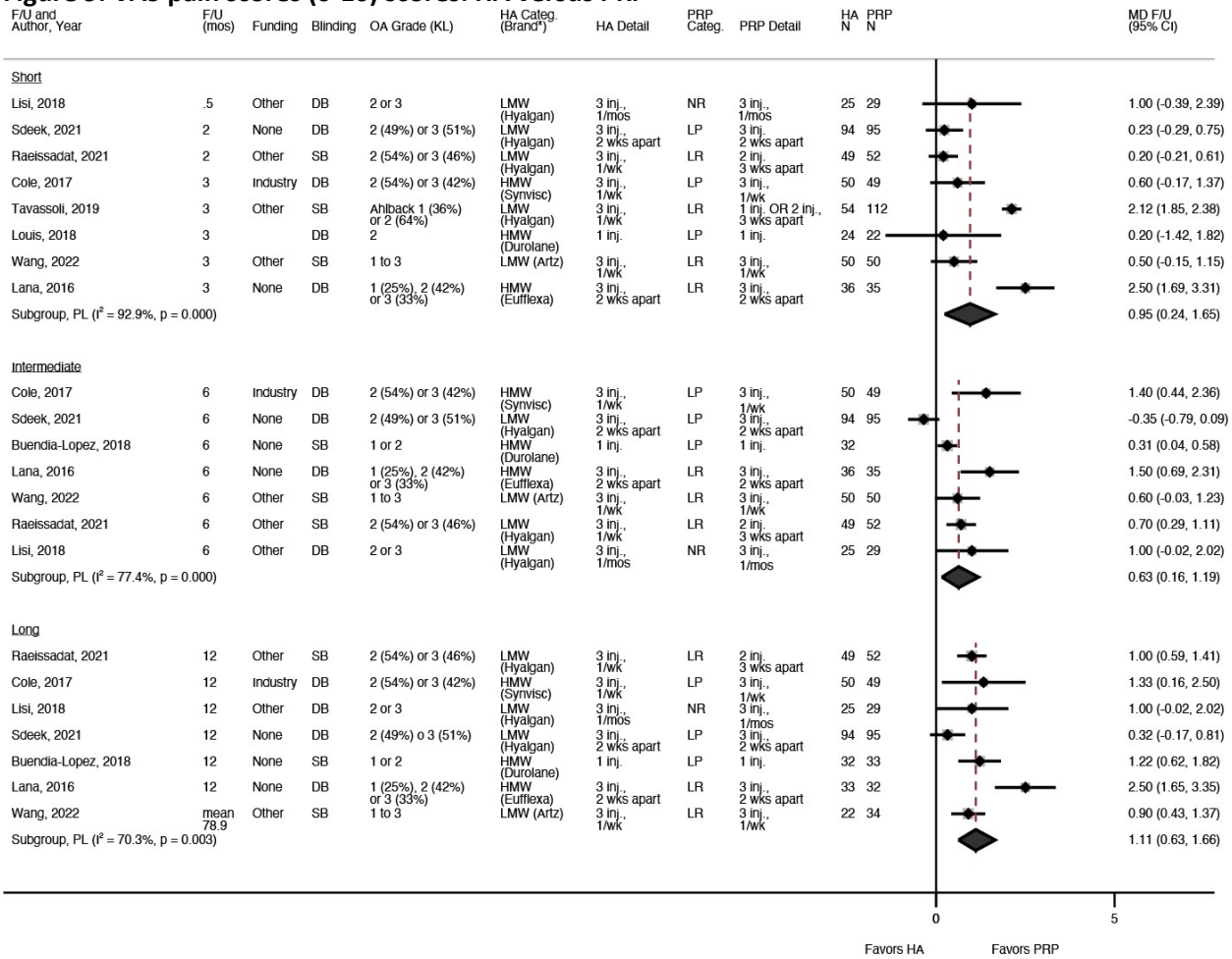
VAS pain scores (0-10 scale) were reported by eight RCTs. Across them at short-term, PRP was associated with small improvement in pain versus HA (8 RCTs, MD 0.95, 95%CI 1.65, I^2= 92.9%),[36,77,83,87,107,126,143,154] (Figure 9). There was substantial heterogeneity, and two extreme outlier estimates were noted.[77,143] One outlier was a poor-quality RCT which reported results based on numbers of knees, not patients.[143] The other outlier from a fair quality RCT reported medians and ranges were reported (instead of means and standard deviations).[77] Removal of these two outliers resulted in substantial reduction in effect size and in heterogeneity. Although the estimate was statistically significant, it did not meet the threshold for small effect (6 RCTs MD 0.33, 95% CI 0.07 to 0.63, I^2=0%),[36,83,87,107,126,154] (Appendix H, Figure H3). Exclusion of four poor quality RCTs[107,126,143,154] suggests that PRP may confer small improvement in pain vs HA, but results were not statistically significant (4 RCTs, MD 1.19, 95% CI -0.06 to 2.30, I^2=77.8%)[36,77,83,87] and the one extreme outlier again noted.[77]

At intermediate term, PRP was associated with small improvement in VAS pain scores versus HA (7 RCTs, MD 0.63, 95% CI 0.16 to 1.19, I^2=77.4%) (Figure 9) and substantial heterogeneity was seen with one RCT favoring HA. Exclusion of the RCT which reported medians and ranges(instead of means and standard deviations),[77] continued to suggest small improvement in pain with PRP versus HA but the effect size

was smaller (6 RCTs, MD 0.49, 95 % CI 0.04 to 1.04).[24,36,83,107,126,154] Exclusion of the four poor quality RCTs,[107,126,143,154] which included this trial did not reduce heterogeneity and slightly increased the effect size, however conclusions that PRP was associated with a small improvement in pain versus HA were the same (4 RCTs, MD 0.92, 95% CI 0.29 to 1.72, I^2=74.7%).[24,36,77,83]

Long term, PRP was associated with a moderate improvement in VAS pain versus HA (7 RCTs MD 1.1, 95% CI 0.63 to 1.66, I^2= 70.3%). Exclusion of the outlier RCT that reported medians and ranges (instead of means and standard deviations)[77] reduced effect size reflecting a small pain improvement favoring PRP over HA and substantially reduced heterogeneity (6 RCTs, MD 0.88, 95% CI 0.57 to 1.24, I2=29.9%).[24,36,83,107,126,154] Following exclusion of four poor-quality trials,[107,126,143,154] PRP was associated with a moderate improvement in pain versus HA at long term (4 RCTs MD 1.52 95% CI 0.76 to 2.28, I^2=58%).[24,36,77,83]

Figure 9. VAS pain scores (0-10) scores: HA versus PRP



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SB = Single blinded

5.1.1.2.3 Outcomes assessing multiple domains

WOMAC Total Score

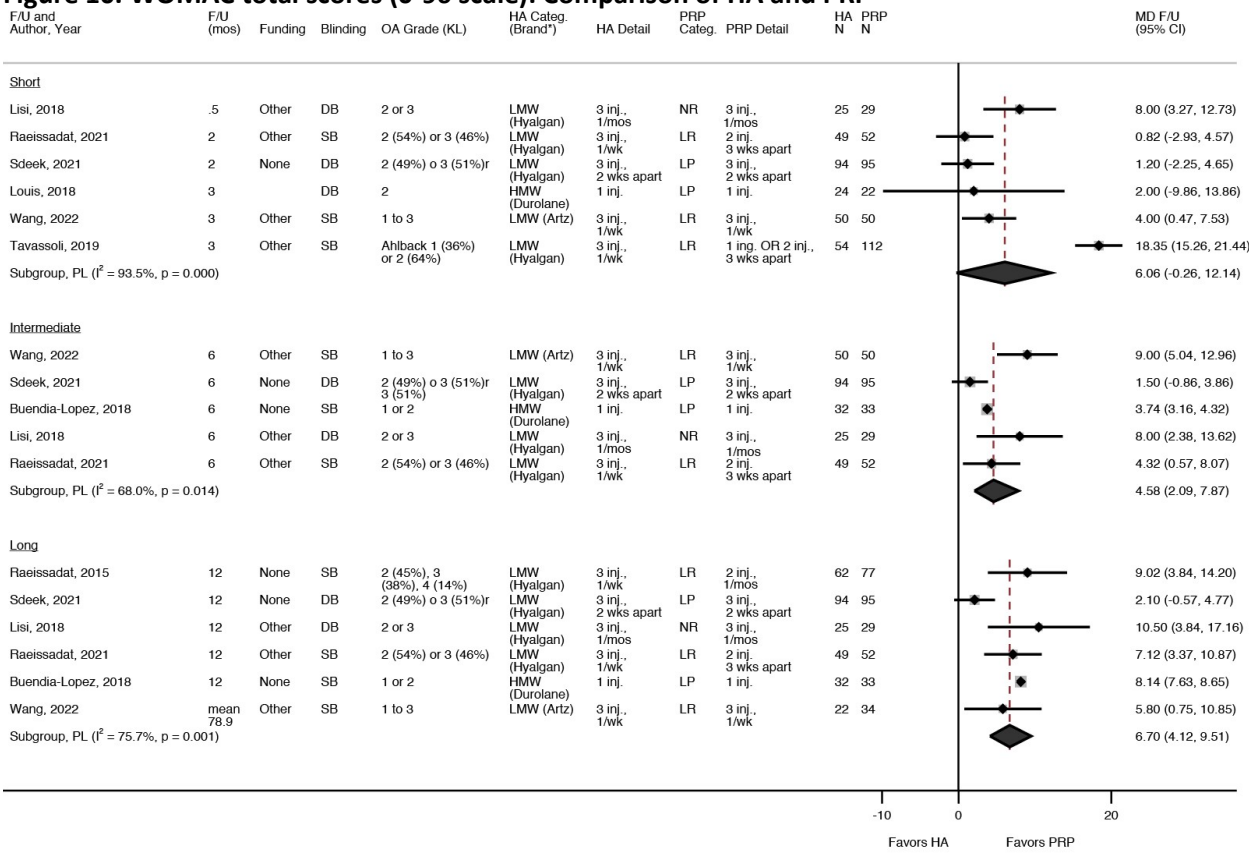
Treatment response based on **WOMAC Total Scores** was reported in one good quality RCT and one poor quality RCT, each using different response thresholds. The good quality RCT reported a moderately lower likelihood of response following single HA injection compared to single PRP injection (N= 46, 45.8% vs. 72.7 % RR 0.63 95%CI 0.38 to 1.04) based on score improvement of > 5 points or 40% from baseline at short term.[87] There was no difference at intermediate term (N=34, 58.8% vs. 52.9%, RR 1.11, 95% CI 0.61 to 2.02); a 26% loss to follow-up is noted however long term. The poor-quality trial compared three HA injections given at 3-week intervals with two PRP injection protocols (single PRP injection and 2 injections at 3-week intervals).[143] The two PRP arms were combined for these analyses. The trial reported results for two response thresholds, a 30% decrease in WOMAC Total Score and a 50% decrease at short term. No HA recipients met either a 30% or 50% decrease in scores from baseline. The proportion of responders following PRP using the 30% threshold was 73.2% and none of PRP recipients met the 50% response threshold.

Six of the 11 RCTs comparing HA versus PRP assessed function based on the **WOMAC Total score** (0-96 scale). Across meta-analyses, effect estimates were imprecise and heterogeneity in estimates was common. It is unclear to what extent study quality and/or differences in preparations or injection protocols may contribute to heterogeneity (Figure 10). There was no difference in function based on the **WOMAC Total score** (0-96 scale) between HA and PRP at short term (6 RCTs MD 6.06, 95% CI -0.26 to 12.14, I^2=93.5%)[83,87,107,126,143,154]; substantial heterogeneity was noted (Figure 10). Exclusion of one poor-quality outlier RCT[143] which reported results based on numbers of knees, not patients reduced the effect size and substantially reduced the heterogeneity (5 RCTs, MD 3.09, 95% CI 0.21 to 6.28, I^2=42.6%).[83,87,107,126,154] The effect estimate was below the threshold for a small effect. Heterogeneity may in part be due to difference in length of post-procedure follow-up, with one trial reported 15 days compare with two to three months in the other trials.[83] Analysis confined to fair or good trials increased effect size and reduced the heterogeneity (2 RCTs, MD 7.18, 95% CI -1.05 to 12.60 I^2=0%).[83,87]

At intermediate term, the estimated mean difference was below the threshold for a small effect and the clinical importance is unclear (5 RCTs, MD 4.58, 95%CI 2.09 to 7.87, I^2=68.0%).[24,83,107,126,154] Analysis confined to fair or good trials decreased the effect size and the heterogeneity was reduced (2 RCTs, MD 3.79, 95% CI 2.92 to 6.29, I^2=54.1%).

Long term, PRP was associated with a small improvement in function versus HA (6 RCTs, MD 6.70, 95%CI 4.12 to 9.51, I^2=75.7%) and there was substantial heterogeneity,[24,83,107,109,126,154] (Figure 10). One poor quality trial reported results at 12 months and 36 months.[126] Sensitivity analysis using the 36 month follow up slightly increased effect size in the meta-analysis and reduced heterogeneity but did not change the conclusions for a small improvement in function with PRP versus HA (6 RCTs, MD 7.03, 95% CI 4.88 to 9.22 I2=59.4%).[24,83,107,109,126,154] Analysis confined to fair or good trials increased the effect size and it remained consistent with a small effect; heterogeneity was reduced (2 RCTs, MD 8.15. 95%CI 7.26 to 9.38, I^2= 0%).[24,83]

Figure 10. WOMAC total scores (0-96 scale): Comparison of HA and PRP



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SB = Single blinded, Wks = Weeks

Additional invasive procedures

One poor quality post-hoc analysis of an RCT reported comparing PRP weekly injections of leukocyte-rich PRP (LR-PRP) for 3 weeks with high-molecular-weight HA followed patient to a mean of 78.9 months (follow-up 85%).[154] HA was associated with substantially higher risk of receiving either arthroscopic knee surgery (AKS) or total knee arthroplasty (TKA) compared with PRP (30.2% versus 11.9%, RR 2.54, 95% CI 0.99 to 6.5). The effect estimate is imprecise. TKA was the most common surgery in both groups (10/13 and 4/5 surgeries.

5.1.1.2.4 Secondary Outcomes

Symptom recurrence (e.g., persistent, or increased pain, reduced function) resulting in need for additional injection of HA or PRP within 2 months after protocol completion was not reported by included RCTs. One poor-quality RCT reported that substantially more HA recipients had "any" reintervention (including re-injection and pain medication use) compared with PRP (56% vs. 16,5%, RR 3.46, 95% CI 1.58 to 7.75). Additional HA injections were given and no additional PRP injections were given, however the timing was not reported by the authors.

Quality of Life: One poor quality RCT reported substantial improvement following PRP versus HA in both the SF-36 MCS (MD 53.01, 95%CI 20.63 to 85.39) and PCS (MD 66.57, 95% CI 35.47 to 97.67) at long term (12 months).[109]

Medication use: One poor-quality RCT reported that 16.6 % of HA recipients and 8.1% of PRP recipients took pain medications. Baseline medication use was not provided, and specific medications were not described.

Return to normal activities: None of the included studies reported on to return to activities.

5.1.1.3 HA versus Steroid

Six RCTs (in six publications)[11,21,25,78,142,148] compared HA with corticosteroids for the treatment of knee OA (Appendix G). Sample sizes ranged from 82 to 442 (total N=1,044). The average age of participants was 62.5 years (range, 57.8 to 70.1), 64.0 percent were female (range, 49% to 85.0%) and the average BMI was 27.8 (range, 26.1 to 28.3). The severity of OA was classified as Kellgren-Lawrence grade 2 in 35.3 percent of participants (range, 22.2% to 48.9%) and grade 3 in 55.8 percent (range, 41.4% to 64.0%), across three trials[78,142,148]; two trials[11,21] included participants with grade 2 or 3 OA only but did not provide more detail and one trial[25] did not report OA grade. Most trials excluded participants with grade 1 (minor) and grade 4 (severe) OA; however, one trial[142] included a small proportion of participants with grade 1 (22.2%) and 4 OA (14.1%). Symptom duration was 4.8 years in one trial[78] reporting duration. One trial[11] required participants to be symptomatic for 3 months for inclusion and no other trials reported a minimum duration required for inclusion.

Single injection (5 trials)[11,25,78,142,148] and two-injection (1 trial)[21] regimens were used for HA therapy; The two-injection trial[21] included a week-long interval between injections. Two trials used low molecular weight formulations (Hyalgan, 1 trial[11]; Hymovis, 1 trial[21]) and four trials used high molecular weight formulations (Durolane, 1 trial[78]; Synvisc, 2 trials[25,142]; Synvisc-One, 1 trial[148]). Doses ranging from 48mg to 60mg per injection where reported. Single (5 trials)[11,25,78,142,148] and two-injection (1 trial)[21] regimens were used for corticosteroid therapy; the two-injection trial[21] included a week-long interval between injections. One trial[78] used methylprednisolone, two trials[25,142] used triamcinolone acetonide, one trial[148] used triamcinolone hexa-acetate, and two trials[11,21] did not report the corticosteroid used. Doses ranged from 20mg to 40mg per injection where reported. No trials reported using imaging guidance. Reporting of cointerventions varied but acetaminophen (3 trials),[21,78,142] NSAIDs (1 trial),[21] and muscle relaxants (1 trial)[142] were most commonly permitted. In general, patients were required to stop using non-acetaminophen pain relievers and steroids before trials entry and were not allowed to use them until the trial was complete. Follow-up ranged from 3 (short term) to 12 months (long term) with most trials reporting short and intermediate term results; one trial[11] reported short term results only and one[21] reported long term results. One trial[78] received industry funding, two trials[11,142] received funding from non-industry sources (e.g., governments, university, etc.), and three trials[21,25,148] reported no funding. Trials were located in India,[148] Iran,[11] Italy,[21] Thailand,[142] Canada and the United States and Sweden,[78] and Brazil[25] (One in each country).

One trial[11] were considered good quality, one[142] fair, two[25,148] poor, and one[21] considered fair in the short term and poor in the intermediate and long term. Primarily methodological shortcomings in fair trials

included lack of care provider and patient blinding and high attrition; in addition, the three poor-quality trials also did not control for confounding and did not use intention to treat.

5.1.1.3.1 Function

Function "Success"

No studies reported on the proportions of participants meeting different thresholds for a clinically important change in function.

Function: scores

One good-quality trial[11] and two poor-quality trials[25,148] comparing HA and steroid injections reported on functional measures (Table 12). Across the reported measures, there was no difference between HA and steroid injections short or intermediate term. The only pooled analysis was across the two poor-quality trials and, again, there was no difference in function across them at short or intermediate term on the KSS Function measure.

Table 12. Summary of function outcomes: HA versus steroid

Outcome	Study Quality	F/U	MD (95% CI)*
Individual RCTs			
WOMAC Physical Function (0-68, lower= better)	Askari 2016 Good	3 mos	0.25 (-3.69 to 4.19)
KOOS ADL (0-100, higher =better)			0.37 (-5.42 to 6.61)
Lysholm (0-100, higher = better)	Campos 2017 Poor	3 mos	-4.0 (-14 to 6.00)
		6 mos	-1.3 (-10.49 to 7.89)
Pooled			**MD (95% CI), I^2**
KSS Function (0-100, higher = better)	2 RCTs (N=160) Campos 2017 Viashya 2017 Poor	3 mos	-2.63(-17.4 to 12.40), I^2=61.6%
		6 mos	-6.63 (-22.6 to 9.73), I^2=67.1%

CI: confidence interval; f/u: follow-up; HA: hyaluronic acid; MD: mean difference; RCT: randomized controlled trial; *calculated

5.1.1.3.2 Pain

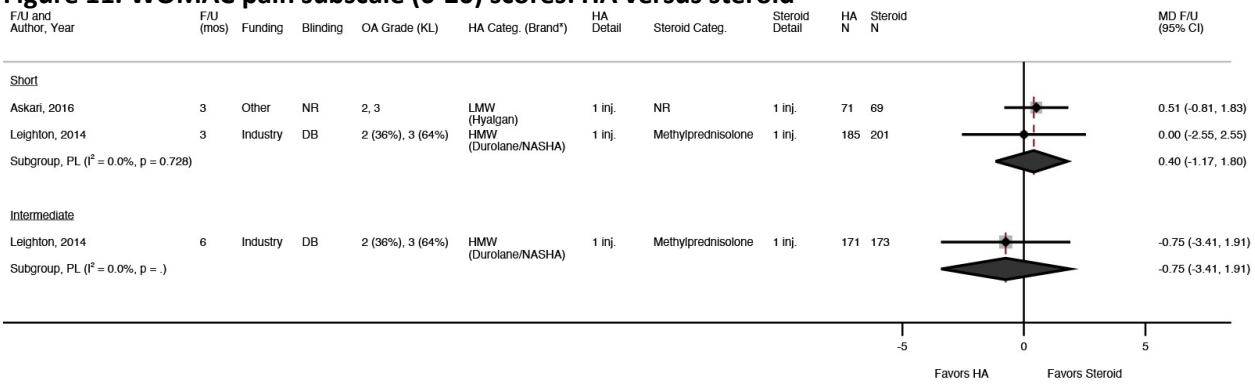
Pain "Success"

No studies reported on the proportions of participants meeting different thresholds for clinically important changes in pain.

Pain scores

Two good quality trials reported **WOMAC pain scores** (0-20 scale).[11,78] There were no differences between HA and steroid injections at short term (2 RCTs, N=526, MD 0.40, 95% CI -1.17 to 1.80, I^2=0%)[11,78] or in the one RCT at intermediate term (1 RCT, N=386, MD -0.75, 95% CI -3.41 to 1.91),[78] (Figure 11).

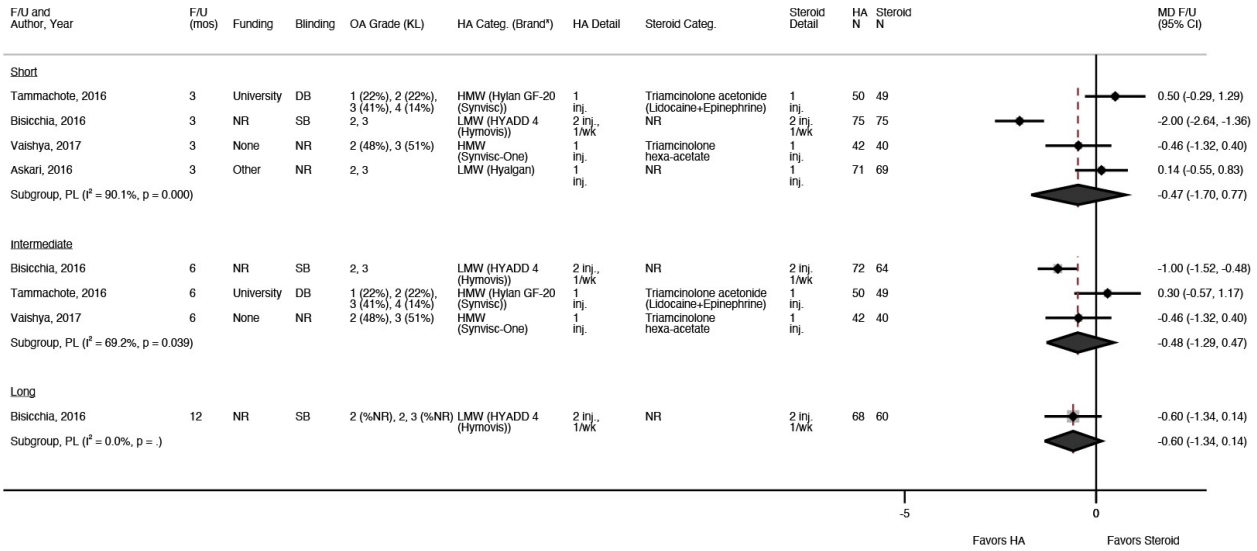
Figure 11. WOMAC pain subscale (0-20) scores: HA versus steroid



Categ. = Category CI = Confidence interval, DB = Double blinded, Dist = Distributed, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis

Four RCTs reported **VAS pain scores** (0-10 scale)[11,21,142,148]. There was no difference between HA and steroid injections at short-term (4 RCTs, N=471, MD – 0.47, 95 % CI -1.7 0 to 0.77, I^2=90.1%). None of the sensitivity analyses changed this conclusion. Exclusion of the outlier trial substantially reduced the effect size and the heterogeneity (3 RCTs, MD 0.09, 95% CI -0.52 to 0.66, I^2=23.8%).[11,142,148] This poor-quality outlier trial was the only trial to use two injections of both HA and steroid; all others were single injection; HA was associated with at moderate improvement in (MD -2.0, 95% CI -2.64 to -1.36) at short term in this trial.[21] It is unclear whether the difference in findings between this trial and the others relates to differences in injection protocols and/or study quality. Analyses excluding the two poor quality RCTs[21,148] reduced effect size and heterogeneity (2 RCTs MD 0.30, 95% CI -0.33 to 0.96, I^2=0%).[11,142] Similarly, at intermediate term, no difference between treatment was seen (3 RCTs, N=317, MD 0.48 95 % CI -1.29 to 0.47, I^2=69.2%).[21,142,148] The same conclusion was reached following exclusion of the same poor-quality outlier that reduced heterogeneity (2 RCTs MD -0.08, 95% CI -1.02 to 0.86, I^2=32.7%) and focus on the only good quality trial at this time (1 RCT, MD 0.30, 95% CI -0.57 to 1.17). There was no difference between HA and steroid injection long term in one poor-quality trial (MD -0.60, 95% CI -1.34 to 0.14)[21]. This poor-quality trial excluded patients who had repeat injections from statistical analyses at 26 weeks potentially impacting both intermediate and long-term results and potentially contributing to positive results favoring HA.

Figure 12. VAS pain (0-10) scores: HA versus steroid

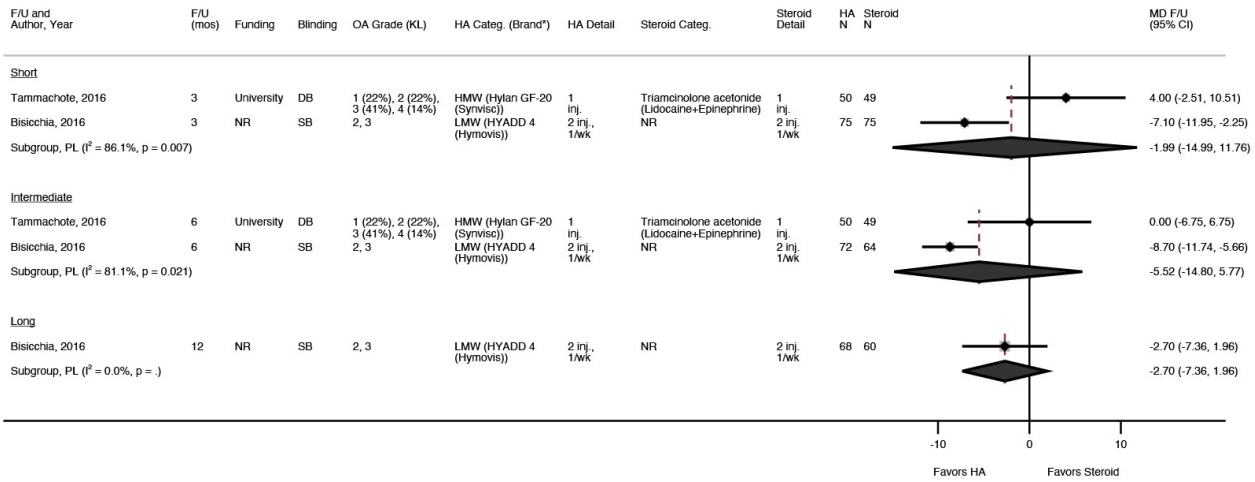


Categ. = Category CI = Confidence interval, DB = Double blinded, Dist = Distributed, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, MD = Mean difference, Mos = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded

5.1.1.3.3 Outcomes assessing multiple domains

There were conflicting results across one fair quality RCT[142] and one poor quality RCT[21] that reported on **WOMAC Total Score** (0-96) at short and intermediate term. There was no difference between single HA and steroid injections in one moderate quality trial at either time. In contrast, the poor-quality trial comparing 2 injections for both treatments found a small improvement in WOMAC total score with HA versus steroid. It is unclear whether the difference in findings relates to differences in injection protocols and/or study quality. The poor-quality trial excluded patients who had repeat injections from statistical analyses at 26 weeks potentially impacting both intermediate and long-term results and potentially contributing to positive results favoring HA. All estimates were imprecise.

Figure 13. WOMAC total (0-96) scores: HA versus steroid



Categ. = Category CI = Confidence interval, DB = Double blinded, Dist = Distributed, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, Inj. = Injection KL = Kellgren-Lawrence grade, LMW = Low molecular weight, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded

One poor quality trial[25] reported no difference between HA and steroid on the **KSS total score** (0-100) at short term (MD -5.0, 95% CI -16.87 to 6.87) but a small improvement in this score at intermediate term favoring HA over steroid (MD -10.3, 95% CI -20.55 to -0.05). All estimates are imprecise.

Additional invasive procedures: One poor quality trial reported that knee arthroplasty was "indicated" in one HA patient and two patients who had steroid injections (1.3% vs. 2.6%).

5.1.1.3.4 Secondary Outcomes

Symptom recurrence

Persistent, or increased pain, reduced function resulting in need for additional injection of HA or PRP within 2 months after protocol completion was not reported by included RCTs. One poor quality trial[21] reported that fewer repeat injections occurred with HA versus steroids (8% vs. 17.3%), however the timing of repeat injections was not specified. Authors state that repeat injections were done with either HA, steroid or PRP regardless of initial treatment assignment. It is unknown which of these agents was used for retreatment patients in either group. Evidence is insufficient.

Quality of Life: This was not reported by included trials.

Medication use: This was not reported by included trials.

Return to normal activities: This was not reported by included trials.

5.1.1.4 HA vs. NSAID

Two RCTs (across two publications)[24,56] compared HA with NSAID intervention for treatment of KOA (Appendix G). Sample sizes were 69 and 62 (total N=131), average age was 59.3 (range, 57 to 61.9), 68.5 percent of participants were female (range, 52.3% to 86.4%), and average BMI was 26.5 (range, 25.0 to 28.1). The severity of OA was classified as Kellgren-Lawrence grade 1 in 28.4 percent of participants (range, 0% to 54.0%), grade 2 in 49.9 percent (range, 46.0% to 54.3%), and grade 3 in 21.6 percent (range, 0% to 45.7%); Both studies excluded participants with grade 4 OA and no minimum duration of OA symptoms or mean duration of symptoms was reported. One RCT[24] used high molecular weight HA (Durolane, 60mg, 2mL) in a single injection and oral etoricoxib (60 mg daily for 52 weeks) while the other RCT[56] used high molecular weight HA (Orthovisc, 30mg/2mL) in a series of three injections given weekly and intramuscular etofenamate (Flexo, 100mg/2mL) in a series of seven injections over 7 days. No imaging guidance was reported for either study. Both trials were considered fair quality, suffering primarily from lack of clarity regarding concealment and inability to blind patients. Neither trial reported any funding.

5.1.1.4.1 Function

Success

One RCT[24] reported on WOMAC physical function success, described as a 20 percent or greater decrease in score. There was no significant difference in function success between groups. No patients in either group met the criteria in the long term (Table 13).

Scores

One RCT[24] reported on WOMAC physical function scores (0-68 scales). HA was associated with a small functional improvement compared to NSAID (MD -4.07, 95% CI-4.48 to 3.66) in the intermediate term, but no difference between groups in the long term (Table 14).

5.1.1.4.2 Pain

Success

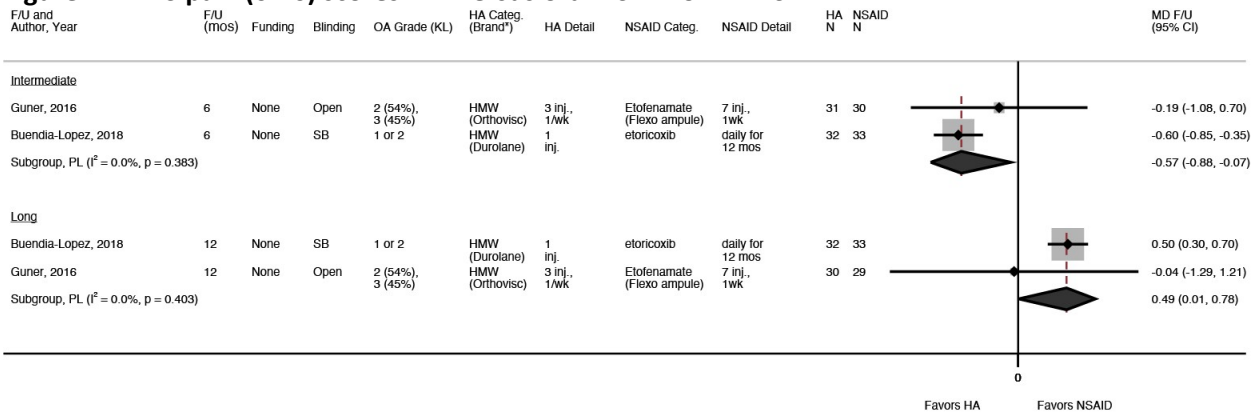
One RCT[24] reported on VAS pain and WOMAC pain success, described as a 20 percent or greater decrease in score for each. There was no significant difference in function success between groups. No patients in either group met the criteria. in the long term (Table 13).

Scores

Both RCTs[24,56] reported VAS pain scores (scale, 0 to 10) and one trial comparing oral etofenamate[24] reported WOMAC pain scores (scale, 0 to 20). Intermediate term across the trials, HA was associated with a small improvement in VAS pain (2 RCTs, MD 0.57, 95% CI -0.88 to 0.07, I^2=0%). Given the heterogeneity in treatments, the trials could be considered separately. Long-term, pooled estimates suggest that NSAIDs were associated with a small pain improvement due to a change in the effect direction in the trial comparing HA to oral etofenamate.[24] The trial comparing HA with IM etofenamate[56] showed no difference between treatments at either time (Figure 14). There was a no improvement in WOMAC pain for HA versus NSAID in the intermediate term in the trial comparing HA with oral etoricoxib as the estimate was below the threshold for a small effect, (MD -0.6 95% CI -0.93, -0.27).

There were also no differences between groups long term, as estimates were again below the threshold for a small effect; the effect was in the opposite direction favoring the NSAID (Table 14). All estimates were imprecise.

Figure 14. VAS pain (0-10) scores: HA versus oral NSAID or IM NSAID*

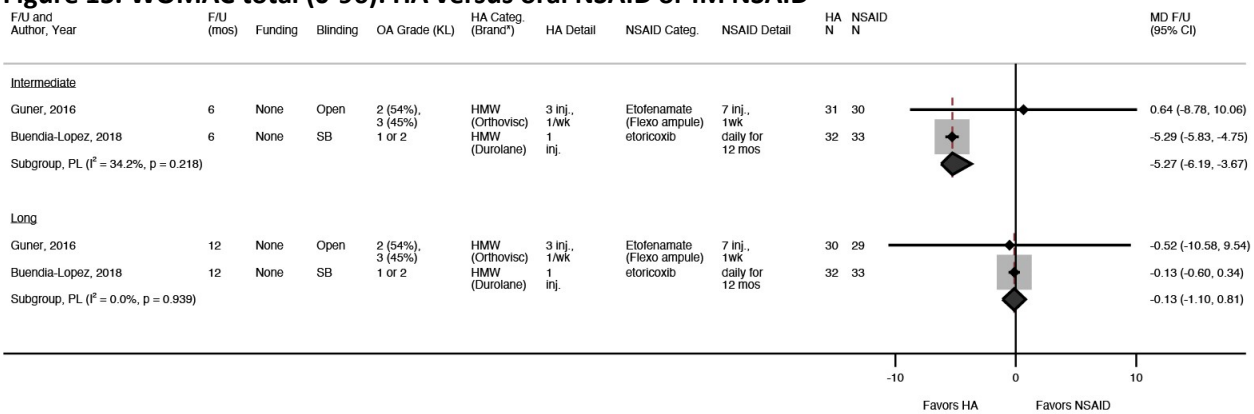


Categ. = Category CI = Confidence interval, Dist = Distributed, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, IM = intramuscular, Inj. = Injection KL = Kellgren-Lawrence grade, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded, Wks = Weeks.
* Oral NSAID was used in Buendia-Lopez, IM NSAID was used in Guner; IM= intramuscular

Outcomes assessing multiple domains

Two RCTs[24,56] reported on WOMAC Total Scores (0-96 scale). At intermediate term, HA was associated with a small improvement on this score (2 RCTs MD -5.27, 95%CI -6.19 to – 3.67, I2=34.2%); results are driven the one trial comparing HA to oral etroicoxib.[24] As discussed above, it is best to consider the two RCTs' results separately; the one trial shows improvement in WOMAC Total score with HA versus oral etroicoxib short term. The trial comparing HA with IM etofenamate showed no difference between treatments at either time (Figure 15).

Figure 15. WOMAC total (0-96): HA versus oral NSAID or IM NSAID*



Categ. = Category CI = Confidence interval, Dist = Distributed, F/U = Follow-up, HA = Hyaluronic acid, HMW = High molecular weight, IM= intramuscular, Inj. = Injection KL = Kellgren-Lawrence grade, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded, Wks = Weeks
*Oral NSAID was used in Buendia-Lopez, IM NSAID was used in Guner.

Table 13. Function Success and Pain Success: HA vs. Oral NSAID for Knee OA

Study	Outcome	Threshold	F/U	HA % (n/N)	Oral NSAID % (n/N)	RR (95% CI)*
Function						
Buendia-Lopez, 2018	WOMAC Physical Function Success	20% Decrease	6 mos.	15.6% (5/32)	12.1% (4/33)	1.29 (0.38, 4.37)
			12 mos.	0% (0/32)	0% (0/33)	incalculable
Pain						
Buendia-Lopez, 2018	VAS Pain Success	20% Decrease	6 mos.	25% (8/32)	18.2% (6/33)	1.38 (0.54, 3.52
			12 mos.	0% (0/32)	6.1% (2/33)	0.26 (0.01, 5.50)
	WOMAC Pain Success	20% Decrease	6 mos.	21.9% (7/32)	15.2% (5/33)	1.44 (0.51, 4.08)
			12 mos.	0% (0/32)	0% (0/33)	incalculable

CI = Confidence interval, F/U = Follow-up, HA = Hyaluronic acid, Mos. = Months, NSAID = Non-steroidal anti-inflammatory drug, RR = Risk ratio, WOMAC = Western Ontario and McMaster osteoarthritis index
*calculated by AAI.

Table 14. Function and Pain Scores: HA vs. Oral NSAID for Knee OA

Study	Outcome	F/U	HA Mean ± SD or median (range)	Oral NSAID Mean ± SD or median (range)	MD (95% CI)*
Function					
Buendia-Lopez, 2018	WOMAC Physical Function Scores (0=68)	0 mos.	32.53 ± 7.1 (n=36)	32.48 ± 6.8 (n=35)	-
		6 mos.	28.62 ± 0.9 (n=32)	32.69 ± 0.8 (n=33)	-4.07 (-4.48, -3.66)
		12 mos.	32.65 ± 0.7 (n=32)	32.78 ± 0.73 (n=33)	-0.13 (-0.48, 0.22)
Pain					
Buendia-Lopez, 2018	WOMAC Pain Scores (0-20)	0 mos.	6.03 ± 1.2 (n=36)	6.12 ± 1.2 (n=35)	-
		6 mos.	5.15 ± 0.84 (n=32)	5.75 ± 0.43 (n=33)	-0.6 (-0.93, -0.27)
		12 mos.	5.96 ± 0.4 (n=32)	5.72 ± 0.45 (n=33)	0.24 (0.03, 0.45)

CI = Confidence interval, F/U = Follow-up, HA = Hyaluronic acid, MD = Mean difference, Mos. = Months, NSAID = Non-steroidal anti-inflammatory drug, OA = Osteoarthritis, RCT = Randomized controlled trial, SD = Standard deviation, WOMAC = Western Ontario and McMaster osteoarthritis index.
*calculated by AAI

Additional invasive procedures: Neither trial reported on additional invasive procedures.

5.1.1.4.3 Secondary Outcomes

Symptom recurrence: Persistent, or increased pain, reduced function resulting in need for additional injection of HA or PRP within 2 months after protocol completion was not reported by included RCTs.

Quality of Life: This was not reported by included trials.

Medication use: This was not reported by included trials.

Return to normal activities: This was not reported by included trials.

5.1.1.5 HA versus Usual Care and Other Active Treatments

Three RCTs that compared HA with usual care,[63] with physical therapy (PT) and with prolotherapy,[115] and with exercise[120] were identified that met inclusion criteria. One RCT that compared different HA preparations also met inclusion criteria.[162] For details regarding study characteristics and patient populations, see Appendix G. Details regarding study quality can be found in Appendix E.

5.1.1.5.1 HA versus usual care

One poor-quality RCT[63] compared HMW HA with guideline-based usual care (including pain medication, physical therapy and lifestyle recommendations). This RCT reported KOOS ADL function scores as well as NRS pain scores both resting and during activity. Data for these measures was graphically presented; means were estimated from author's graphs. No information on estimate variance (e.g., standard deviation) was reported and results for test of significance are reported only for the whole follow up period. The estimated mean differences in KOOS ADL short term may be consistent with small functional improvement but estimates at intermediate and long term are below the threshold for a small effect. Authors state that HA was favored, p= 0.010, across the study period. Authors report no difference between HA and usual care for NRS pain during activity across the study period (p=0.060). All estimated differences between groups were below the threshold for a small effect. (Table 15). Authors also report that HA was associated with a slightly higher likelihood of meeting OMERACT-OARSI response criteria than those receiving usual care (57% vs. 34%, RR 1.67, 95% CI 1.16 to 2.40) long term.

Table 15. Summary of pain and function outcomes: HA versus usual care (Hermans 2019)

Study	Outcome	F/U	HA (n=77) Mean ± SD or median (range)	Usual Care (n=79) Mean ± SD or median (range)	MD (95% CI)*
Function					
Hermans, 2019 N=156	KOOS ADL (0-100 (best))	0 mos.	53.0 ± NR	62.0 ± NR	-
		3 mos.	67.0 ± NR	61.3 ± NR	-5.7 (NR)
		9 mos.	66.2 ± NR	62.4 ± NR	-3.8 (NR)
		12 mos.	68.2 ± NR	64.2 ± NR	-4.0 (NR) (Authors report p=0.010 across the study period)
Pain					
		0 mos.	6.5 ± NR	5.75 ± NR	-

Hermans, 2019 N=156	NRS Pain Activity (0-10 (worst))	3 mos.	5.1 ± NR	5.5 ± NR	-0.4 (NR)
		6 mos.	5.2 ± NR	5.25 ± NR	-0.05 (NR)
		12 mos.	5 ± NR	5.25 ± NR	-0.25 (NR) (Authors report p=0.060 across the study period)

CI = Confidence interval, F/U = Follow-up, HA = Hyaluronic acid, KOOS ADL = Knee injury and osteoarthritis outcome score function in daily living, MD = Mean difference, Mos. = Months, NR = Not Reported, SD = Standard deviation, WOMAC = Western Ontario and McMaster osteoarthritis index.

5.1.1.5.2 HA versus physical therapy

One fair quality RCT[115] comparing HA with physical therapy (PT) reported results for the short term on the following outcomes: KOOS ADL, KOOS Sport and Recreation (S&R), VAS pain (0-10) and KOOS pain and KOOS total. KOOS subscores and total are a 0-100 scale. There was no difference between HA and PT in function based on KOOS ADL MD=6.2, 95% CI -0.82 to 13.21) however a small improvement favoring PT over HA was seen on the KOOS S&R (MD5.3, 95% CI 4.32 to 6.28). Physical therapy was associated with moderate improvement in VAS pain (MD 1.85, 95% CI 1.36 to 2.34, 0-10 scale) and small pain improvement based on the KOOS Pain subscale MD 8.2, 95% CI 5.10, 11.30). Based on the KOOS total score, which includes the pain, ADL and other domains, HA was associated with improvement over PT (MD-20.0, 95% CI -27.77 to -12.23) (Table 16).

Table 16. Summary of pain and function outcomes: HA versus physical therapy

Study	Outcome	F/U	HA Mean ± SD or median (range)	Physical Therapy Mean ± SD or median (range)	MD (95% CI)*
Function					
Rezasoltani, 2020 (N=60)	KOOS ADL (0-100 (best))	0 mos.	33.7 ± 13.6 (n=30)	34.7 ± 12.9 (n=30)	-
		3 mos.	36.5 ± NR (n=27)	42.7 ± NR (n=28)	6.2 (-0.81, 13.21)
	KOOS S&R (0-100 (best))	0 mos.	10.8 ± 1.9 (n=30)	13.0 ± 1.8 (n=30)	-
		3 mos.	12.0 ± NR (n=27)	17.3 ± NR (n=28)	5.3 (4.32, 6.28)
Pain					
Rezasoltani, 2020 (N=60)	VAS Pain (0-10 (worst))	0 mos.	6.7 ± 0.7 (n=30)	7.2 ± 1.1 (n=30)	-
		3 mos.	5.75 ± NR (n=27)	3.9 ± NR (n=28)	1.85 (1.36, 2.34)
	KOOS Pain (0-100 (best))	0 mos.	20.2 ± 6.6 (n=30)	21.3 ± 5.0 (n=30)	-
		3 mos.	22.3 ± NR (n=27)	30.5 ± NR (n=28)	8.2 (5.10, 11.30)
Measures with multiple domains					
Rezasoltani, 2020 (N=60)	KOOS Total (0-100 (best))	0 mos.	89.9 ± 14.3 (n=30)	94.0 ± 15.1 (n=30)	-
		3 mos.	78 ± NR (n=27)	58 ± NR (n=28)	-20.0 (-27.77, -12.23)

ADL = Function in daily living, CI = Confidence interval, F/U = Follow-up, HA = Hyaluronic acid, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, NR = Not Reported, SD = Standard deviation, S&R = Sports and recreation, VAS = Visual analog score

5.1.1.5.3 HA versus prolotherapy

One fair quality RCT[115] comparing HA with prolotherapy reported short term outcomes only for KOOS total, ADL, and S&R function scores as well as VAS pain (0-10) and KOOS pain. KOOS subscores and total are a 0-100 scale. Prolotherapy was associated with substantial improvement in function versus HA on the KOOS ADL (MD 25.3, 95% CI 17.98 to 32.62) as well as a small benefit on KOOS S&R (MD 5.7, 95% CI 4.67 to 6.73). Prolotherapy was also associated with a large improvement compared to HA in VAS pain (MD 3.25, 95% CI 2.70 to 3.80) and a moderate improvement in KOOS pain (MD 10.8, 95% CI4.67 to 6.73) (Table 17). The KOOS total score, which includes the pain, ADL and other domains, suggest substantial benefit for HA, however (MD -31, 95% CI -38.41 to -23.59).

Table 17. Summary of pain and function results: HA versus prolotherapy

Study	Outcome	F/U	HA Mean ± SD or median (range)	Prolotherapy Mean ± SD or median (range)	MD (95% CI)*
Function					
Rezasoltani, 2020 (N=55)	KOOS ADL (0-100 (best))	0 mos.	33.7 ± 13.6 (n=30)	39.6 ± 14.1 (n=30)	-
		3 mos.	36.5 ± NR (n=27)	61.8 ± NR (n=28)	25.3 (17.98, 32.62)
	KOOS S&R (0-100 (best))	0 mos.	10.8 ± 1.9 (n=30)	12.4 ± 2.0 (n=30)	-
		3 mos.	12.0 ± NR (n=27)	17.7 ± NR (n=28)	5.7 (4.67, 6.73)
Pain					
Rezasoltani, 2020 (N=55)	VAS Pain (0-10 (worst))	0 mos.	6.7 ± 0.7 (n=30)	6.5 ± 1.3 (n=30)	-
		3 mos.	5.75 ± NR (n=27)	2.5 ± NR (n=28)	3.25 (2.70, 3.80)
	KOOS Pain (0-100 (best))	0 mos.	20.2 ±6.6 (n=30)	21.5 ± 5.9 (n=30)	-
		3 mos.	22.3 ± NR (n=27)	33.1 ± NR (n=28)	10.8 (4.67, 6.73)
Measures with multiple domains					
Rezasoltani, 2020 (N=60)	KOOS Total (0-100 (best))	0 mos.	89.9 ± 14.3 (n=30)	99.4 ± 13.7 (n=30)	-
		3 mos.	78 ± NR (n=27)	47 ± NR (n=28)	-31 (-38.41, -23.59)

ADL = Function in daily living, CI = Confidence interval, F/U = Follow-up, HA = Hyaluronic acid, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, NR = Not Reported, SD = Standard deviation, S&R = Sports and recreation, VAS = Visual analog score

5.1.1.5.4 HA versus exercise

One poor-quality RCT[120] comparing HA with exercise reported WOMAC function and WOMAC pain scores. There was no difference between HA and exercise in WOMAC function (reported as 0-1700 scale) in the short term (MD 89.2, 95% CI -32.26 to 212.66) or the long term and results are very imprecise There was no difference between groups for pain (Table 18).

Table 18. Summary of pain and function results: HA versus exercise

Study	Outcome	F/U	HA (n=53) Mean ± SD or median (range)	Exercise (n=51) Mean ± SD or median (range)	MD (95% CI)*
Function					
Saccomano, 2016	WOMAC Function (0-1700(worst))	0 mos.	842.4 ± 384.9	706.9 ± 254.0	-----
		3 mos.	685.7 ± 342.7	596.5 ± 298.9	89.2 (-34.26, 212.66)
		6 mos.	691.4 ± 363.8	618.5 ± 310.4	72.9 (-56.91, 202.71)
Pain					
Saccomano, 2018	WOMAC Pain (0-500(worst))	0 mos.	241.2 ± 101.9	216.0 ± 97.5	-----
		3 mos.	177.7 ± 100.5	154.6 ± 92.0	23.1 (-13.91, 60.11)
		6 mos.	181.5 ± 98.0	161.6 ± 90.2	19.9 (-16.28, 56.08)

CI = Confidence interval, F/U = Follow-up, HA = Hyaluronic acid, MD = Mean difference, Mos. = Months, NR = Not Reported, SD = Standard deviation, WOMAC = Western Ontario and McMaster osteoarthritis index.

5.1.1.5.5 HA (nonanimal-derived) versus HA (animal-derived)

One fair-quality RCT (N=349)[162] compared a noncross-linked, animal-derived HA product (Artz®; molecular weight 620-1,170 kDa) versus a stabilized, nonanimal source (bacterial fermentation) HA formulation (Durolane®; molecular weight 100,00 kDa) in patients with mild to moderate knee OA (KL Grades 2 and 3). The trial was conducted in China and was industry funded. Most patients were women (77%) with a mean age of 60 years old. Four injections of the animal-derived HA were administered in one group; a single injection of the nonanimal HA product followed by and three subcutaneous sham injections using an empty syringe were administered in the other group. There was a week interval between injections for both groups. Authors only report outcomes based on per-protocol analyses. There was no difference in function, WOMAC pain success (response), WOMAC Pain Scores (0-20 scale) or OMERACT-OARSI response between the two HA formulations. There was a substantially higher likelihood of success when only the "walking on a flat surface" item from the WOMAC Pain score was considered. See Table 19 below for results.

Table 19. Summary of outcomes for per-protocol, repeated measures analyses at 6 months: HA (Artz, Nonanimal derived) vs. HA (Durolane, Animal derived)

RCT Quality	Outcome	Artz* Change scores (95% CI) or % (n/N)	Durolane* Change scores (95% CI) or % (n/N)	Effect Size (95% CI) MD (Durolane – Artz) or OR
Zhang 2015 (N=319) Fair	WOMAC Physical Function (0-68) Scores	−12.58 (−13.39, −11.77)	−13.16 (−13.97, −12.35)	MD −0.58 (−1.69, 0.53)
	WOMAC Pain (0-20) Success†	81.6% (129/158)	78.9% (127/161)	OR 0.96 (0.65, 1.41)
	WOMAC Pain Success† Walking, flat surface item	96.8% (153/158)	91.9% (148/161	**OR 2.26 (1.23, 4.12)**

	WOMAC Pain (0-20) Scores	−6.05 (−6.39, −5.71)	−6.15 (−6.49, −5.81)	MD −0.10 (−0.56, 0.37)
	OMERACT-OARSI responders†	148 (93.7%)	151 (93.8%)	OR 1.12 (0.63, 2.05)

HA = hyaluronic acid; OA = osteoarthritis; OARSI = The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; OMERACT = Outcome Measures in Rheumatology committee; RCT = randomized controlled trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
*Artz recipients received 4 doses; A single dose Durolane followed by 3 subcutaneous sham injections using an empty syringe were delivered.
†Authors do not provide thresholds for response/success.

5.1.2 Key Question 1b: Harms and Complications (Safety) of HA for Knee OA

Key Points:

- There was substantial heterogeneity with regard to how adverse events were categorized, reported and described.
- Based on authors' definitions, serious AEs seem to be uncommon following HA injection (0% to 4.3%); SAEs ranged from 0% to 3.2% in the saline placebo group and no statistical differences were reported between groups.
- Serious HA treatment-related AEs ranged from 0% to 1.55%. All trials reporting these compared HA to saline placebo, reporting no events for that group.
- Treatment-related AEs (variably defined, not specified as serious) were more common and generally there were no differences between HA and comparator groups.
    - For comparisons of HA with saline, events related to HA ranged from 0% to % 26.9% compared with 0% to 25.8% following saline injection. Differences were statistically significant in one RCT (15.7% vs. 5.5%, RR 2.89, 95% CI 1.18 to 7.04)
    - HA was associated with high risk of treatment related AEs compared with steroid in 1 RCT (21.7% vs. 6.8%, RR 3.20, 95%CI 1.85 to 5.54) and compared with usual care in another RCT (45% vs. 18%, RR 2.56, 95% CI 1.50 to 4.38)
    - For comparisons of HA with PRP, adverse events were poorly reported and were rare (<1%); there were no differences between HA and PRP.
- In one study comparing different two HA products found no differences between them in reported AEs. Severe AEs (not specified) were seen in 4.6% vs. 3.4%, any treatment-related AEs were seen in 9.8% vs. 13.1% and the proportion patients reporting at least one event was 42.5% vs. 47.4%.

Detailed Analysis

Across RCTs of HA, adverse events were poorly reported. There was substantial heterogeneity with regard to the types of adverse events, how they were categorized and how they were reported. Most trials did not provide a definition of what constituted a serious adverse event. Some studies describe serious adverse events that were not deemed to be treatment related, others merely stated that there were no serious adverse or no adverse events but provide no definitions. The frequency of reported AEs varied substantially across trials. Patients may have experienced more than one event (Table 20).

Six RCTs (in seven publications)[9,15,46,54,55,59,74] reported information on serious treatment related AEs, all comparing HA to placebo (saline). One trial[46,54] reported a pseudo-septic reaction in the HA group, but no other serious treatment related AEs were reported. One RCT reported two withdrawals from HA due to inability to tolerate the treatment and no withdrawals from the saline group.[55] Two RCTs comparing HA with PRP reported patient withdrawal[24,55] and two others making this comparison report that no serious AEs occurred[126,143]; there were no differences between treatments.

Seventeen RCT (in 18 publications)[4,15,24,25,55,56,59,74,78,83,87,102,126,135,142,143,148,162] reported on serious AEs not related to treatment: seven comparing HA and placebo (saline),[4,15,55,59,74,102,135] six comparing HA with PRP,[24,55,83,87,126,143] four comparing HA and steroid,[25,78,142,148] one trial comparing HA and NSAID[56] and one trial[162] comparing HA preparations. One trial[59] comparing HA with placebo reported joint pain, peripheral edema, and rash across two participants receiving HA and two participants receiving placebo; No other trials reported specific events. No trials showed a significant difference between HA and any treatment in instance of these AEs. Similarly, there was no difference between different HA preparations in one RCT.[162] Many RCTs made blanket a statement that no serious advents occurred in either group (0% denotes this).

Fifteen RCTs (in 17 publications)[4,9,15,24,46,54,55,59,63,74,78,83,102,135,137,143,162] reported on non-serious treatment-related AEs: nine (11 publications) comparing HA with placebo (saline),[4,9,15,46,54,55,59,74,102,135,137] four comparing HA with PRP,[24,55,83,143] one trial each comparing HA with steroid[78] and HA with usual care[63] and one trial[162] comparing HA preparations. One trial[9] comparing HA with placebo noted a significantly higher risk of treatment-related AEs (RR 2.89, 95% CI 1.18 to 7.04), as did the trial[78] comparing HA with steroid (RR 3.20, 95% CI 1.85 to 5.54) and the trial[63] comparing HA with usual care (RR 2.56, 95% CI 1.50 to 4.38).

Sixteen trials (in 18 publications)[4,9,15,21,46,54,56,59,63,74,78,102,135,137,142,148,154,162] reported on non-serious, non-device related AEs: eight trials (10 publications) comparing HA with placebo (saline),[4,9,15,46,54,59,74,102,135,137] four trials comparing HA with steroid, [21,78,142,148] two trials comparing HA with PRP,[87,154] one trial comparing HA with NSAID[56] and one trial[63] comparing HA with usual care. Only one trial[78] comparing HA with steroid noted a significant associated risk in any of these AEs: There was a significantly lower risk of various other AEs associated with HA versus steroid (RR 0.85, 95% CI 0.72 to 0.99), but a significantly increased risk of mild pain associated with HA versus steroid (RR 5.43, 95% CI 2.48 to 11.89). An additional trial comparing HA preparations reported similar proportions of patients experiencing ≥1 treatment-emergent AEs but did not describe severity or type of AE.[162]

Table 20. Adverse events described in RCTs of HA

Adverse event	Study	Descriptions reported	Comparison	HA % (n/N)	Control % (n/N)	RR (95% CI)
Serious Related AEs	Hangody, 2018	NR	HA vs. Saline	0% (1/135)	0% (0/63)	-
	Arden, 2014	NR	HA vs. Saline	0% (0/108)	0% (0/110)	-
	Bao, 2018	NR	HA vs. Saline	0% (0/20)	0% (0/20)	-
	Ke, 2021	NR	HA vs. Saline	0% (0/218)	0% (0/220)	-
	Farr, 2019/ Gomoll, 2021†	Knee stiffness and pain (pseudo-septic reaction)	HA vs. Saline	1.55% (1/64)	0% (0/68)	-

	Gormeli, 2017	Unable to tolerate treatment after first injection	HA vs. saline (1 inj.)	4.3% (2/46)	4.4% (0/45)	-
	Gormeli, 2017	Unable to tolerate treatment after first injection	HA vs. PRP (3 inj.)	4.3% (2/46)	4.3% (2/46)	1.00 (0.15, 6.80)
	Buendia-Lopez, 2019	Withdrawal due to Pain and swelling	HA vs. PRP	6.3% (2/32)	0% (0/33)	-
	Lisi, 2018	NR	HA vs. PRP	0% (0/28)	0% (0/30)	-
	Tavassoli, 2019	NR	HA vs. PRP (2 PRP groups)	0% (0/27)	0% (0/56)	-
	Sdeek, 2021	NR	HA vs. PRP	0% (0/94)	0% (0/95)	-
Serious AEs	Hangody, 2018	Arthralgia, peripheral edema, rash	HA vs. Saline	1.5% (2/135)	3.2% (2/63)	0.47 (0.07, 3.24)
	Petterson, 2019	NR	HA vs. Saline	4.3% (8/184)	2.7% (5/185)	1.61 (0.54, 4.83)
	Bao, 2018	NR	HA vs. Saline	0% (0/20)	0% (0/20)	-
	Strand, 2012	NR	HA vs. Saline	3.2% (8/249)	0% (0/128)	-
	Ke, 2021	NR	HA vs. Saline	0% (0/218)	0% (0/220)	-
	GEL 200, SSED Takamura	NR	HA vs. Saline	1.7% (7/404)	1.5% (6/410)	1.18 (0.40, 3.49)
	Gormeli, 2017	NR	HA vs. Saline	0% (0/46)	0% (0/45)	-
	Vaishya, 2018	NR	HA vs. Steroid	0% (0/42)	0% (0/40)	-
	Tammachote, 2016	NR	HA vs. Steroid	0% (0/50)	0% (0/49)	-
	Leighton, 2014	NR	HA vs. Steroid	4.1% (9/221)	2.7% (6/221)	1.50 (0.54, 4.14)
	Campos, 2017	NR	HA vs. Steroid	0% (50 knees)	0% (0/53 knees)	-
	Guner, 2016	NR	HA vs. NSAID	0% (0/30)	0% (0/29)	-
	Buendia-Lopez, 2019	NR	HA vs. PRP	0% (0/32)	0% (0/33)	-
	Lisi, 2018	NR	HA vs. PRP	0% (0/28)	0% (0/30)	-
	Gormeli, 2017	NR	HA vs. PRP	0% (0/46)	0% (0/46)	-
	Louis, 2018	HA: Post-traumatic knee sprain, amygdalotomy PRP: Post-traumatic knee sprain	HA vs. PRP	8.3% (2/24)	4.2% (1/24)	
	Tavassoli, 2019	NR	HA vs. PRP (both groups)	0% (0/27)	0% (0/56)	-
	Sdeek, 2021	NR	HA vs. PRP	0% (0/94)	0% (0/95)	-
	Zhang, 2015	Severe AEs (NR, treatment related unclear)‡	HA vs. HA	4.6% (8/174)	3.4% (6/175)	1.34 (0.48, 3.78)

		Serious AEs (NR, none treatment related)‡	HA vs. HA	3.4% (6/174)	1.7% (3/175)	2.01 (0.51, 7.9)
Treatment-Related AEs (general, not serious)	Hangody, 2018	NR	HA vs. Saline	2.2% (3/135)	0% (0/63)	-
	Petterson, 2019	NR	HA vs. Saline	7.1% (13/184)	5.4% (10/185)	1.31 (0.59, 2.91)
	Arden, 2014	NR	HA vs. Saline	15.7% (17/108)	5.5% (6/110)	2.89 (1.18, 7.04)
	Bao, 2018	NR	HA vs. Saline	0% (0/20)	0% (0/20)	-
	Strand, 2012	NR	HA vs. Saline	26.9% (67/249)	25.8% (33/128)	1.04 (0.73, 1.49)
	Strand, 2016*	NR	HA vs. Saline	12.0% (15/125)	13.2% (14/106)	0.91 (0.46, 1.79)
	Ke, 2021	NR	HA vs. Saline	7.3% (16/218)	7.3% (16/220)	1.01 (0.52, 1.97)
	Farr, 2019/ Gomoll, 2021†	Knee stiffness and pain (pseudo-septic reaction	HA vs. Saline	1.6% (1/64)	0% (0/68)	-
	GEL 200, SSED Takamura	Includes arthralgia, joint swelling, joint effusion	HA vs. Saline	6.2% (25/404)	6.6% (27/410)	0.94 (0.56, 1.59)
	Gormeli, 2017	NR	HA vs. saline	0% (0/46)	0% (0/45)	-
	Leighton, 2014	NR	HA vs. Steroid	21.7% (48/221)	6.8% (15/221)	3.20 (1.85, 5.54)
	Hermans, 2019	Knee flare, gastro-intestinal AE, other	HA vs. Usual care	45.0% (35/77)	18% (14/79)	2.56 (1.50, 4.38)
	Buendia-Lopez, 2019	NR	HA vs. PRP	0% (0/32)	0% (0/33)	-
	Lisi, 2018	NR	HA vs. PRP	0% (0/28)	0% (0/30)	-
	Gormeli, 2017	NR	HA vs. PRP	0% (0/46)	0% (0/46)	-
	Tavassoli, 2019	NR	HA vs. PRP (both PRP groups)	0% (0/27)	0% (0/56)	-
	Zhang, 2015	Any AE related to treatment, may include severe/serious AEs	HA vs. HA	9.8% (17/174)	13.1% (23/175)	0.74 (0.41, 1.34)
Other AEs	Hangody, 2018	Headache, arthralgia, spinal pain, back pain, nasopharyngitis	HA vs. Saline	24.7% (33/135)	17.4% (11/63)	1.40 (0.76, 2.59)
	Petterson, 2019	Includes joint stiffness	HA vs. Saline	49.5% (91/184)	54.1% (100/185)	0.91 (0.75, 1.11)
	Arden, 2014	NR	HA vs. Saline	40.7% (44/108)	40% (44/110)	1.02 (0.74, 1.41)
	Bao, 2018	NR	HA vs. Saline	0% (0/20)	0% (0/20)	-
	Strand, 2012	Includes joint stiffness	HA vs. Saline	19.7% (49/249)	16.4% (21/128)	1.20 (0.75, 1.91)
	Strand, 2016*	Includes joint effusion, upper respiratory infection	HA vs. Saline	17.6% (22/125)	21.7% (23/106)	0.81 (0.48, 1.37)
	Ke, 2021	Includes pyrexia, axillary pain, chest discomfort, peripheral	HA vs. Saline	41.7% (91/218)	48.6% (107/220)	0.86 (0.70, 1.06)

		edema, chills, malaise, and thirst				
	Farr, 2019/ Gomoll, 2021†	NR	HA vs. Saline	1.6% (1/64)	0% (0/68)	-
	GEL 200, SSED Takamura	Includes arthralgia, joint swelling, joint effusion	HA vs. Saline	37.9% (153/404)	40.0% (164/410)	0.95 (0.80, 1.12)
	Vaishya, 2018	NR	HA vs. Steroid	2.4% (1/42)	2.5% (1/40)	0.95 (0.06, 14.72)
	Bissichia, 2016	Includes sensation of heaviness, pruritus	HA vs. Steroid	6.6% (5/75)	5.3% (4/75)	1.25 (0.35, 4.47)
	Tammachote, 2016	knee pain and swelling	HA vs. Steroid	0% (0/50)	0% (0/49)	-
	Leighton, 2014	NR	HA vs. Steroid	54.3% (120/221)	64.3% (142/221)	0.85 (0.72, 0.99)
	Guner, 2016	NR	HA vs. NSAID	0% (0/30)	0% (0/29)	-
	Hermans, 2019	Removal of tibia staple, radius fracture, fibroadenoma, abducens nerve paresis, peroneal tendon ganglion, rib fracture, neurofibromatosis, gout, spondylolisthesis, removal of sebhorric verruca, partial parotidectomy due to atypical Whartin tumor, dermatological flebectomy, actinic keratosis	HA vs. Usual care	9.1% (7/77)	7.6% (6/79)	1.20 (0.42, 3.40)
	Zhang, 2015	Patients with ≥1 treatment-emergent AE, (severity, treatment-related not specified)	HA vs. HA	42.5% (74/174)	47.4% (83/175)	0.90 (0.71, 1.13)
	Wang 2022	infection, poor healing, or neurological lesion	HA vs. PRP	0% (0/43)	0% (042)	-
Mild pain	Petterson, 2019	Includes arthralgia, joint swelling, joint stiffness; Others NR	HA vs. Saline	3.8% (7/184)	3.8% (7/185)	1.01 (0.36, 2.81)
	Strand, 2012	NR	HA vs. Saline	7.3% (19/249)	9.4% (12/128)	0.81 (0.41, 1.62)
	Strand, 2016	NR	HA vs. Saline	7.2% (9/125)	9.4% (10/106)	0.76 (0.32, 1.81)
	Ke, 2021	NR	HA vs. Saline	8.7% (19/218)	7.7% (17/220)	1.13 (0.60, 2.11)
	Leighton, 2014	NR	HA vs. Steroid	17.2% (38/221)	3.2% (7/221)	5.43 (2.48, 11.89)
	Bissichia, 2016	Injection site discomfort, injection site erythema, injection site pain, arthralgia, sensation of heaviness, pruritus	HA vs. Steroid	2.7% (2/75)	2.7% (2/75)	1.00 (0.14, 6.91)
	Louis. 2018	Pain during injection	HA vs. PRP	8.3% (2/24)	12.5% (3/24)	0.67 (0.12, 3.64)

	Tavassoli, 2019	Mild worsening of pain relieved by acetaminophen	HA vs. PRP (both groups)	0% (0/27)	12.5% (7/56)	-
Swelling	Petterson, 2019	Includes arthralgia, joint swelling, joint stiffness; Others NR	HA vs. Saline	1.1% (2/184)	0.5% (1/185)	2.01 (0.18, 21.99)
	Strand, 2012	NR	HA vs. Saline	14.1% (35/249)	11.7% (15/128)	1.20 (0.68, 2.11)
	Strand, 2016	NR	HA vs. Saline	17.6% (22/125)	12.3% (13/106)	1.44 (0.76, 2.71)
	Ke, 2021	NR	HA vs. Saline	3.7% (8/218)	0.9% (2/220)	4.04 (0.87, 18.79)
	Leighton, 2014	NR	HA vs. Steroid	2.3% (5/221)	0.5% (1/221)	5.00 (0.59, 42.45)
Pain & swelling	Tammachote, 2016	knee pain and swelling	HA vs. Steroid	2.0% (1/50)	0% (0/49)	-

AE = adverse event, CI = confidence interval, HA = hyaluronic acid, NR = not reported, NSAID = non-steroidal anti-inflammatory drug, RR = risk ratio, SSED = Summary of safety and effectiveness data
*Strand, 2016 is an open-label extension of Strand, 2012
†AE data from Gomoll 2021 used
‡Difference between severe and serious AEs not reported and unclear.

5.1.3 Key Question 1c: Differential Efficacy and Safety of HA for Knee OA

None of the new trials identified by the update search reported subgroup analyses or did formal tests for interaction to evaluate heterogeneity of treatment effect for knee OA. One trial included in the prior 2016 PRP report that was carried over to this report, reported subgroup analyses based on severity of OA (early vs. advanced).[55] The results from the prior 2016 report have been verified and checked for accuracy and are repeated below.

Studies included
One small trial (N=162)[55] reported subgroup analyses for **HA versus placebo (saline) injections and versus PRP injections**, however no formal evaluation of differential efficacy via test for interaction was reported. Authors do not state if subgroup analysis was planned *a priori* or conducted post hoc.

Results
Based on our calculations of effect sizes and evaluation of the extent to which subgroup confidence intervals overlapped, stage of OA may modify the effect of treatment, such that PRP patients with early OA reported better function as evaluated by the patient-reported IKDC measure as well as better quality of life as evaluated by the patient-reported EQ-VAS scale compared with those with advanced OA following PRP (Table 21). This is based on the observation that the MD estimates are different for the early and advanced OA groups and there is little or no overlap in the confidence intervals, suggesting that these groups may respond differently. Future studies are needed to confirm and explore this further.

Table 21. Knee OA: Differential Efficacy for HA vs. Saline and HA vs. PRP

RCT	F/U	Outcome,	Subgroup	HA Mean ± SD	PRP* Mean ± SD	MD (95% CI)†
Gormeli 2017	6 mos.	**IKDC** (0-100 (worst))	Early OA	-50.7 ± 5.6 (n=25)	-59.7 ± 6.0 (n=56)	9.6 (6.8, 12.4)
			Advanced OA	-44.4 ± 5.3 (n=14)	-47.1 ± 4.4 (n=27)	2.7 (-0.5, 5.8)
		Quality of life (EQ-VAS) (0-100 (worst))	Early OA	-64.0 ± 6.0 (n=25)	-71.5 ± 5.3 (n=56)	7.5 (4.8, 10.1)
			Advanced OA	-55.1 ± 5.4 (n=14)	-57.1 ± 4.64 (n=27)	2.0 (-1.3, 5.3)
		Outcome,	**Subgroup**	**HA Mean ± SD**	**Saline Mean ± SD**	**MD (95% CI)†**
		IKDC (0-100 (worst))	Early OA	-50.7 ± 5.6 (n=25)	-36.6 ± 5.6 (n=27)	-14.1 (-17.2, -11.0)
			Advanced OA	-44.4 ± 5.3 (n=14)	-36.3 ± 3.5 (n=13)	-8.1 (-11.7, -4.5)
		Quality of life (EQ-VAS) (0-100 (worst))	Early OA	-64.0 ± 6.0 (n=25)	-48.4 ± 5.1 (n=27)	-15.6 (-18.7, -12.5)
			Advanced OA	-55.1 ± 5.4 (n=14)	-47.2 ± 5 (n=13)	-7.9 (-12.0, -3.8)

CI = Confidence interval, EQ-VAS: EuroQol visual analog scale; f/u: follow-up; HA = Hyaluronic acid; IKDC: International Knee Documentation Committee Subjective Knee Form; MD = Mean difference; Mos. = Months; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD = Standard deviation.

*Two PRP groups were combined (3 vs. 1 PRP injection) to create a single PRP group.

†Calculated by AAI (nee Spectrum Research, Inc.) to compare effect sizes and overlap of confidence intervals for early and advanced OA groups.

5.1.4 Key Question 1d: Cost-Effectiveness of HA for Knee OA

Summary of studies and key points:

No full economic studies comparing PRP to conventional, conservative care were identified. One U.S. based study compared HA with PRP.[123] One study compared HA with conservative care in patient with hip OA[90]; all others focused on HA use in knee OA.[27,62,64,117,118,123,144]

One systematic review of full economic studies comparing HA with usual care, placebo or NSAIDS for treatment of knee OA was identified.[121] It included a total of nine economic studies including four older studies[30,72,145,160] captured and described in the prior 2010 and 2013 HTA reports on HA as well as five economic studies published after that report.[27,62,64,118,144] Our search identified three additional recent studies[90,117,123] not included in the systematic review. This update report focuses on the US based studies published after the 2013 HTA report.

Eight full economic studies[27,62,64,90,117,118,123,144] and one systematic review[121] published evaluating the cost-effectiveness of HA for treatment of knee OA and published subsequent to the prior reports were identified for this update. All were cost-utility analyses (CUA) and employed decision analytic models. Seven of the economic studies[27,62,64,90,117,118,144] identified for inclusion compared HA with various forms of conventional care, primarily conservative care; one compared HA with PRP injections.[123] One study[118]

compared different HA products to each other and to conventional care; only comparison of HA with conventional care is reported for this study. Four studies were conducted in the U.S.[62,117,118,123] and three were conducted in European countries[64,90,144] and one in Columbia.[27] The systematic review was conducted in France.[121] Six studies were industry funded,[27,62,90,117,118,144] one study was funded by the Dutch government[64] and one did not report funding.[123] Authors of the systematic review report that no funding was received.[121]

The included studies ranged from poor to fair quality (QHES from 58 to 79 out of 100 points). Studies performed various levels of sensitivity analyses. The rigor of sensitivity analyses was a limitation in some studies.

Costing years ranged from 2009 to 2019 in the studies that reported this. Time horizons ranged from 52 weeks to a simulated time horizon of 20 years. All studies were conducted from a payer or healthcare system perspective (i.e., including only direct costs).

Tables detailing the studies are found in Appendix I.

Key findings are summarized below.

- The systematic review reported a wide range of cost-effectiveness estimates; ICERs ranged from between €240 and €53,225 per QALY gained. Authors state that conclusions regarding the cost-effectiveness of HA were difficult to assert given the substantial heterogeneity across studies with regard to populations, interventions, comparators and modeling methods used in individual studies. They note that industry sponsored analyses found HA to be more favorable than academic studies.
- Consistent with the systematic review, there was substantial heterogeneity related to populations, methods of modeling and health systems.
- All included studies evaluated the cost-effectiveness of HA for knee OA. One study also included evaluation of HA for hip OA.
- Across four economic studies conducted in the U.S.:
    - The three US-based studies comparing HA with various forms of conservative care all concluded that HA was cost-effective at a willingness to pay of $50,000/QALY.
        - HA was reported to be the dominant strategy in two studies and ICER was not calculated. Base case ICERS ranged from $4499/QALY to 38,471/QALY.
        - Sensitivity analyses suggest a broad range of ICERS with a range of $77,500/QALY to $124,000/QALY at the higher end. Response rates for the different treatment groups generally had the most impact on ICERS.
        - One poor-study concluded that HMW HA was cost effective at this level in patients with early/mid stage knee OA compared with specific conservative management options (PT, braces, NSAIDS/analgesics) but that its cost-effectiveness in late stage knee OA was less apparent. Authors note uncertainty regarding the response of patients with late stage knee OA to management options.[117]
        - General limitations across studies included no or little specification or modeling of adverse events, lack of specification regarding components and costs of conservative care options (most studies), methods of determining utilities based on WOMAC scores which may overpredict utility values in severe disease.

  - One poor-quality U.S.-based study compared HA with PRP., reported an ICER of $12,628.15/QALY for PRP versus HA
    - Authors concluded that PRP injections were not more cost-effective than HA, but that a series of PRP injections should be considered a reasonable alternative to HA.
    - Limited sensitivity analyses were reported. Cost-effectiveness was impacted by PRP costs and WOMAC scores used to determine utility values. Adverse events were not modeled, nor were costs related to PRP preparation. Authors assumed that costs related to use of conservative measures would be equal in the HA and PRP groups.
- Across four economic studies conducted outside of the U.S.:
  - Authors conclude that HA is more cost-effective than conventional conservative care for treatment of knee OA.
  - One study evaluating HA for hip OA also concluded that it was more cost-effective than conventional conservative care.
  - General limitations across studies included little no modeling of potential adverse events, use of data from non-randomized studies (some studies) and limited sensitivity analyses in two of the studies.
  - The applicability of these models is unclear given differences in health systems.

Detailed results

Appendix I, Tables I1 and I2 summarize characteristics, findings and limitations of the included studies. QHES ratings for each study can be found in Appendix E, Tables E21 and E22.

U.S.-based Studies

Hatoum 2014[62]

Study overview: This poor-quality CUA (QHES 67/100) evaluated the cost effectiveness of two courses of 3-weekly high molecular weight HA injections in two scenarios using decision analytic modeling from a payer/healthcare system perspective. One model compared HA and continuance of the same conventional care and a second model compared HA and what they termed escalating conventional care in patients with middle to moderate knee OA who had not adequately responded to conventional care.

Data on treatment response for HA were from an older randomized placebo-controlled trial and related open-label observational extension study in patients with moderate to server pain due to knee OA. However, data on conventional care response rates for model 1 are not specified. For model 2, data on conventional care response was from a different RCT. Similarly, data for costs (and amounts for cost) of conventional care were from different sources and perspectives for the two models. Components of conventional care, and details of their cost, were not well defined for either model. For model 1, it appears that conventional care primarily consisted of NSAIDs, analgesics and steroid injections. In the discussion authors suggest that for model 2 conventional care included a full range of conventional care to include NSAIDS, analgesics, steroid injections, and surgical options such as total knee arthroplasty (TKA) but do not detail costs or utilization of such options, more expensive options such as TKA. Authors

added 50% of costs associated with conventional care to the HA costs, which differed by model given the different sources of costs for conventional care. Utilities were derived from WOMAC scores. For modeling, authors assumed no improvement with conventional care for model 1 (no gain in QALY) while model 2 assumes that some in the conventional arm may respond. Authors assume that there is neither improvement nor deterioration of OA in patients receiving conventional care. Models assumed two courses of HA. Details of potential harms or adverse events were not described for models. Costs and outcomes were not discounted due to the apparent time horizon of 52 weeks.

Base case and sensitivity analyses: Reported treatment costs for HA versus conventional care with NSAIDS were $3469 and $4562 (2012 USD) respectively for model 1. HA was generally the dominant treatment strategy (less costly, more effective) versus conventional care for Model 1 so no ICER was reported. For model 2 authors report annual treatment costs as $1446 and $516 for HA compared with escalating conventional care an ICER of $38,741 is within a willingness to pay threshold of $50,000.

One-way sensitivity analyses were done by varying response rates as well as the baseline costs and utilities by ± 20% for both models. Authors report that response rates for both HA and conventional care had the greatest impact on ICERs. Criteria for response were not described. For Model 2 the highest ICERs of $124,000/QALY were seen when HA response rates were lower (45%) and $77,500/QALY when a high response rate (48%) for conventional care was modeled. Sensitivity analysis for low versus high QALY gained/year led to an ICER range for HA of $55,000/QALY to $29,649/QALY. Additional analyses evaluating the impact of lower versus higher end of the 95% confidence interval of QALYs only for the HA arm were conducted for model 1. HA continued to dominate except when the lower end of the 95% confidence interval for utility was taken, yielding an ICER of $6748/QALY. Sensitivity analyses using Monte Carlo simulation was done for model 2 in addition to varying utilities, response rates and costs. HA was cost-effective at a willingness to pay of $50,000/QALY was seen in approximately 70% of simulations.

Limitations: Models differed with respect to sources of data for components and cost of conventional care included in the models. Authors suggest this may have biased the outcomes against HA. The components of escalating conventional care were poorly specified. It is unclear how rates for more invasive conventional care such as TKA were considered or modeled, thus it is not clear to what extent this is consistent with author's claim that model 2 is consistent with "real world" practice. Calculation of utilities based on WOMAC scores may overpredict utility values in severe disease. Potential harms or adverse events were not modeled, and downstream healthcare resource utilization was not provided in the RCT used as a basis for model 1.

Rosen, 2016[118]

Study overview: This fair-quality study (QHES 79/100) evaluated cost effectiveness of five different HA injections (Synvisc® 3 injections, Durolane® 1 injection, Hyalgan® 3 injections, Supartz® 3 injections, Euflexxa® 3 injections) using analytic modelling via a payer perspective. This model compared the various HA regimens both to each other and to conventional care. For the purposes of this cost effectiveness evaluation, comparisons of the HA regimens compared to conventional care were the primary focus. The study was industry funded.

Data on HA treatment were from five separate RCTs (one for each HA formulation) published between 2002 and 2012. Utility score data for Euflexxa were abstracted from another economic analysis[62] and utility score data for conventional care were extracted from an RCT comparing HA in combination with usual care with usual care alone[112]; The sources of utility score data for the other HA formulations were not specified. Cost data for the HA treatments, physician visits, and injection cost were derived from a Medicaid fees database and wholesale supplier database, while cost data for usual care was derived from a publication modelling cost of non-operative knee OA treatment.[86] The individual components of care listed (physician visit, injection cost) and cost of HA treatments were well-described but cost of conventional care and specific components was not well-defined or justified by the authors. Full cost of conventional care was included in the HA treatment arms of the model, however detailed costs, rationale for models chosen were not provided. Authors note that QALY gained was calculated by subtracting average baseline utility score for a given treatment from the average six-month post-treatment utility score. Scores from different RCT sources and somewhat different methods for determining utilities were used based on product and for conventional care. Modeling of harms or adverse events was not reported.

Base case and sensitivity analyses: Six-month treatment costs for conventional care were $321.50 and costs for HA were as follows: Euflexxa® cost $838.90, Supartz® cost $758.90, Synvisc® cost $1073.90, Durolane® cost $676.62, and Hyalgan® cost $659.90. ICERs for all HA treatments versus conventional care (Euflexxa®: $4,419.13, Supartz®: $6,420.80, Synvisc®: $8,004.25, Durolane®: $6,481.67, Hyalgan®: $7,869.77) were well below the willingness-to-pay threshold of $50,00)/QALY.

One-way sensitivity analyses were performed by changing the cost and utility score of treatments by ± 20%. Authors report that cost-utility remained within the willingness-to-pay threshold for all HA treatments in the sensitivity analyses. No other sensitivity analyses evaluating drivers of costs etc. consideration of OA progression (or changes in disease status), need for joint replacement or probabilities for sustained cost-effectiveness were reported.

Limitations: The method used to convert WOMAC scores to utility scores may have limited the usable literature base. Furthermore, variation in year, use of older publications and location of RCTs used may generate heterogeneity across studies and between groups that could affect model estimates. Finally, full cost of conventional care was attributed to total cost in all HA arms and cost of adverse effects and non-conventional, non-HA treatments required or use of steroids were not accounted for; limited sensitivity analyses were reported.

Rosen, 2020[117]

Study overview: This poor-quality study (QHES 67/100) evaluated cost effectiveness of treatment with HMW HA (Euflexxa®, 3 injections), LMW HA, physical therapy and exercise, braces and orthosis, and NSAID/analgesic medication using analytic modelling via a payer perspective. This model compared HMW HA to the other listed interventions in both early/moderate stage and late-stage knee OA. The study was industry funded.

Data on effectiveness and complications for the various treatments were derived from various published and unpublished literature sources but not explained further. Parameters for costs, benefits and harms

of the various treatments were derived from prior literature, expert opinion, and estimates from unpublished literature. A decision tree model (via TreeAge Pro 2011®) was used to simulate state of knee OA in patients in each simulated treatment arm. Cost-effectiveness assessment utilized cost, utility, and complication rates; Costs are itemized in supplemental material as are sources for utilities, however derivation of utilities was not described beyond references provided. Complications included in models were as follows: acute local skin reactions, synovitis, and sepsis were included for HA, potential minor AEs were included for physical therapy/exercise as well as braces/orthosis, and gastrointestinal and cardiovascular AEs were included for NSAIDs; complication rates and incorporation of their impact on utilities is described. QALY was determined by multiplying health-state utility gained by the time horizon of 6 months.

Base case and sensitivity analyses: Six-month treatment costs were as follows: HMW HA cost $608, LMW HA cost $693, physical therapy and exercise cost $901, braces and orthosis cost $200, and NSAIDs/analgesics cost $338. ICERs were calculated separately for patients with early/moderate stage knee OA and patients with late-stage knee OA. In early/moderate stage patients, HMW HA was dominant over both LMW HA and physical therapy and exercise (less costly, more effective) and ICERs for HMW HA compared to braces and orthosis and NSAIDs/analgesics were $7,157.89 and $10,384.62 respectively. These ICERs were well within the willingness-to-pay threshold of $50,000/QALY.

One-way sensitivity analyses were performed for the early/moderate stage knee OA analysis only by changing the cost and utility score of treatments by ± 10% (reported only for patients with early/moderated knee OA). HMW IA-HA remained dominant versus LMW IA-HA and PT and exercise based on these sensitivity analyses. HMW HA remained cost effective at the lower and higher cost ranges versus braces and orthoses (7508.77 to 6807.02 respectively) and versus NSAID and analgesic use ($11,684.62– $9084.62) at the WTP threshold of $50,000/QALY.

One-way sensitivity analyses were performed by considering responder rates between 10% and 50% for HA in patients with late-stage knee OA. Changes in responder rates for conventional care options do not appear to have been modeled (reporting is unclear). Authors report that cost-utility did not change versus any comparator treatments for HMW HA. Responder rates did impact cost-effectiveness. Late-stage patients were analyzed assuming a 50 percent responder rate and 10 percent responder rate, which authors justified as a fair range in comparison to a 39 percent response rate they cite from a separate publication. In the late stage 50% response rate analysis, HMW HA dominated LMW HA and was within the willingness-to-pay threshold of $50,000 versus both physical therapy and exercise (ICER $36,875) and braces and orthosis ($11,600) but was not within the WTP threshold versus NSADIs/analgesics (ICER $67,000). In the late stage 10% response rate analysis, HMW HA dominated LMW HA and was within the willingness-to-pay threshold of $50,000 for physical therapy and exercise (ICER $8,027.03) but was dominated by NSAIDs/analgesics and was not within the willingness-to-pay threshold versus braces and orthosis (ICER $67,333.33).

Limitations: RCTs included in our current HTA generally included patients with K-L grades 1-3 and very few compared HA directly with conventional care and provided limited information benefits, harms and adverse events. Various sources including expert opinion were used to fill these gaps. The impact of direct evidence from head-to-head trials on the cost-effectiveness is unknown. Responder rates, complication cost, and utility scores at different stages of knee OA were identified via assumptions and evidence support from high quality sources for some assumptions is unclear. The model also assumes

that conservative care is effective in those experiencing late-stage knee OA. Authors state that data used for conservative care modeling for late-stage OA may not represent treatment effects for these treatments. Further they acknowledge that response rates for late OA are largely unknown and based on expert opinion and indirect evaluation. Limited detail of how modeling was conducted was provided. Limited one-way sensitivity analyses were conducted, and clear drivers of cost effectiveness were not evaluated described. Sensitivity analyses differed for the stages of OA evaluated. It is unclear whether a larger than 10% change in HA costs changes in early/moderate stages OA or late stage for in conservative management or progression to joint replacement may impact cost-effectiveness findings as these were not explored. It is also unclear how changes in response rates for the treatments evaluated would impact cost-effectiveness in early/moderate stage OA.

Samuelson 2020[123]

Study overview: This poor-quality CUA (QHES 58/100) evaluated the cost-effectiveness of three courses of intra-articular PRP to HA viscosupplementation for the treatment of knee OA using a decision tree model. Authors do not report perspective, but it is assumed to be a payer perspective. The model assumed 1. Otherwise healthy individuals presenting to an orthopedic physician as a new patient for symptomatic knee OA, 2. Patients underwent typical conservative (non-surgical) treatment measures, and upon failing and not meeting indication for operative intervention or wished to avoid operation, were offered PRP or HA to improve function and provide symptomatic pain relief, 3. Patients had the average and typical response to injections represented by WOMAC scores, 4. Patients had the same average improvement in their condition within their respective groups, and 5. Patients were followed over the course of 1 year. Treatment consisted of three injections of either PRP (leukocyte content not reported) or HA (Euflexxa). Utilities were converted from WOMAC scores. The costs of other common treatments were not modeled because they assumed the use of these treatments would be the same across groups. Other patient and treatment characteristics were not detailed. Future costs and benefits were discounted at 3%, and cost-effectiveness was set at threshold for cost per QALY of <$50,000.

Base case and sensitivity analyses: The base model reported that three PRP injections were more effective than three HA injections by 0.11 QALYs, but that cost of PRP was higher ($8,635.23 per QALY) than HA ($5,331.75 per QALY). The ICER for PRP compared to HA was $12,628.15 per QALY. Authors concluded that PRP is not more cost-effective than HA, but PRP is more effective at 1 year.

Sensitivity analyses examined the difference in cost per injection, finding that if the cost of HA (base cost $141.03 per injection) was greater than $292.16 per injection, then PRP would be more cost-effective. Similarly, the cost of PRP (base cost $675) would need to be less than $398.88 before it would be considered more cost-effective. Sensitivity analyses on the threshold of utility value improvements found that those receiving PRP injections would need to improve by a utility value of greater than 0.4 (utility value ≥0.84 at 1 year) to be more cost-effective, and that HA would need to improve utility by less than 0.09 (utility value ≤0.53 at 1 year) in order for PRP to be considered cost-effective.

Limitations: Reported limitations included the complete absence of the costs of other common and conservative treatments for knee OA, and the disregard for the heterogeneity of costs based on location, contractual agreements, and insurance status, and that the costs may not be generalizable. Other minor limitations included the lack of time involved in performing treatments, as well as the lack

of adverse events in the model that are associated with either PRP or HA. Further limitations include a lack of clarity on a number of items, including the perspective of analysis, transparency of variables included in the model and which data were modeled, the handling of uncertainty in the model, model methodology and the potential for bias, and sources of funding.

Studies based outside of the U.S.

Hermans 2018[64]

Study overview: This fair-quality CUA (QHES 78/100) evaluated the cost-effectiveness of 3-weekly high molecular weight hyaluronic acid (HMW HA) added to conventional care compared with conventional care (NSAIDS, physical therapy, lifestyle recommendations) for treatment of knee OA from a societal (medical and productivity costs) and Dutch healthcare system perspective (medical costs only). Data were from a poor-quality RCT (N=156)[63] included in this review. Authors used regression analyses and inverse probability weighting to calculate estimates for pain and quality of life measures that were adjusted for baseline differences. Patients were aged between 18 and 75, with Kellgren-Lawrence grade 1 to 3 knee OA, had pain >3 months and pain severity > 2 on numeric rating scale. For the societal perspective costs related to productivity were derived from a patient-reported PRODuctivity and Disease Questionnaire which included costs for unpaid work (e.g., household work done by others), knee-related work absences and lost productivity while at work based on quality and quantity of work. Health utilities were derived from EQ-5D scores. A 52-week time horizon was used. Modeling of potential harms or adverse events was not described. Assumptions regarding disease progression were not described. The analysis was commissioned by the Dutch Government.

Base case and sensitivity analyses: Based on estimates adjusted for baseline imbalances, reported treatment costs for HMW HA added to usual care versus conventional care alone were €7,754 and €7,270, respectively. Productivity costs were similar in both groups, with €6.160 in the treatment group compared to €6, 141 in the control group. Gain in QALYs was slightly higher in the intervention group (0.779 versus 0.727 for conventional care alone) with an ICER of €9,100/QALY from a societal perspective and €8,700/QALY from a healthcare perspective. Limited detail for one-way sensitivity analyses and potential cost drivers was provided. Authors report that knee replacement costs were the primary driver of medical costs; 9 were done in the HA group, 7 were done in the conservative care group, however authors' tables indicate no surgeries in either group. Productivity costs are largest drivers from societal perspective in both groups. Considering a willingness-to-pay threshold of €20,000/QALY, the probability that HMW-HA is cost-effective is 64% from the societal perspective and 86% from the health system perspective, based on nonparametric bootstrapping analyses. The probability that HA is dominant was 39% from the societal perspective and 9% from healthcare perspective (unadjusted estimates).

Limitations: Authors cite small sample size as a limitation and indicate that the impact off excluding patients with more advanced (KL Grade 4) OA and those with inflammatory arthritis or deformities ins uncertain. Limited information regarding some assumptions and model inputs was provided details of sensitivity analyses are provided. Modeling of harms was not reported. The applicability of this study to the US healthcare system is unclear.

Thomas 2017[144]

Study overview: This fair-quality CUA (QHES 77/100) evaluated the cost-effectiveness of three IA injections of HA (Arthrum H 2%, 40 mg/2mL) given at 1-week intervals versus NSAIDs (i.e., conventional care) alone for the treatment of unilateral knee OA from a French healthcare system perspective. The primary endpoint of the study was the impact of treatment on NSAID consumption. The study was industry funded. Data on effectiveness came from a prospective, multicenter observational study (N=401) conducted from May 2014 through November 2014 with a 6-month follow-up period. Mean patient age was 64 years (range, 40 to 75 years), 57% were female, with Kellgren-Lawrence grade 2 (53%) or grade 3 (47%) OA. At baseline, mean WOMAC score was 48.2 (30 to 60 for inclusion) and mean EQ-5D score 43; NSAID use was a mean 2.2 units per month. Sample sizes in both treatment groups were similar (i.e., 202 vs. 199, respectively) as were all other patient characteristics except for age (HA patients were older: 65.6 vs. 62.3 years, <0.0001). Costs for medical consultations (general, specialist and paramedical practitioners), hospitalizations, radiological examinations, drug consumption (HA, NSAIDs, analgesics, corticosteroids, symptomatic slow action drugs, and proton pump inhibitors), devices (orthotics, knee brace, cane or walker, wheelchair), stays in healthcare centers, medical transportations and sick leave over the course of follow-up were derived from national databases. Authors state that indirect costs (i.e., resulting from consequences of the disease treatment such as adverse events) were also considered but did not describe further. Health utilities were derived from WOMAC and EQ-5D scores. QALYs were calculated from the differences of EQ-5D scores between groups, weighted by the time spent at health states. The study protocol states that a probabilistic sensitivity analysis was conducted using bootstrapping method, but authors did not provide further details or results of sensitivity analyses. Cost discounting was not described; however, due to the short time horizon (52 weeks) it is likely that costs were not discounted.

Base case and sensitivity analyses: All indexes showed improvement with IA HA (with a significant difference over NSAIDs) as shown by a reduction in the WOMAC scores (pain, stiffness, function) and an increase in EQ-5D scores (3 and 6 months, p<0.0001). The incidence of sick leave was also lower in the HA group. Drug/NSAIDs consumption also decreased over time (from 100% at inclusion to 66% at 3 months and 44% at 6 months) in the HA group resulting in a 46.7% decrease in expense and an improved estimated benefit/risk ratio according to the authors. Global cost during 52 weeks (6 months before inclusion and 6 months of follow-up) was nearly identical between HA and NSAIDs with an increase of only €9.03 in the HA group over the 6 month follow-up. The authors concluded that treatment with HA was more cost-effective (i.e., no additional costs in the IA HA intervention group) with a gain of QALYs equivalent to half a month (0.042), after 6-month follow-up with an ICER of €9.03/0.042 = €215 per QALY for HA (vs. NSAIDs) which is well below a willingness-to-pay threshold of US$50,000 per QALY.

Limitations: The only reported limitation was that data came from a nonrandomized, observational study. There was poor reporting of models used and no sensitivity analyses performed. The study does not factor in any adverse events.

Castro 2015[27]

Study overview: This fair-quality CUA (QHES 76/100) evaluated the cost-effectiveness of HA (Hylan G-F 20) compared with conventional supportive therapy (CST) for the treatment of knee OA from a Colombian healthcare system perspective. The study was industry funded.

Monte Carlo simulations and one-way sensitivity analyses (i.e., simulation of effectiveness outcomes) were carried out using a hypothetical cohort of 1,000 patients with knee OA and relied on probabilities

of disease progression from published literature, and a distribution of knee OA based on disease severity scale according to K-L grade 1 (22.4%), grade 2 (37.4%), grade 3 (33.5%), and grade 4 (6.7%) stratified by age (<50, 50-59, 60-69, 70-79, <80 years). Most patients were in the 70-to-79-year age group (36%) and 59% were male. It was assumed that HA treatment consisted of 6 ml of Hylan G-F 20 injected once or twice over the course of a year. CST included NSAIDs, opioids, corticosteroids, exercise and PT, lifestyle modification, and invasive treatment (arthroscopy or arthroplasty). QALYs were calculated from WOMAC scores derived from randomized controlled trials of Hylan G-F 20. Treatment costs were taken from two databases. Simulations were conducted at different interval horizons (i.e., 5 to 20 years) considering patients' demographics, disease progression and initial disease severity. Clinical outcomes included: disease progression, symptom improvement, no change or worsening of symptoms, and need for TKR. Probabilistic sensitivity analyses were performed for costs and transition probabilities between degrees of knee OA and included: 1) percentage variation in the WOMAC score to 6 months (i.e., efficacy); 2) health state utilities for the WOMAC interval; and 3) cost of health care services by the WOMAC interval used. Costs were discounted using a 3% discount rate with alternatives rates as appropriate in the sensitivity analyses.

Base case and sensitivity analyses: WOMAC scores for function, pain, and stiffness were significantly improved in the intervention (HA) group for a time horizon of up to 20 years. Results from the simulation showed that: 87% of patients treated with Hylan G-F 20 showed improvement in symptoms (versus 25% of patients treated with CST); 6.4% of patients treated with Hylan G-F 20 underwent TKR (versus 12.8% of patients treated with CST); and for patients with grade 4 OA treatment with Hylan G-F 20 delayed the need for TKR by 3 years versus patients treated with CST.

Simulations at 5, 10, 15, 20 years showing deltas of QALYs versus deltas of costs between Hylan G-F 20 and CST show higher cost effectiveness and health outcomes for treatment with HA over CST (i.e., average total cost by patient was US $27,541 for Hylan G-F 20 and US $ 27,203 for CST in a 20- year time horizon). Economic evaluations (from Drummond's model) show a QALY improvement of 1.09 in favor Hylan G-F 20 over CST. Treatment with HA was found to be more cost-effective (i.e., ICER was dominant according to authors [ICER NR]) over the first 10 years with a QALY of 8.12 for Hylan G-F 20 (i.e., 0.31 higher than CST) with a $576 reduction in treatment costs in favor of HA (Hylan G-F 20) compared with CST. HA treatment becomes progressively less effective/beneficial after 10 years up to 20 years, likely due to natural aging process and disease progression. Results were robust in sensitivity analyses.

Limitations: Stated limitation is that most of the variables used (from the literature) may differ from the Columbian population. Other limitations included: model and simulation assume equal probabilities of disease progression with CST; the study does not factor in any adverse events.

Migliore 2019[90]

Study overview: This poor-quality CUA (QHES 59/100) used a Markov model to evaluate the cost effectiveness of one and three intra-articular injections of Hylan G-F 20 compared to conventional therapy in patients with knee OA, as well as one Hylan G-F 20 injection compared to conventional therapy in patients with hip OA. Both models included states for KL grade two to four, total knee or hip replacement, the after-replacement period, and death. The models also included variables for the probability of gastrointestinal and cardiovascular AEs, the incidence of pulmonary embolism, and mortality. The models assumed effectiveness values were the same for one or three injections in knee OA patients. Efficacy was defined as the number of patients having a meaningful reduction in knee or

hip OA symptoms. The model ran for 5-years in 6-month cycles and included a 3.5% per year discount. While authors did report data sources, including expert opinion, they did not describe them.

The models included 100 patients with OA KL grade two, three, or four. In knee OA patients, patients received either one (in 6 mL) or three injections (in 2 mL) of Hylan G-F 20 (Synvisc-One). Hip OA patients received either one injection of 2 mL of Hyland G-F 20 (Synvisc); hip injections were assumed to be ultrasound-guided due to the difficulty in injecting into the hip without affecting the joint cavity and carried additional costs. Molecular weight and other important features were not reported. Conventional therapy included Acetaminophen or NSAIDs. Other patient and intervention details were not reported.

Additional variables included indirect costs based on productivity loss and treatment failures to provide a societal perspective. Additional treatments and costs related to visits were not included in the model because they were assumed to be similar for all treatments. Models were primarily from the perspective the Italian National Health Service.

Base case and sensitivity analyses: In knee OA patients, one (€2,854.02 per QALY) and three (€2,854.02 per QALY) injections of HA was considered cost-effective compared to acetaminophen (€2,502.86 per QALY) and NSAIDs (€2,767.77 per QALY). The ICER (using a threshold of €25,000) for one injection of HA compared to acetaminophen was €3,160.61 per QALY, and compared to NSAIDs was €7,440.07 per QALY; The ICER for three injections of HA compared to acetaminophen was €3,845.82 per QALY, and compared to NSAIDs was €10,229.83 per QALY. Regarding AEs, the model estimated 55 and 36 serious AEs and ten and eight deaths for one injection protocol and three HA injections respectively compared to NSAIDs. They did not report on acetaminophen.

In Hip OA patients, one HA injection (€2,922.23 per QALY) was considered cost-effective compared to acetaminophen (€2,653.94 per QALY) and NSAIDs (€2,855.93 per QALY). The ICER (defined as a threshold of €25,000) compared to acetaminophen was €937,10 per QALY, and compared to NSAIDs was reported as dominated. In the NSAIDs cohort, there were 26 serious AEs and five deaths.

One-way sensitivity analyses included variation in ICER to under €17,000 per QALY, with all models continuing to determine HA as cost-effective when parameters were within plausible ranges. Overall, they reported that HA remained robust under €17,000 per QALY for parameters under all plausible ranges with three exceptions: 1. When effective acetaminophen treatment exceeded the utility of either HA scheme; 2. When efficacy of HA is less than NSAIDs; 3. When the utility assigned to treatment failure increases the ICER to €22,000 for 1 injection of HA and €25,000 for 3 injections of HA. However, authors reported limited information for sensitivity analyses.

Budget impact analyses based on literature and expert opinion found an increase per patient per year of €99.99 for one HA injection and €122.49 for three injections for knee OA compared to conventional therapy, and that the treatments had a marginal impact on health-care expenditures. For hip OA, there was an additional €151.06 per patient per year compared to conventional therapy.

Limitations: The only reported limitation is that data were sourced from non-Italian studies, and that therefore the results may not be generalizable to their population. Other major limitations included ambiguity in the assumptions modeled, where they pulled data, and how measured and converted

outcomes. Authors mentioned references for model parameters, assumptions, and outcomes, but did not provide specific details on how utilities were modeled.

It should be noted that these healthcare systems and reimbursements differ from the US context, and therefore applicability to Washington State may be unknown.

5.2 Key Question 2: Platelet Rich Plasma (PRP) for Knee OA

5.2.1 Key Question 2a: Efficacy and Effectiveness of PRP for Knee OA

5.2.1.1 PRP vs. Placebo

Randomization by patient

Nine RCTs[19,35,41,43,55,81,95,100,161] compared PRP with placebo for the treatment of OA (Appendix G). Sample size ranged from 33 to 644 (total N=1683). The average age was 57 years (range, 52 to 68 years), 58% were female (range, 29% to 97%), and the average BMI was 28.69 kg/m^2(range, 25.8 to 30.89 kg/m^2). OA severity was classified as grade 0 in only one trial[81], but varied across interventions (PRP + saline: 8.5%; PRP alone: 3.7%; saline alone: 0%). Four trials[35,43,81,161] reported KL grade 1 participants (mean 16.46%, range 3.2% to 27.6%), six trials[19,35,43,81,95,161] on KL grade 2 (mean 54.21, range 40.1% to 83%), and five trials[19,35,43,95,161] on KL grade 3 (mean 36.2%, range 11.3% to 58.8%). One trial[55] reported by early and late OA, with 67.4% early OA (defined as KL grades 0 through 3) and 67.4% late OA (defined as KL grade 4). One trial[41] reported that all patients were KL grade 2 or 3, but did not report details. Only one trial[100] reported by Ahlback grade, with distribution as 71% vs. 72% vs. 54% grade 1, 21% vs. 20% vs. 39% grade 2, and 4% vs. 4% vs. 7% grade 3 for PRP (1 injection), PRP (2 injection) and placebo groups respectively. Mean symptom duration was reported across 4 trials[19,41,81,95] as 6.47 years (range, 4.4 to 50 10.3 years). Two trials did not report symptom duration, but did report minimum symptom duration in their inclusion criteria as either ≥1 month[35] or ≥4 months.[55]

Single injection (4 trials),[55,95,100,161] two-injection (2 trials),[41,100] and three-injection (6 trials)[19,35,43,55,81,161] regiments were used for PRP therapy. Most trials had 1-week intervals between injections, though this varied up to one month. Four trials[19,41,81,100] used leukocyte-poor, Four trials[35,43,55,161] used leukocyte-rich PRP, and one trial[95] did not report details. Additional treatments varied as needed: three trials permitting paracetamol,[43,55,161] one trial acetaminophen,[19] and three trials reporting none[35,41,100]; other trials did not report on this. Previous surgery or arthroplasty were common exclusion criteria.[41,43,55,81,95] Two trials[35,161] included patients with unilateral OA only, four trials[19,43,95,100] bilateral OA, and two trials[41,55] included patients with either unilateral or bilateral OA; one trial was unclear.[81] Of note, in two trials[41,95] patients with bilateral OA received a single injection in the more symptomatic or painful knee. Three trials included additional interventions groups, one for HA[55], one for plasma[41] (which was explicitly excluded from the present review) and one for triamcinolone hexacetonide.[95]

Follow-up ranged from 1 (short term) to 60 (long term) months; most trials included follow-up for 3 (short term),[35,41,81,95,100,161] 6 (intermediate),[35,43,55,81,100,161] and 12 (long term)[19,35,81,95,161] months. Two trials included longer-term follow-up at 24 months[35,161] and 60 months[35]. Four trials[19,35,81,100] received non-industry funding, four trials reported no funding[41,43,95,161], and no trials received industry funding; one other[55] did not report funding details. Trials were located in Turkey[43,55,161], Brazil[41,95] Australia[19,81], India[100], and China[35].

Two trials[19,81] were considered good quality, and seven[35,41,43,55,95,100,161] were considered fair quality. Common methodological limitations included unclear allocation concealment methods and little detail about and/or lack of blinding of care providers. Two trials[100,161] comparing different injection regimens (1 vs. 2 PRP injections) with placebo had differential loss-to-follow-up in the two injection groups. Of note, in another trial comparing PRP with placebo,[35] although loss-to-follow-up (overall and differential) rates were acceptable, patients who had total knee arthroplasty (TKA) or additional injections during the

study period were excluded and not accounted for in analyses; authors do not provide the number of patients excluded for this reason. This trial did not get credit for intention to treat and the impact of these exclusions on the results is unclear

Randomization by knee

Three additional studies compared PRP to placebo[53,82,158] for the treatment of primarily bilateral knee OA and randomized by knees (as opposed to patients) (Appendix G). While they self-describe as RCTs, for purposes of this report they are considered observational cohort studies (nonrandomized studies of interventions [NRSIs]) since the randomization was done to two knees within the same patient. Patient factors may influence outcomes for both treatments. Two trials enrolled patients with bilateral knee OA (40 knees in 20 patients in each trial) and randomized one knee to receive PRP and the other knee to receive placebo (in the same patient).[53,158] The third trial enrolled patients with bilateral or unilateral OA (58 knees, number of patients unclear); patients with unilateral OA received only a single randomized injection, while bilateral OA patients received different injections (PRP or placebo) in each knee.[82] Across the trials, mean age was 59 (range, 50 to 63) years, mean BMI 24.37 kg/m^2 (range, 23.98 to 24.98 kg/m^2), and 71% were female (range, 63% to 75%).

OA severity was reported as Kellgren-Lawrence (KL) grade 1 or 2 in one trial,[53] though they did not specify details. The other two trials reported OA severity using the Ahlback system: 33.64% were stage 1 (range, 15% to 70%) and 42% were stage 2 (range, 30% to 51) across 2 trials,[82,158] and 36% were stage 3 in one trial.[82] Only one trial reported mean symptoms (5.2 years)[158]; the other two trials required patients to be symptomatic for at least 4 months.[53,82]

Single injection (2 trials)[53,158] and weekly three-injection (1 trial)[82] regimens were used for PRP and placebo. PRP injections were leukocyte-rich in one trial[53], and leukocyte-poor in two trials[82,158]. Additional treatments included paracetamol,[82] acetaminophen,[158] and conservative management (including adjuvant drugs, NSAIDs, and/or therapeutic exercise programs).[53] Placebo was saline in all trials. In two trials PRP and placebo were given in identical volume (2 mL and 4 mL respectively),[82,158] while the third gave patients 4 mL of placebo and 8 mL PRP[53]. Two trials included follow-up at 3 (short-term) and 6 (intermediate-term)months[53,158]; the other reported at 2 (short-term), 6 (intermediate-term), and 12 months(long-term).[82] Two trials[82,158] reported non-industry funding, and one[53] did not report funding. Two trials were conducted in Taiwan[82,158] and one in India[53].

All three NRSIs[53,82,158] were considered fair quality and were generally well-done studies. The primary methodological limitation across the studies trials was unclear blinding of the care providers.

5.2.1.1.1 Function

Function "Success" (Responders)

No trial reported on this.

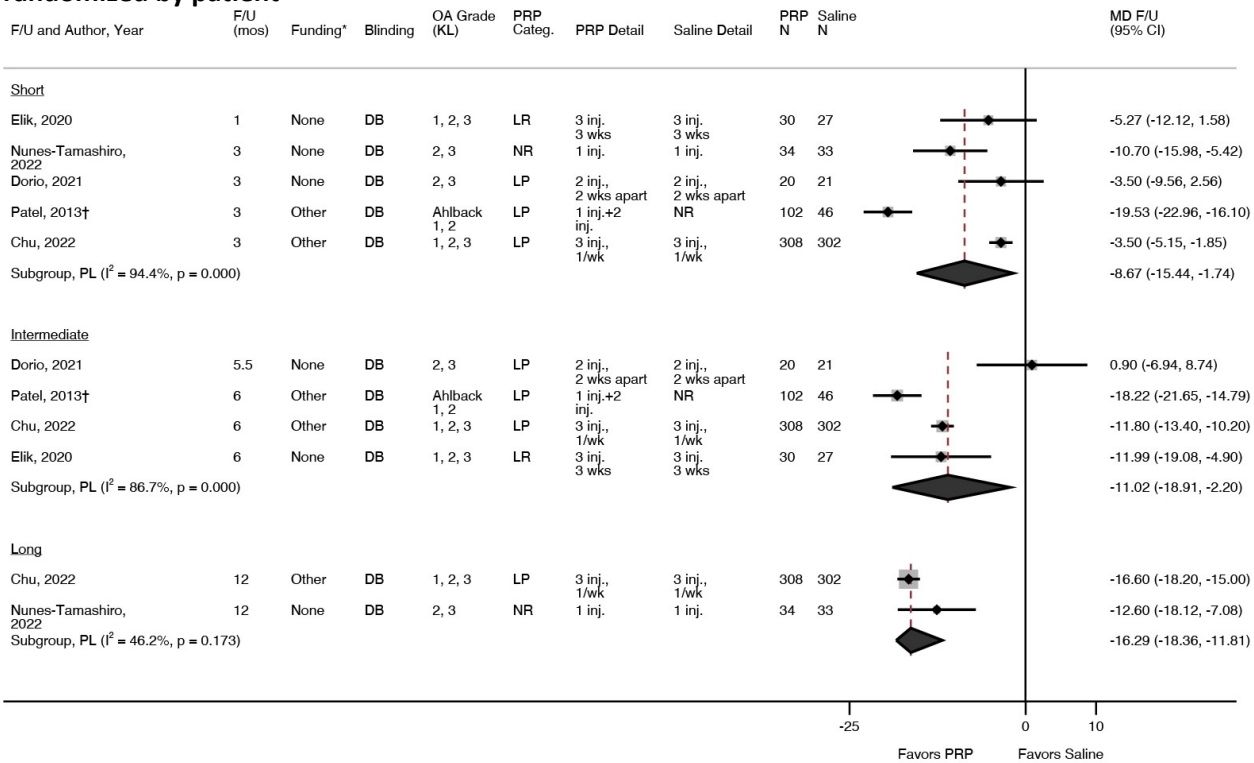
WOMAC physical function scores

Five RCTs (all fair quality)[35,41,43,95,100] comparing PRP with placebo (i.e., saline) that randomized by patient reported Western Ontario and McMasters University Osteoarthritis Index (WOMAC) physical function scores (0-68 scale), Figure 16. The number of and interval between injections varied across the trials. PRP was associated with a moderate improvement in function at short (5 RCTs, MD -8.67, 95% CI -15.44

to -1.74, I^2=94%)[35,41,43,95,100] and intermediate term (4 RCTs, MD -11.02, 95% CI -18.91 to -2.20, I^2=87%)[35,41,43,100] and a large improvement at long term (2 RCTs, MD -16.29, 95% CI -18.36 to -11.81, I^2=46%)[35,95] compared with placebo, but estimates were imprecise and there was substantial heterogeneity at short and intermediate term. Exclusion of an outlier trial[100] at short term resulted in a small functional improvement favoring PRP and reduced heterogeneity (4 RCTs, MD -5.06, 95% CI -9.44 to -1.78, I^2=55%), Appendix H, Figure H4. This trial enrolled patients with bilateral knee OA and treated both knees (same treatment); results were reported out of knees not patients. At intermediate term, exclusion of one outlier trial[41] resulted in a larger, but still moderate, effect favoring PRP but did not reduce heterogeneity (3 RCTs, MD -14.11, 95% CI -19.29 to -8.92, I^2=82%), Appendix H, Figure H4. Of note, the larger trial (N=610)[35] excluded patients who underwent knee surgery/TKA or who had additional injections during the study period; authors do not report how many patients were lost for these reasons and the impact on results is unclear.

Across two fair-quality NRSIs[53,158] that randomized by knee, PRP was associated with a small improvement in function at short term compared with placebo (MD -5.88, 95% CI -10.23 to -1.31, I^2=87%) but the estimate was imprecise, and heterogeneity was high (Figure 17). At intermediate term across the same two trials, although there was a statistical association suggesting small functional improvement with PRP versus placebo, the estimated mean difference was below the threshold for a small effect and the clinical importance is unclear (MD -3.14, 95% CI -5.01 to -1.55, I^2=0%).

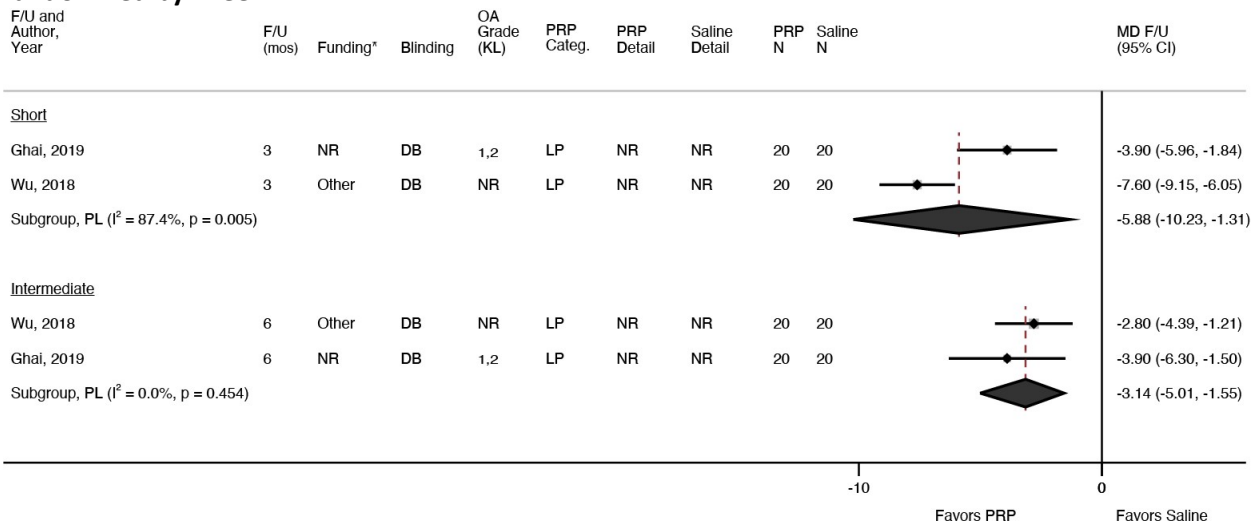
Figure 16. PRP versus placebo: WOMAC physical function scores (0-68 scale) from RCTs that randomized by patient*



Categ. = category; CI = confidence interval; DB = double blind; FU = follow-up (scores); KL = Kellgren-Lawrence; LP = leukocyte poor; LR = leukocyte rich; MD = mean difference; mos. = months; NR = not reported; PL = profile likelihood; PRP = platelet-rich plasma; RCTs = randomized controlled trial; wks = weeks; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

*Patel reported out of knees.

Figure 17. PRP versus placebo: WOMAC physical function scores (0-68 scale) from RCTs that randomized by knee

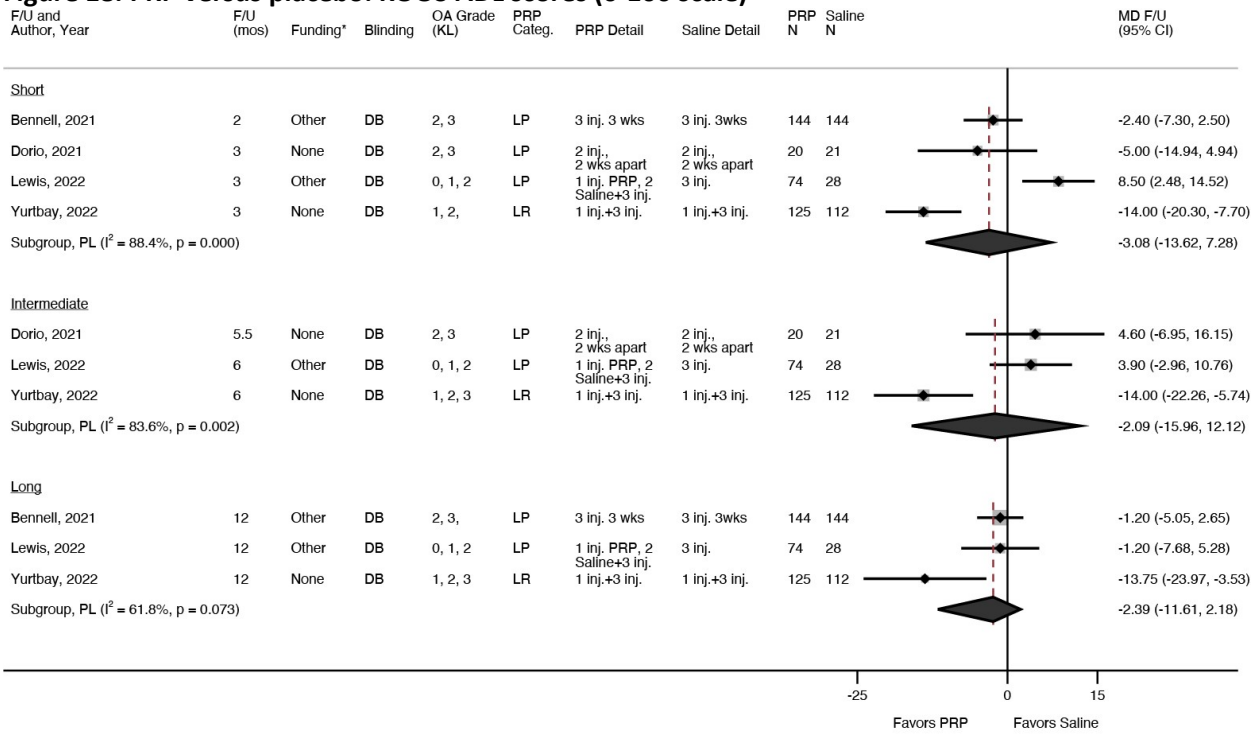


Categ. = category; CI = confidence interval; DB = double blind; FU = follow-up (scores); KL = Kellgren-Lawrence; LP = leukocyte poor; MD = mean difference; mos. = months; NR = not reported; PL = profile likelihood; PRP = platelet-rich plasma; RCTs = randomized controlled trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

KOOS ADL and Sports and Recreation scores

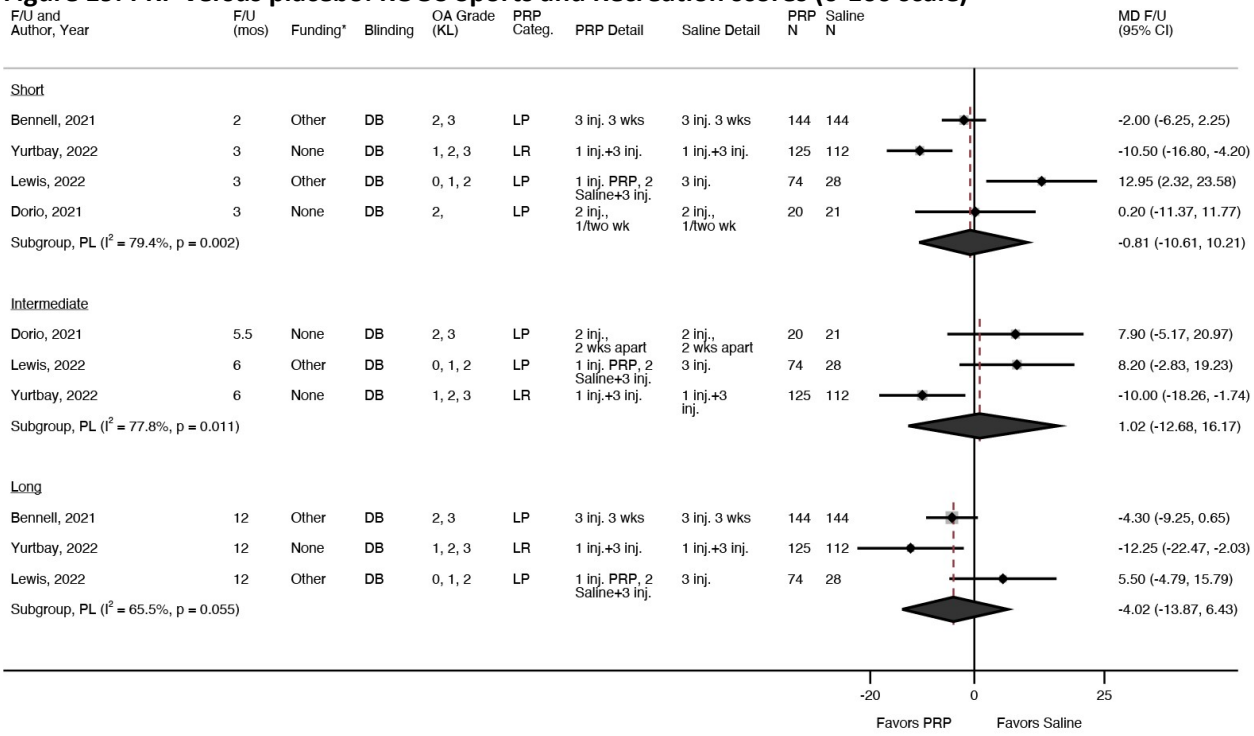
Four RCTs (2 good and 2 fair quality)[19,41,81,161] that compared PRP with placebo (i.e., saline) reported KOOS ADL and KOOS Sports and Recreation scores (0-100 scale for both). The number of and interval between injections varied across the trials. There were no differences between treatment groups in pooled analyses at short (4 RCTs), intermediate (3 RCTs) or long term at 12 months (3 RCTs) for either measure (Figures 18 and 19). For all timepoints across both measures, estimates were imprecise, and heterogeneity was high. Removal of the outlier trial [161] at intermediate and long term did not change conclusions but eliminated (or decreased) heterogeneity (Appendix H, Figures H5 and H6). Similarly, there were no differences long term at 24 months in one poor-quality RCT (N=237; KOOS ADL: MD -4.50, 95% CI -16.68 to 7.68; KOOS Sport: MD -6.50, 95% CI -18.68 to 5.68).[161]

Figure 18. PRP versus placebo: KOOS ADL scores (0-100 scale)



Categ. = category; CI = confidence interval; DB = double blind; FU = follow-up (scores); KL = Kellgren-Lawrence; KOOS ADL = Knee Injury and Osteoarthritis Outcome Score Activities of Daily Living subscale; LP = leukocyte poor; LR = leukocyte rich; MD = mean difference; mos. = months; NR = not reported; PL = profile likelihood; PRP = platelet-rich plasma; RCTs = randomized controlled trial; wks = weeks.

Figure 19. PRP versus placebo: KOOS Sports and Recreation scores (0-100 scale)

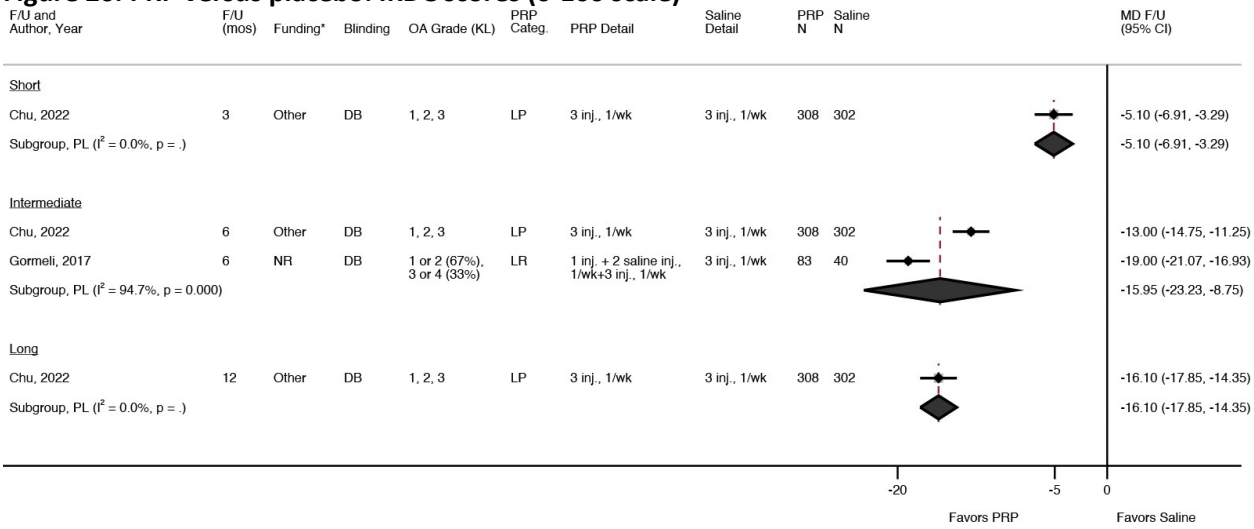


Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, OA = Osteoarthritis, PRP = Platelet-rich plasma, Wks = Weeks

IKDC scores

Two fair-quality trials[35,55] reported IKDC scores (0-100 scale), Figure 20. One large RCT (N=610)[35] reported a small improvement in function with PRP versus placebo (saline) short term (MD -5.10, 95% CI -6.91 to -3.29) and a moderate improvement long term (MD -16.10, 95% CI -17.85 to -14.35). At intermediate term, the pooled estimate across both RCTs showed a moderate improvement in function with PRP (pooled MD -15.90, 95% CI -23.22 to -8.75, I^2=93.9), though the estimate was imprecise, and heterogeneity was high. Of note, the larger trial (N=610)[35] excluded patients who underwent knee surgery/TKA or who had additional injections during the study period; authors do not report how many patients were lost for these reasons and the impact on results is unclear.

Figure 20. PRP versus placebo: IKDC scores (0-100 scale)



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, N/A = Not applicable, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma

5.2.1.1.2 Pain

Pain "Success"

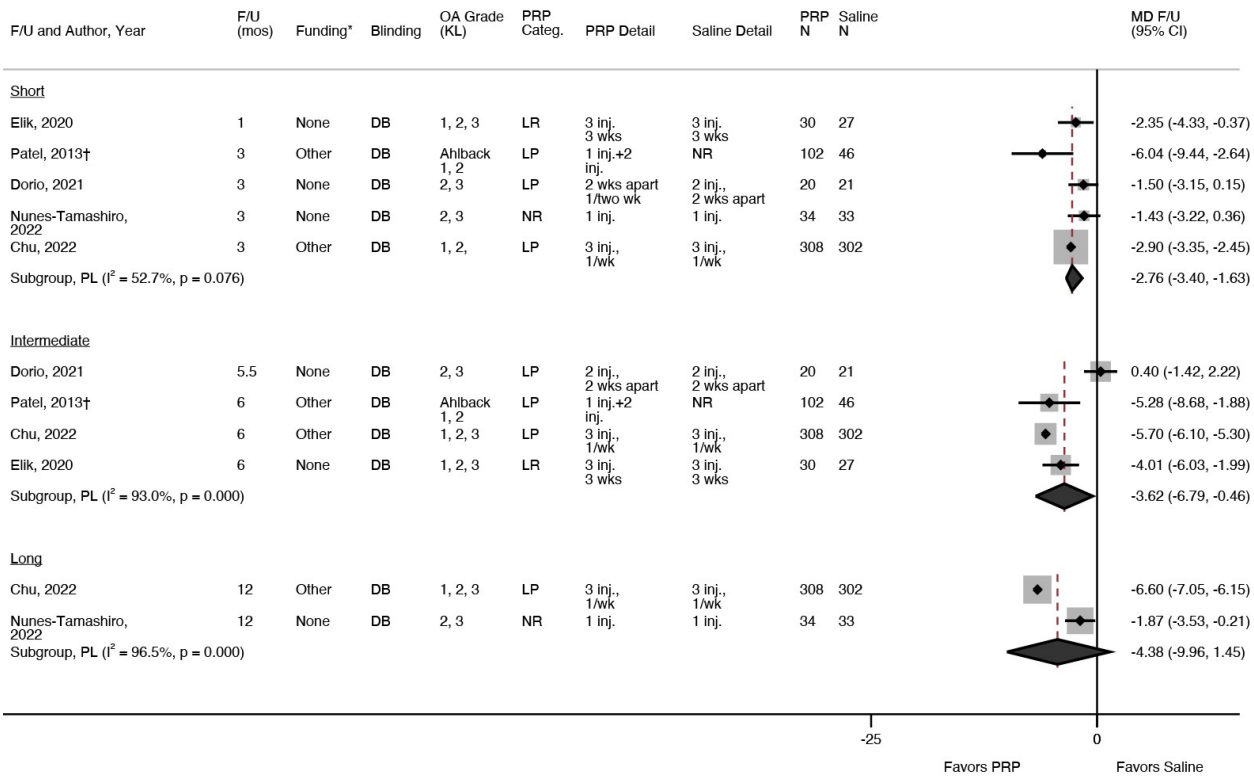
No trial reported on this.

WOMAC pain

Five RCTs (all fair quality)[35,41,43,95,100] comparing PRP with placebo (i.e., saline) that randomized by patient reported WOMAC pain subscale scores (Figure 21). PRP was associated with a moderate improvement in pain at short (5 RCTs, MD -2.76, 95% CI -3.40 to -1.63, I^2=52.7%)[35,41,43,95,100] and intermediate term (4 RCTs, MD -3.62, 95% CI -6.79 to -0.46, I^2=93%)[35,41,43,100] but there was no difference at long term (2 RCTs, MD -4.38, 95% CI -9.96 to 1.45, I^2=96.5%)[35,95] compared with placebo. Exclusion of one outlier trial[100] at short term attenuated the effect size slightly, increased precision and reduced heterogeneity but did not change the overall conclusion (4 RCTs, MD -2.71, 95% CI -3.14 to -1.23, I^2=38.0%), Appendix H, Figure H7; this trial enrolled patients with bilateral knee OA and treated both knees (same treatment). At both intermediate term and long term, the pooled estimates were imprecise and there was substantial heterogeneity. At intermediate term, removal of one outlier[41] resulted in PRP being associated with a large improvement in pain compared with placebo (3 RCTs, MD -5.63, 95% CI -6.12 to -4.24, I^2=23.9%), Appendix H, Figure H7. At long term, individually both RCTs showed an effect favoring PRP but the magnitude of that effect was very different: the larger trial (N=610),[35] which treated patients with three injections of PRP and placebo, reported a large improvement (MD -6.60, 95% CI -7.05 to -6.15) while the second smaller trial (N=67)[95] which used single injections of PRP and placebo showed a small improvement (MD -1.87, 95% CI -3.53 to -0.21). Of note, the larger trial (N=610)[35] excluded patients who underwent knee surgery/TKA or who had additional injections during the study period; authors do not report how many patients were lost for these reasons and the impact on results is unclear.

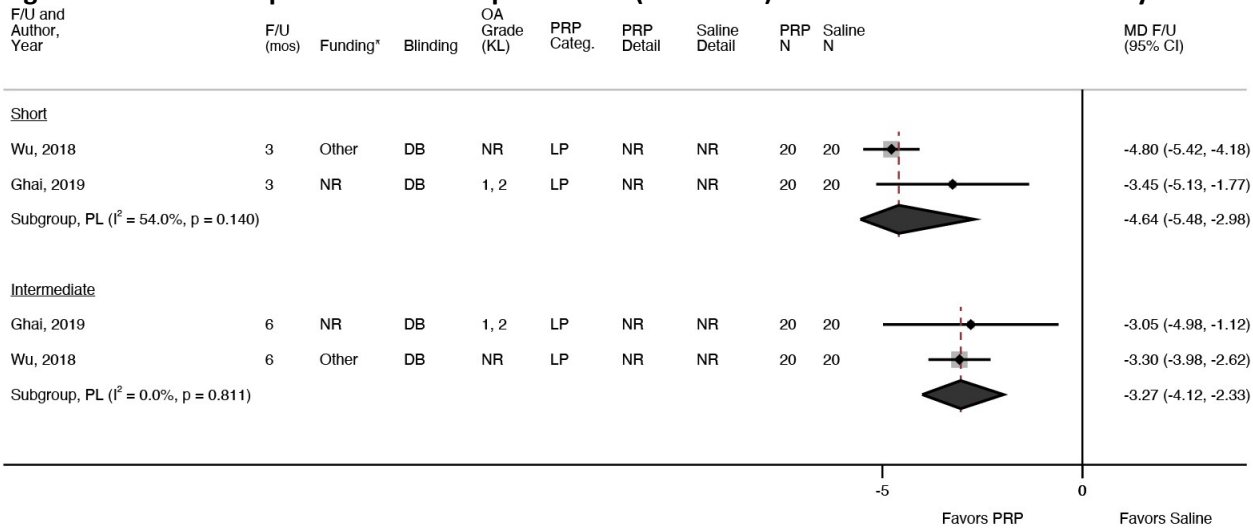
Two fair-quality NRSIs[53,158] that randomized by knee reported a large improvement in pain based on WOMAC pain subscale scores at short term (2 RCTs, MD -4.64, 95% CI -5.48 to -2.98, I^2=54.0%) and a moderate improvement at intermediate term (2 RCTs, MD -3.27, 95% CI -4.12 to -2.33, I^2=0%) with PRP versus placebo (saline), Figure 22.

Figure 21. PRP versus placebo: WOMAC pain scores (0-20 scale) from RCTs that randomized by patient*



Cat. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, N/A = Not applicable, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index
*Patel reported out of knees.

Figure 22. PRP versus placebo: WOMAC pain scores (0-20 scale) from RCTs that randomized by knee

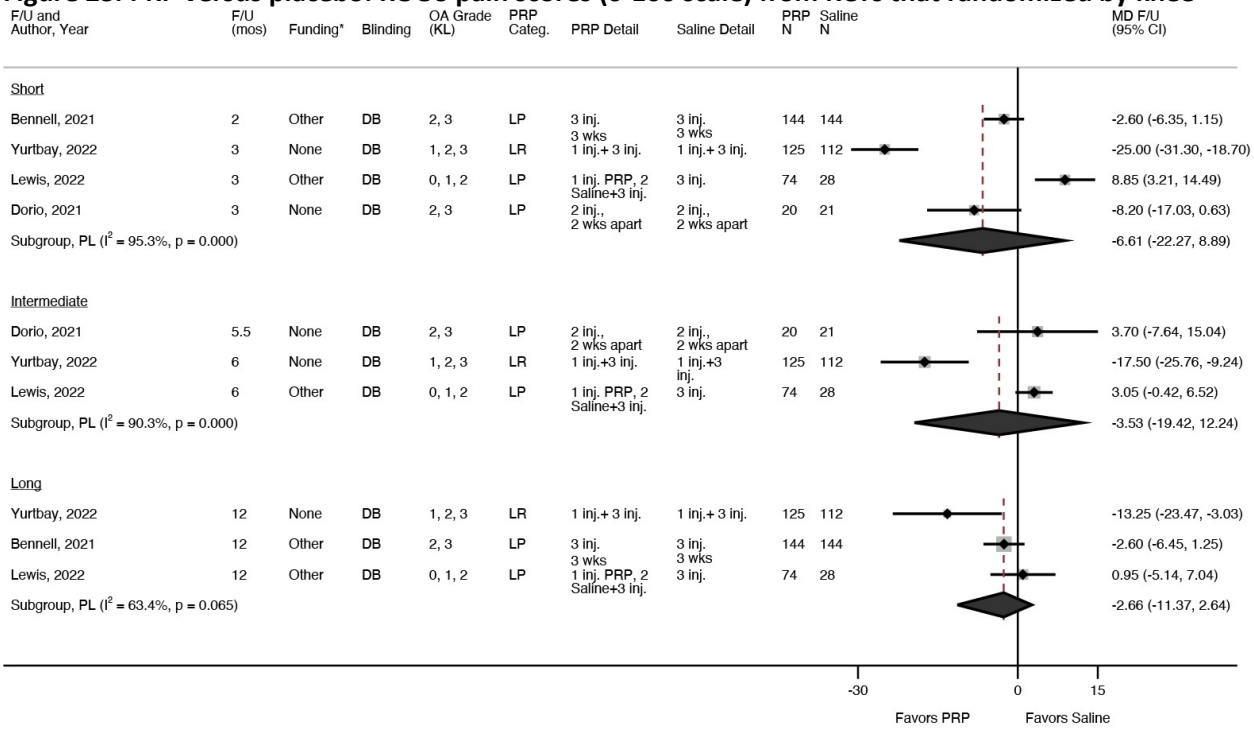


Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index

KOOS pain scores

Four RCTs (2 good and 2 fair quality)[19,41,81,161] that compared PRP with placebo (i.e., saline) reported KOOS Pain scores (0-100 scale). The number of and interval between injections varied across the trials. There were no differences between treatment groups in pooled analyses at short (4 RCTs), intermediate (3 RCTs) or long term at 12 months (3 RCTs) (Figure 23). For all timepoints, estimates were imprecise, and heterogeneity was high. Removal of the outlier trial [161] at intermediate and long term did not change conclusions but eliminated (or decreased) heterogeneity (Appendix H, Figure H8). Similarly, there were no differences long term at 24 months in one poor-quality RCT (N=237; MD -4.50, 95% CI -16.68 to 7.68).[161]

Figure 23. PRP versus placebo: KOOS pain scores (0-100 scale) from RCTs that randomized by knee



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, KOOS = Knee injury and osteoarthritis outcome score, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, Wks = Weeks

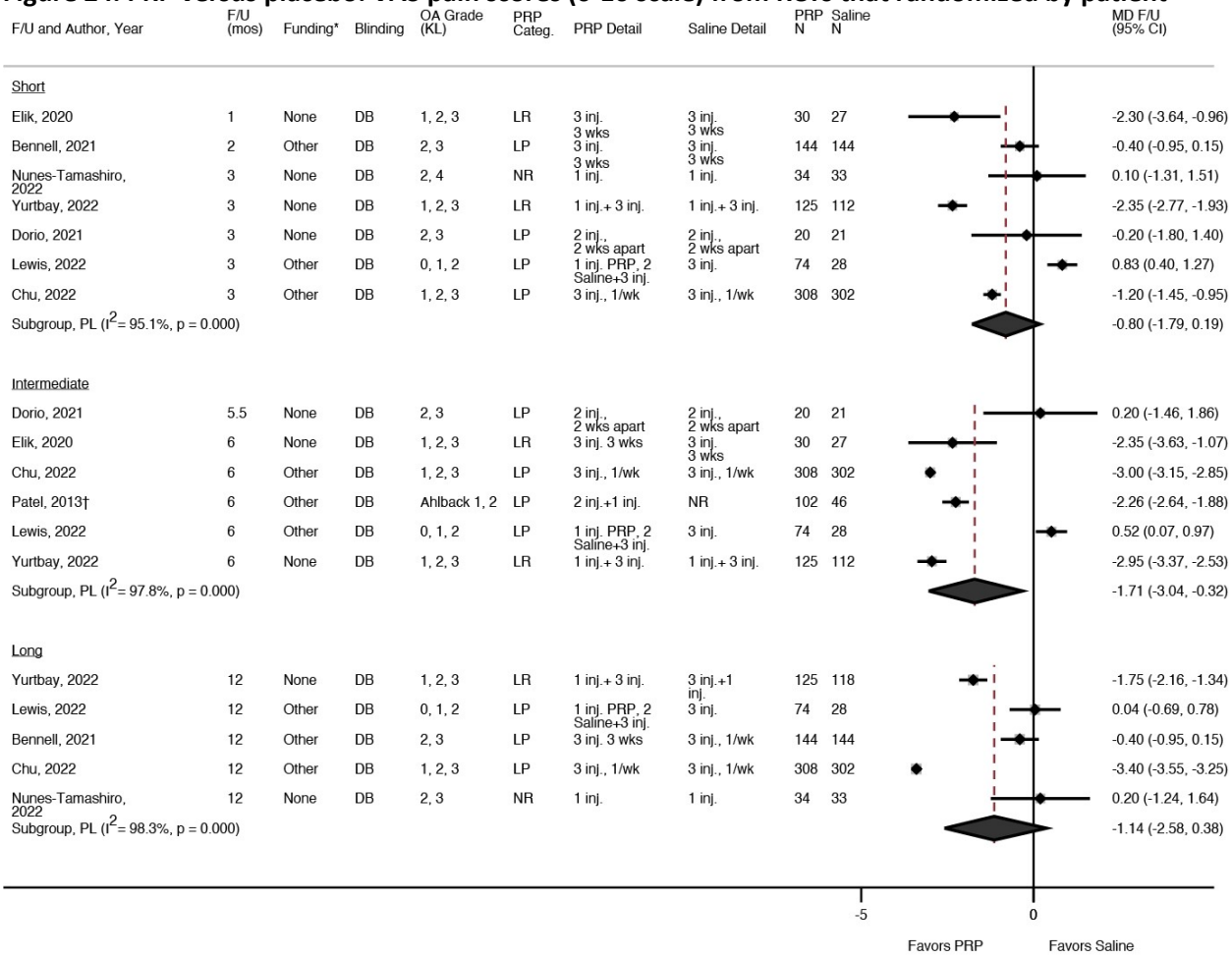
VAS pain scores

Eight RCTs, two good quality[19,81] and six fair quality,[35,41,43,95,100,161] reported pain using a VAS scale measured a variety of ways (e.g., at rest, on movement, at night, not specified). For the purposes of this report, we combined trials that reported VAS pain on movement with those that did not specify how pain was measured (e.g., not otherwise specified, NOS) as this provides the most conservative estimate. There were no differences between PRP and placebo (saline) in pain improvement on VAS short term (7 RCTs, MD -0.80, 95% CI -1.79 to 0.19, I^2=95.1%)[19,35,41,43,81,95,161] and long term (5 RCTs, MD -1.14, 95% CI -2.58 to 0.38, I^2=98.3%),[19,35,81,95,161] (Figure 24). At intermediate term, PRP was associated with moderate pain improvement compared with saline (6 RCTs, MD -1.71, 95% CI -3.04 to -0.32, I^2=98.7%)[35,41,43,81,100,161] Given the heterogeneity in the estimates, VAS on movement (4 RCTs, 1 good and 3 fair quality)[19,41,43,95] and VAS NOS (4 RCTs, 1 good and 3 fair quality)[35,81,100,161] were analyzed separately and the results were similar. Only VAS NOS at intermediate term was statistically significant and favored PRP (small effect) but the effect estimate was imprecise and there was still substantial heterogeneity (4 RCTs, MD -1.93, 95% CI -3.75 to -0.10, I^2=98.6%).[35,81,100,161] One of the good quality trials (N=102)[81] that compared one injection of PRP followed by two injections of saline (PRP group) versus 3 injections of saline (placebo group) reported VAS pain NOS and found less improvement (small effect) with PRP compared with saline at short (3 months, MD 0.83, 95% CI 0.40 to 1.27) and intermediate term (6 months, MD 0.52, 95% CI 0.07 to 0.97) but there was no difference between groups long term (12 months, MD 0.04, 95% CI -0.69 to 0.79). The second good quality trial reported VAS pain on movement and found no difference

between treatment groups short or long term. Of note, the larger trial (N=610)[35] excluded patients who underwent knee surgery/TKA or who had additional injections during the study period; authors do not report how many patients were lost for these reasons and the impact on the trials results is unclear.

One fair-quality NRSI (N=40 knees in 20 patients)[53] that randomized knees to a single injection of PRP or placebo (saline) reported a large improvement in pain with PRP versus saline short term (3 months, MD -2.15, 95% CI -3.24 to -1.06) but there was no difference between groups intermediate term (6 months, MD -0.85, 95% CI -2.52 to 0.82).

Figure 24. PRP versus placebo: VAS pain scores (0-10 scale) from RCTs that randomized by patient*



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, VAS = Visual analog scale, Wks = Weeks

*Patel reported out of knees.

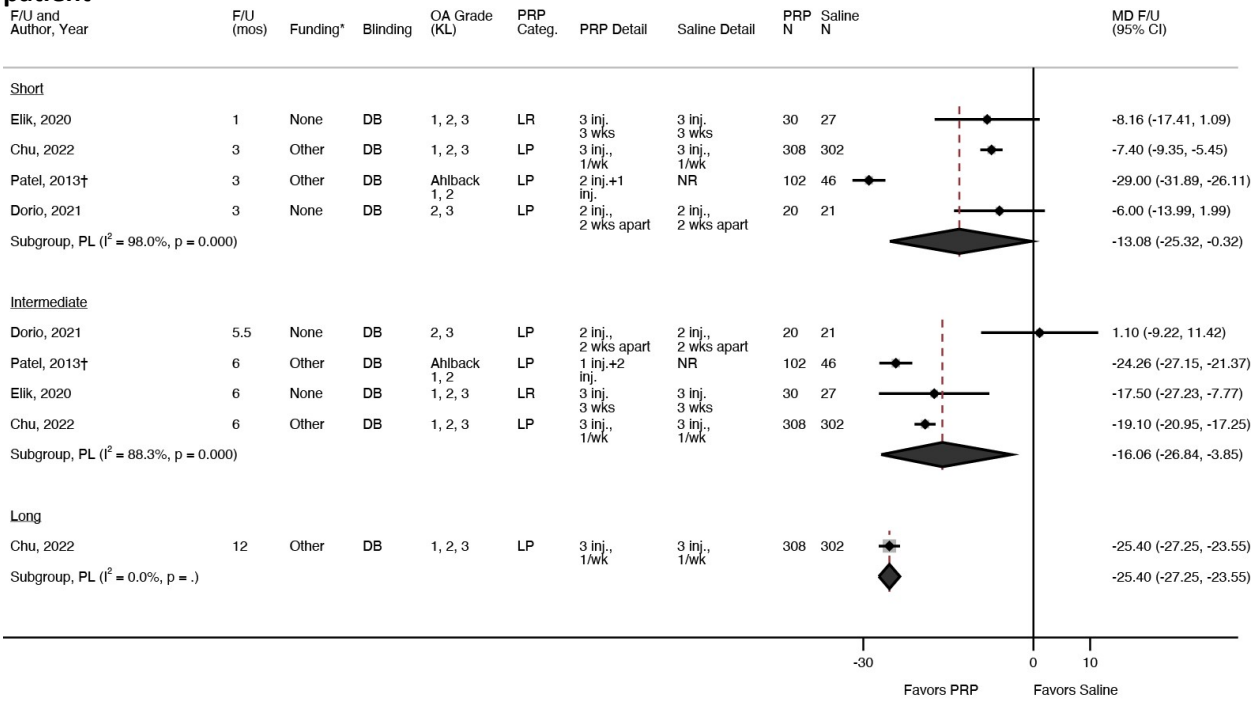
5.2.1.1.3 Outcomes assessing multiple domains

WOMAC total scores

Five RCTs that randomized by patients reported WOMAC total scores (0-96) (same 5 trials that reported WOMAC physical function scores)[35,41,43,95,100] but only four contributed to the meta-analysis. One trial[95] reported WOMAC total scores that were incongruous with the score scale and could not be reconciled and therefore were excluded. Compared with placebo (saline), PRP was associated with a moderate improvement in function short (pooled MD -13.08, 95% CI -25.32 to -0.32, I^2=98.0%) and intermediate term (pooled MD -16.06, 95% CI -26.84 to -3.85, I^2=88.3%) across the same four RCTs[35,41,43,100] and a large improvement long term in one large RCT (N=610, MD -25.40, 95% CI -27.25 to -23.55),[35] Figure 25; estimates at short and intermediate term were very imprecise and heterogeneity was substantial. After removal of outlier trials at short term[100] and intermediate term[41] (Appendix H, Figure H9) there was a small improvement in function favoring PRP short term (3 RCTs, MD -7.36, 95% CI -9.82 to -4.71, I^2=0%)[35,41,43] and heterogeneity was eliminated, and a large improvement favoring PRP intermediate term (3 RCTs, MD -21.04, 95% CI -25.60 to -15.87, I^2=77.9%)[35,43,100] but heterogeneity remained high. Of note, the larger trial (N=610)[35] excluded patients who underwent knee surgery/TKA or who had additional injections during the study period; authors do not report how many patients were lost for these reasons and the impact on the trials results is unclear.

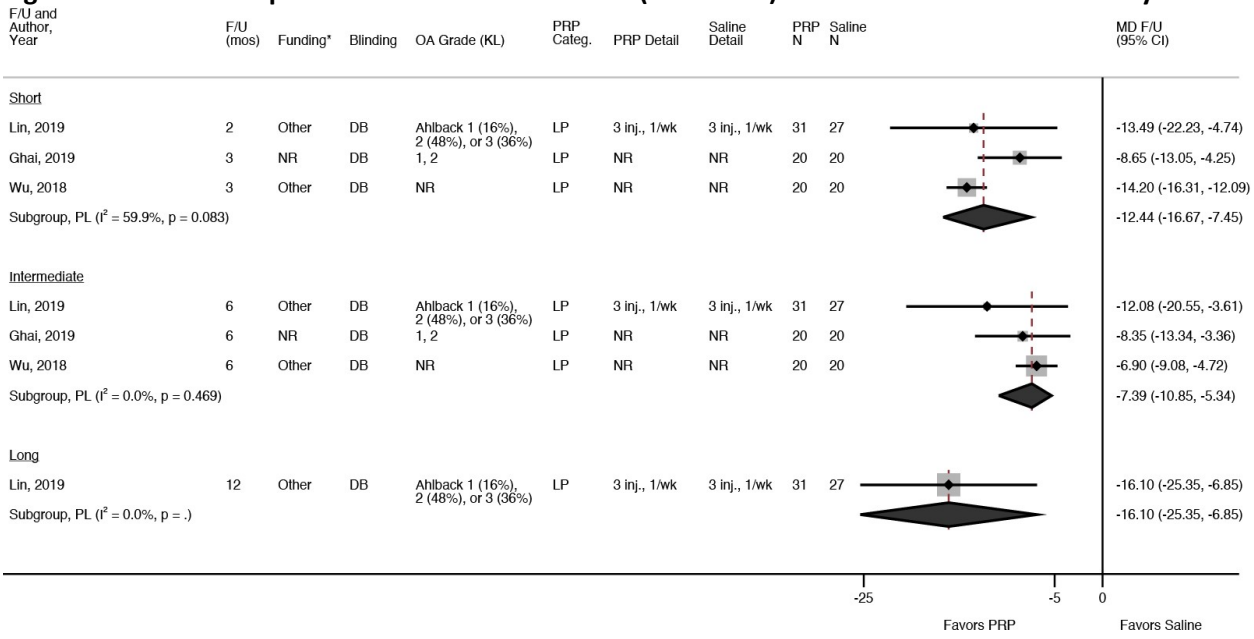
Across three fair-quality RCTs[53,82,158] that randomized by knee, PRP was associated with moderate improvements in function at short (3 RCTs, MD -12.44, 95% CI -16.67 to -7.45, I^2=60%)[53,82,158] and long term (1 RCT, MD -16.10, 95% CI -25.35 to -6.85, I^2=0%)[82] and a small improvement at intermediate term (3 RCTs, MD -7.39, 95% CI -10.85 to -5.34, I^2=0%),[53,82,158] Figure 26.

Figure 25. PRP versus placebo: WOMAC total scores (0-96 scale) from RCTs that randomized by patient*



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index, Wks = Weeks
*Patel reported out of knees.

Figure 26. PRP versus placebo: WOMAC total scores (0-96 scale) from RCTs that randomized by knee



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index, Wks = Weeks

KOOS total scores

One good quality trial (N=102)[81] that compared two PRP regimens (1 vs. 3 injections) with placebo reported KOOS total scores (0-100 scale), Table 22. At short term, PRP (1 or 3 injections) was associated with less improvement (small effect) compared with three saline injections; this finding was driven by the PRP group that received three injections (moderate effect favoring saline group, MD 10.50, 95% CI 1.46 to 19.54). There were no differences between treatment groups or treatment regimens at intermediate and long term.

Table 22. KOOS Total scores: PRP versus saline

Author Quality	Time	PRP regimen	PRP (n=74) Mean (SD)	Saline (n=28)* Mean (SD)	MD (95% CI)†
Lewis 2022 Good	3 mos.	1 injection (+ 2 injections of saline) (n=47)	64.7 (14.8)	68.4 (14.3)	3.70 (-4.90 to 12.30)
		3 injections (n=27)	57.9 (13.4)		**10.50 (1.46 to 19.54)**
		1 or 3 injections (n=74)	61.3 (14.1)		**7.10 (0.91 to 13.29)**
	6 mos.	1 injection (+ 2 injections of saline) (n=47)	67.5 (14.9)	65.6 (14.3)	-1.90 (-10.52 to 6.72)
		3 injections (n=27)	58.8 (14.6)		6.80 (-2.50 to 16.10)
		1 or 3 injections (n=74)	63.2 (14.8)		2.45 (-3.82 to 8.72)
	12 mos.	1 injection (+ 2 injections of saline) (n=47)	66.4 (16.0)	62.0 (16.6)	-4.40 (-14.23 to 5.43)
		3 injections (n=27)	62.6 (13.7)		-0.60 (-10.72 to 9.52)
		1 or 3 injections (n=74)	64.5 (14.9)		-2.50 (-9.52 to 4.52)

CI = confidence interval; PRP = platelet-rich plasma; RR = risk ratio; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
*3 injections of saline.
†Calculated by AAI. Direction of the KOOS scale (0-100) was flipped such that a negative score is better (i.e., favors the intervention, PRP) and a positive score favors the control.

OMERACT-OARSI

One small, fair-quality RCT (N=41)[41] that compared 2 injections (2 weeks apart) of PRP versus placebo (saline) reported treatment response based on OMERACT-OARSI criteria, a composite outcome which combines thresholds for improvement in pain and function. PRP was associated with a small increase in the likelihood of achieving response at short term (3 months) but there was no difference between groups at intermediate term (6 months), Table 23.

Table 23. OMERACT-OARSI Responders: PRP versus saline

Author Quality	Definition	Time	PRP	Saline	RR (95% CI)
Dorio, 2021 Fair	1) improvement in pain (VAS overall pain) or function (WOMAC physical function) ≥50% and absolute improvement ≥20 OR 2) improvement in at least 2 of the following 3 criteria: a) pain ≥20% and absolute improvement ≥10, b) function ≥20% and absolute improvement ≥10, c) patient global assessment for improvement ≥20% and absolute improvement ≥10	3 mos.	95% (19/20)	76% (15/21)	**1.33 (1.00 to 1.77)**
		6 mos.	80% (16/20)	86% (18/20)	0.93 (0.71 to 1.24)

CI = confidence interval; PRP = platelet-rich plasma; RR = risk ratio; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

5.2.1.1.4 Need for secondary invasive procedures

The need for secondary invasive procedures was not well reported by the included trials. Across one good and one fair quality RCT (N=545), there was no difference in the frequency of total knee arthroplasty or other knee surgery after treatment with PRP versus placebo (2.2% vs. 2.6%, respectively, RR 0.87, 95% CI 0.30 to 2.55).[19,161] Follow-up ranged from 12 to 24 months.

5.2.1.1.5 Secondary Outcomes

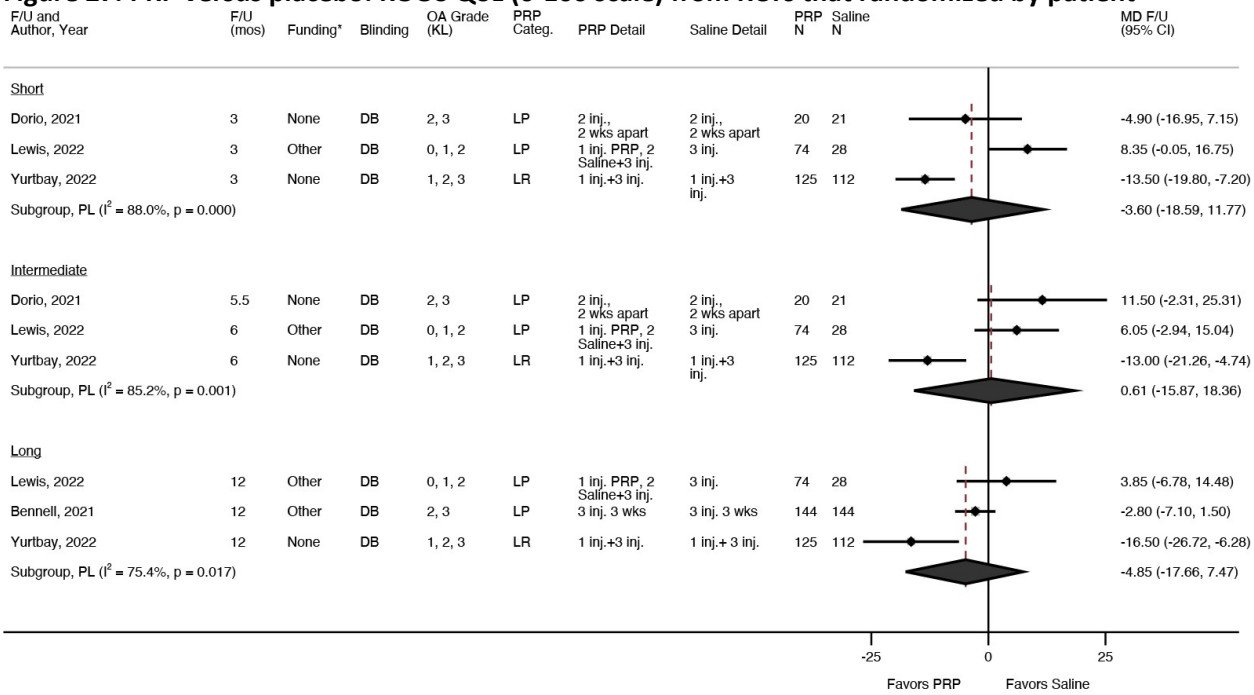
Symptom recurrence

Symptom recurrence (e.g., persistent, or increased pain, reduced function) resulting in need for additional injection of PRP or placebo within 2 months after protocol completion was not reported by included RCTs. One good-quality trial (N=282)[19] reported that one patient in each group (PRP and saline, 0.7% for both) received an injection by 2 months but this was reported as a cointervention and it is unclear what type of injection was given (Appendix F).

Quality of life

Quality of life (QoL) was reported using a variety of different measures and the results varied (See Appendix F). All trials reporting QoL randomized by patients. Four RCTs (N=668) (2 good, 2 fair quality)[19,41,81,161] reported the **KOOS QoL subscale**; there were no differences between PRP and placebo in pooled estimates at any timepoint (short, intermediate or long) and estimates were imprecise and there was substantial heterogeneity (Figure 27). Removal of the outlier trial[161] at intermediate and long term did not change the conclusions but significantly reduced or eliminated heterogeneity (Appendix H, Figure H10). One fair-quality trial (N=57)[43] found that PRP was associated with a small improvement on the **SF-36 PCS** at short and intermediate term and a moderate improvement on the **SF-36 MCS** short term (no difference intermediate term) compared with placebo (Appendix H, Figure H11). A sixth fair-quality trial (N=123)[55] reported a moderate improvement intermediate term with PRP versus placebo based on the **EQ-VAS** for patient global assessment of health; improvement was more pronounced in the arm that received three injections of PRP versus one injection compared to placebo (MD -18.70, 95% CI -21.13 to -16.27).

Figure 27. PRP versus placebo: KOOS QoL (0-100 scale) from RCTs that randomized by patient



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, KOOS QoL = Knee injury and osteoarthritis outcome score quality of life, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, Wks = Weeks

Medication use

One good-quality trial (N=282)[19] reported the proportion of patients who used various medications (i.e., acetaminophen, topical anti-inflammatory drugs, NSAIDs, oral glucocorticoids and oral opioids) at least once over the prior month. There was no difference between the PRP and placebo groups in the proportion of patients who used any medication at 2 months (40% vs. 34%; RR 1.18, 95% CI 0.87 to 1.61) and 12 months (36% vs. 39%; RR 0.92, 95% CI 0.68 to 1.24) or who used any of the specific medication types (Appendix F).

5.2.1.2 PRP vs. HA

Results for PRP vs. HA can be found in section 5.1.1.2 evaluating HA vs. PRP

5.2.1.3 PRP vs. Steroid

Nine RCTs compared PRP to steroids for the treatment of knee OA (Appendix G).[44,49,50,67,71,75,91,95,103] Sample size ranged from 51 to 70 (total N=598), 68% were female (range, 15% to 90.9%), and mean BMI was 28.13 kg/m^2 (range, 24.6 to 31.2 kg/m^2). OA severity was reported in all trials using the Kellgren-Lawrence grades: one trial[50] reported grade 1 in 4% of patients receiving placebo, and 0% in PRP; six trials[44,49,50,75,91,95] reported grade 2 in 46% (range, 25% to 100%); six trials[44,49,50,71,91,95] reported grade 3 in 60% (range, 29% to 75%); two trials[50,71] reported grade 4 in 32.7% (range, 0% to 71%). Two other trials[67,103] reported Kellgren-Lawrence grades as inclusion criteria without reporting distribution: in one[67] all patients were either grade 1 or 2, and grade 2 to 4 in the other.[103] Mean symptoms were only

reported in two trials[49,103] (mean 5.14 years; range 1.93 to 10.3 years). Two other trials[91,95] required patients to have OA symptoms for a minimum of 3 months. Two trials[44,67] included patients with unilateral knee OA, one trial[95] in bilateral knee OA, two trials[49,71] included patients with either unilateral or bilateral OA, and four trials[50,75,91,103] did not report. In two trials[49,95] all bilateral knee OA patients received the randomized injection in both knees.

Single injection (5 trials)[44,49,50,71,95], two-injection (1 trial)[103] and three-injection (2 trials)[67,91] regimens were used for PRP and steroid therapy. One trial[75] poorly described injection methods, so it was unclear how many injections were given. The two-injection regimen was for both interventions and were done in 4-week intervals[103]; one of the three-injection regimens was weekly[67] and the other was done in 4-week intervals.[91] One trial[75] did not report the number of injections, but did report that injections were given "between 2 and 6 months". Patients across all trials received the same number of injections regardless of randomization. One trial[49] used leukocyte-rich PRP, three trials[44,67,71] used leukocyte-poor PRP, and five trials[50,71,75,95,103] did not report. PRP volume ranged from 2 to 8 mL, while steroid volume ranged from 1 to 6 mL. Six trial used triamcinolone[44,50,75,91,95,103], one trial[71] used betamethasone, and two trials[49,67] did not report the steroid used. Additional treatments included NSAIDs,[44,71] acetaminophen,[91] acetaminophen-codeine,[103] physical exercise[49] and routine clinical practices[71]; all other trials did not report any additional therapies. Follow-up ranged from 1 month (short-term) to 13 months (long-term); with seven trials reporting at short-term results,[44,49,50,67,71,95,103] six trials reporting intermediate-term results,[44,49,50,71,75,91] and three trials reporting long-term results.[44,67,95] Two trials[71,91] reported non-industry funding, three trials[44,49,95] reported no funding, and four trials[50,67,75,103] did not report on funding. Trials were located in Brazil[50,95] (2 trials), Pakistan[75,103] (2 trials), Iran[49,91] (2 trials), Spain[71] (1 trial), China[67] (1 trial), and Latvia[44] (1 trial).

Three trials[50,71] were considered fair quality, and six[44,49,67,75,91,103] were considered poor quality. Common methodological limitations were unclear allocation concealment, unclear blinding of care providers, and baseline difference in patient characteristics across groups.

5.2.1.3.1 Function

Function "Success"

No trial reported on this.

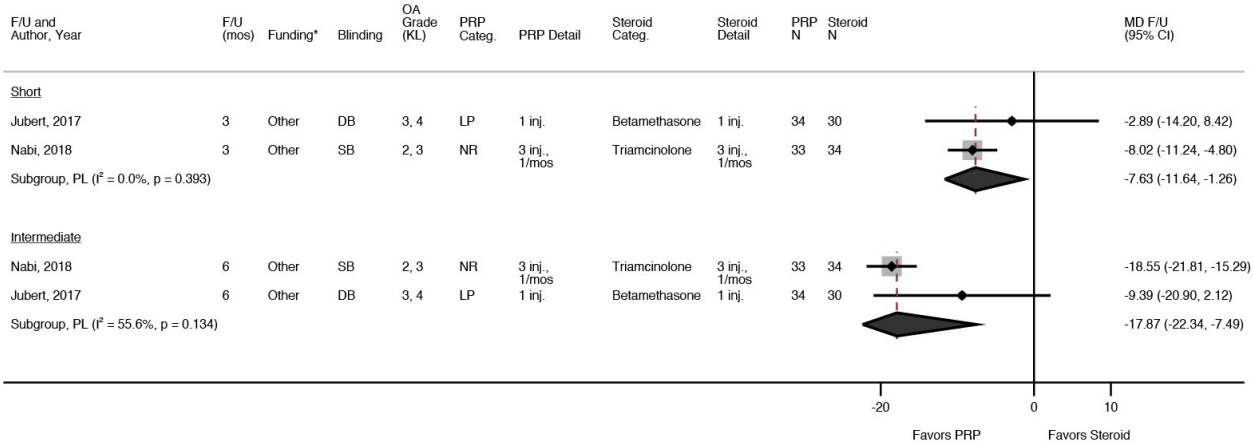
KOOS ADL and Sports and Recreation subscale scores

Three RCTs, one fair[71] and two poor[49,91] quality, reported KOOS ADL and KOOS Sport and Recreation scores (0-100 scale). One of the poor-quality trials[49] was a consistent outlier (favoring PRP). If patients were symptomatic in both knees, both knees were treated; the second knee was injected 3 weeks after the first and results were reported out of knees (not patients). Given both the study quality and the difference in the treatment protocol and reporting compared to the other trials, this RCT[49] was excluded from pooled analyses (see Appendix F for data for this trial).

In pooled analyses across two RCTs (one fair and one poor quality),[71,91] PRP was associated with a small improvement in function compared with steroids short term (MD -7.63, 95% CI -11.64 to -1.26, I^2=0%) and a moderate improvement intermediate term (MD -17.87, 95% CI -22.34 to -7.49, I^2=55.6%) based on KOOS ADL scores (Figure 28). There were no differences in function between groups at either timepoint based on KOOS Sport and Recreation scores (Figure 29). When the trials were considered separately, the

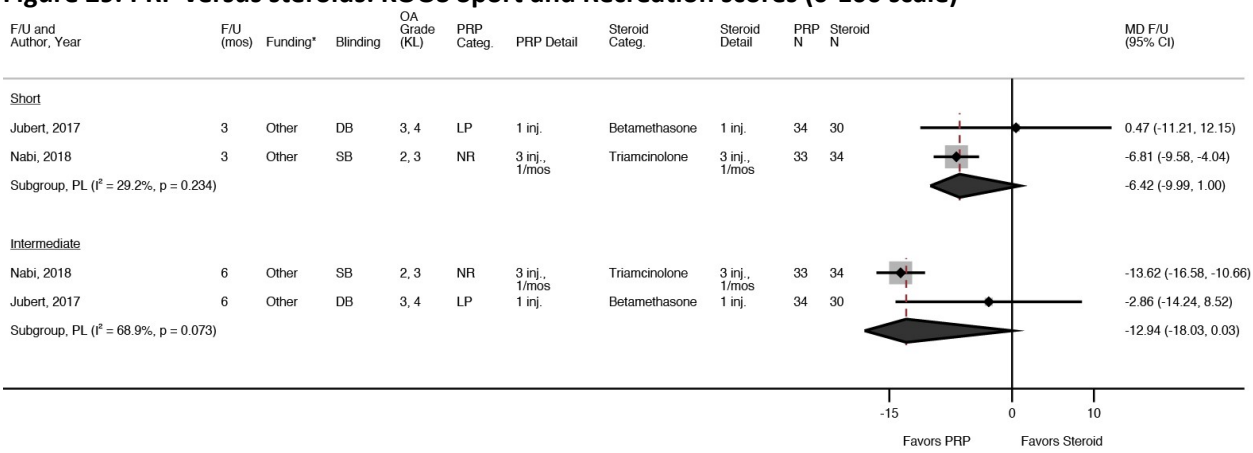
fair-quality trial (N=64)[71] that compared a single injection of PRP versus a single injection of betamethasone found no differences between groups at any time on either functional measure whereas the poor-quality trial (N=67)[91] that compared 3 injections (given at monthly intervals) of PRP versus triamcinolone found PRP associated with small improvements short term and moderate improvements intermediate term on both the KOOS ADL and Sports and Recreation measures. In addition to the differences in number of injections and types of steroids used, OA severity differed somewhat between the two trials with one trial (fair-quality)[71] enrolling patients with Kellgren-Lawrence grades 3 and 4 and the other (poor-quality)[91] grades 2 and 3.

Figure 28. PRP versus steroids: KOOS ADL scores (0-100 scale)



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, KOOS ADL = Knee injury and osteoarthritis outcome score function in daily living, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma

Figure 29. PRP versus steroids: KOOS Sport and Recreation scores (0-100 scale)



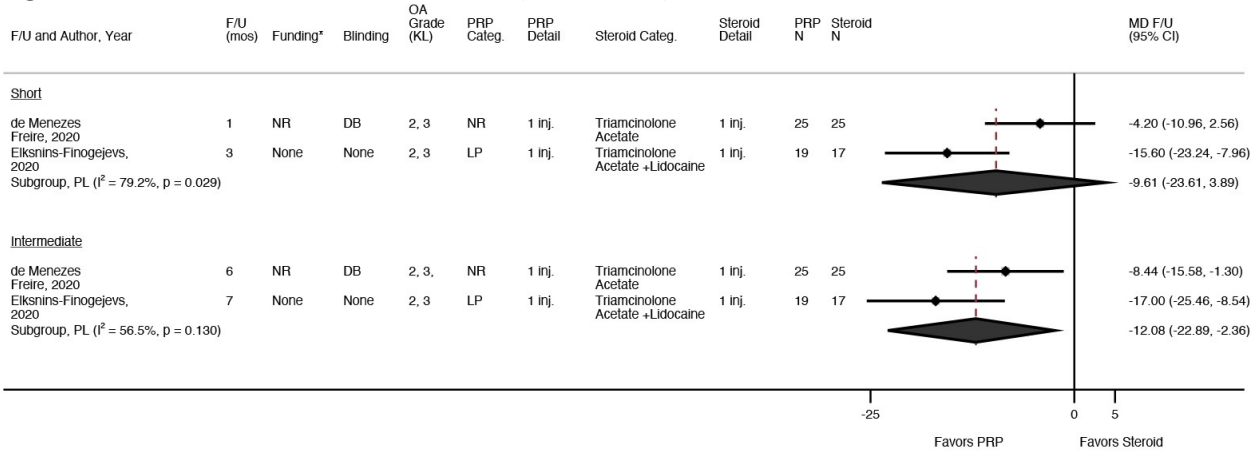
Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, KOOS = Knee injury and osteoarthritis outcome score, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma

Knee Society Score (KSS)

In pooled analyses across two RCTs, one fair[50] and one poor[44] quality, that compared single injections of PRP and triamcinolone acetate (with and without lidocaine) there was no difference between treatment groups in KSS scores short term (MD -9.61, 95% CI -23.60 to 3.89, I^2=79.2%) but a moderate

improvement favoring PRP intermediate term (MD -12.08, 95% CI -22.89 to -2.36, I^2=56.5%), Figure 30. Estimates were imprecise at both timepoints. Individually, the poor-quality trial showed moderate improvements in function with PRP at both times while the fair quality trial found a small improvement with PRP intermediate term only (no difference between groups short term). Both trials enrolled patients with Kellgren-Lawrence grade 2 and 3 OA. The reason for the heterogeneity in results is unclear.

Figure 30. PRP versus steroids: KSS Scores (0-100 scale)



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, KSS = Knee society score, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma

WOMAC physical function and IKDC scores

Three trials reported functional results not amenable to pooling. Two RCTs, one fair quality[95] and one poor quality,[75] reported WOMAC physical function scores and found no difference between groups at any timepoint (short, intermediate or long term), Table 23. The fair-quality trial compared a single injection of PRP versus a single injection of triamcinolone hexacetonide while the poor-quality trial compared PRP versus triamcinolone acetonide plus lidocaine and did not report the number of injections given but made a statement that "the injection was repeated after 2 months until 6 months". A third poor quality RCT[44] reported that a single injection of PRP was associated a large improvement in function based on IKDC scores at short, intermediate and long term compared with a single injection of triamcinolone and lidocaine, Table 24.

Table 24. PRP vs. steroid: function and pain outcomes not amenable to pooling

Outcome	Study Quality	F/U	PRP Mean (SD)	Steroid Mean (SD)	MD (95% CI)*
Function					
WOMAC function (0-68, lower = better)	Nunes-Tamashiro, 2022 *Fair*	3 mos.	13.5 (10.5) (n=34)	12.1 (10.3) (n=33)	1.4 (-3.58 to 6.38)
		12 mos.	12 (10.8) (n=34)	14.2 (12.1) (n=33)	-2.2 (-7.70 to 3.30)
	Khan, 2018 *Poor*	6 mos.	8.6 (5.9) (n=52)	6.9 (7.2) (n=51)	1.6 (-0.89 to 4.17)
IKDC (0-100, lower = better)	Elksnins-Finogejevs, 2020 *Poor*	3 mos.	78.7 (11.4) (n=19)	58.2 (15.9) (n=17)	**-20.5 (-29.63 to -11.37)**
		7 mos.	77.5 (14.2) (n=19)	56.3 (17.4) (n=17)	**-21.2 (-31.65 to -10.75)**

Outcome	Study Quality	F/U	PRP Mean (SD)	Steroid Mean (SD)	MD (95% CI)*
		13 mos.	62 (15.6) (n=19)	39.8 (16.3) (n=17)	**-22.2 (-32.65 to -11.75)**
Pain					
WOMAC pain (0-20, lower = better)	Nunes-Tamashiro, 2022 *Fair*	3 mos.	4.24 (3.35) (n=34)	4.09 (3.75) (n=33)	-0.51 (-4.18 to 3.88)
		12 mos.	3.68 (3.44) (n=34)	4.09 (3.96) (n=33)	-0.41 (-2.19 to 1.37)
	Khan, 2018 *Poor*	6 mos.	3.26 (3.97) (n=52)	4.34 (2.25) (n=51)	-1.08 (-2.32 to 0.16)

CI: confidence interval; f/u: follow-up; HA: hyaluronic acid; MD: mean difference; NS: not statistically significant; NSAIDs: Nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale *calculated

5.2.1.3.2 Pain

Pain "Success"

No trial reported on this.

WOMAC Pain scores

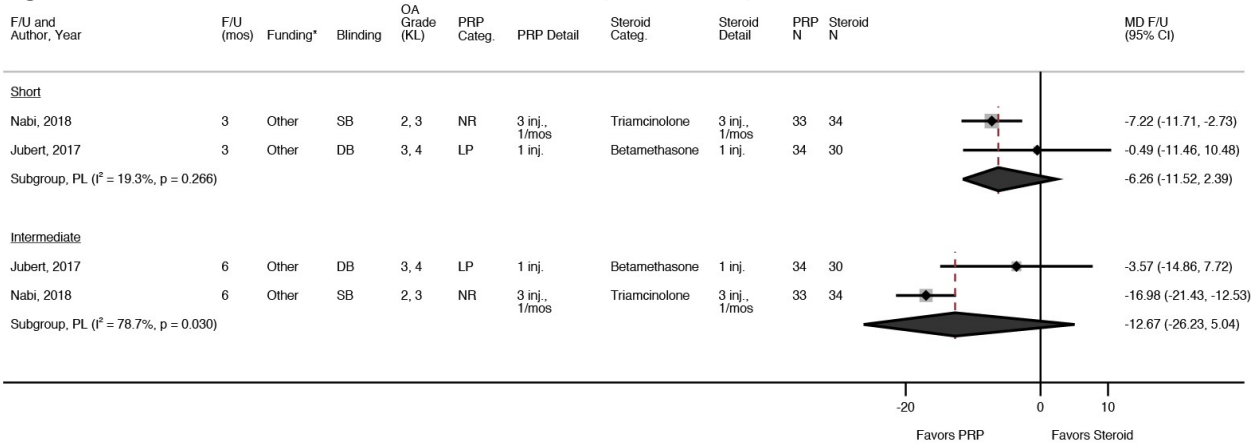
Two RCTs, one fair quality[95] and one poor quality,[75] reported WOMAC pain scores and found no difference between groups at any timepoint (short, intermediate or long term), Table 23 (above). The fair-quality trial compared a single injection of PRP versus a single injection of triamcinolone hexacetonide while the poor-quality trial compared PRP versus triamcinolone acetonide plus lidocaine and did not report the number of injections given but made a statement that "the injection was repeated after 2 months until 6 months".

KOOS Pain scores

Three RCTs, one fair[71] and two poor[49,91] quality, reported KOOS Pain scores (0-100 scale). One of the poor-quality trials[49] was a consistent outlier (favoring PRP). If patients were symptomatic in both knees, both knees were treated; the second knee was injected 3 weeks after the first and results were reported out of knees (not patients). Given both the study quality and the difference in the treatment protocol and reporting compared to the other trials, this RCT[49] was excluded from pooled analyses (see Appendix F for data).

In pooled analyses across two RCTs (one fair and one poor quality),[71,91] there were no differences in KOOS pain scores between PRP and steroids at either timepoint (short or intermediate term) (Figure 31). When the trials were considered separately, the fair-quality trial (N=64)[71] that compared a single injection of PRP versus a single injection of betamethasone found no differences between groups at any time whereas the poor-quality trial (N=67)[91] that compared 3 injections (given at monthly intervals) of PRP versus triamcinolone found PRP associated with a small improvement in pain short term and a moderate improvement intermediate term. In addition to the differences in number of injections and types of steroids used, OA severity differed somewhat between the two trials with one trial (fair quality)[71] enrolling patients with Kellgren-Lawrence grades 3 and 4 and the other (poor quality)[91] grades 2 and 3.

Figure 31. PRP versus steroids: KOOS Pain scores (0-100 scale)



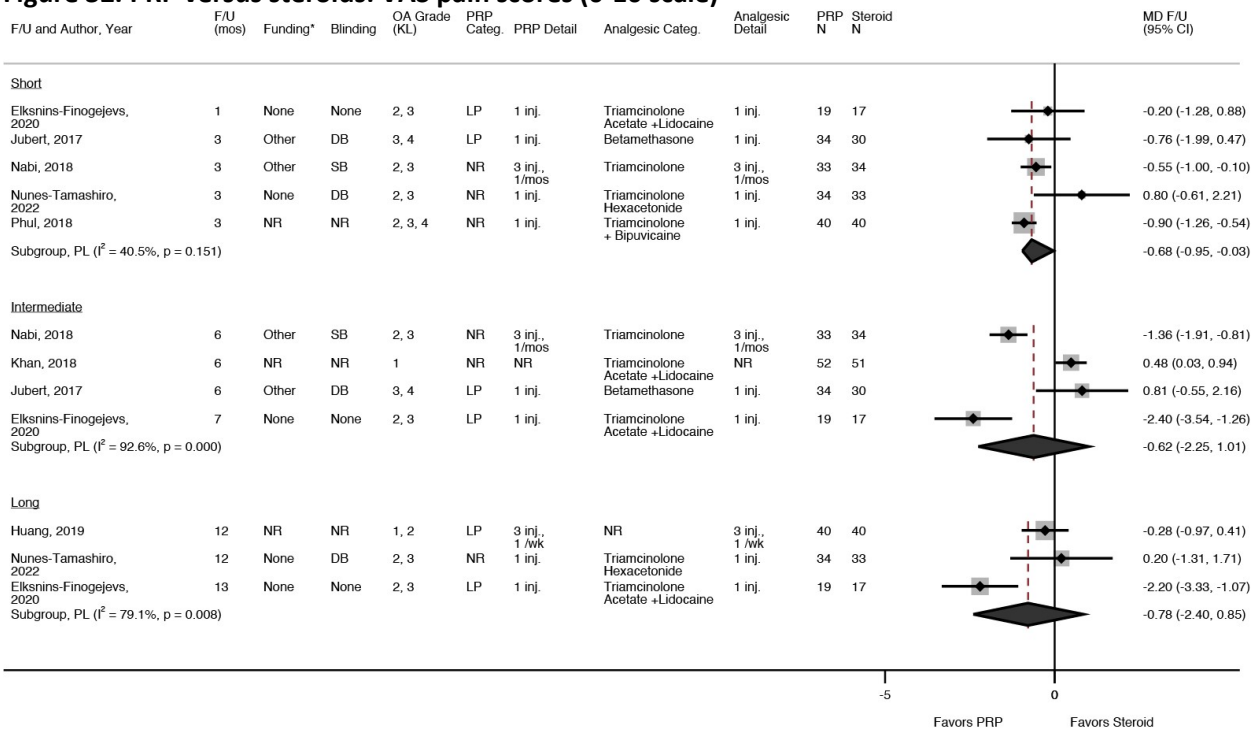
Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, KOOS = Knee injury and osteoarthritis outcome score, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma

VAS Pain scores

Eight RCTs, two fair[71,95] and six poor[44,49,67,75,91,103], reported VAS pain scores (0-10 scale). One of the poor-quality trials[49] was a consistent outlier (favoring PRP). If patients were symptomatic in both knees, both knees were treated; the second knee was injected 3 weeks after the first and results were reported out of knees (not patients). Given both the study quality and the difference in the treatment protocol and reporting compared to the other trials, this RCT[49] was excluded from pooled analyses (see Appendix F for data).

PRP was associated with a small improvement in pain on VAS at short term compared with steroids (5 RCTs, MD -0.68, 95% CI -0.95 to -0.03, I^2=40.5%)[44,71,91,95,103]; there were no differences between groups at intermediate (4 RCTs)[44,71,75,91] and long term (3 RCTs)[44,67,95] in pooled analyses but estimates were imprecise and there was a lot of heterogeneity (Figure 32). Differences in number of injections and types of steroids used (with and without lidocaine), OA severity, and study quality may explain some of the variation across the individual trials.

Figure 32. PRP versus steroids: VAS pain scores (0-10 scale)



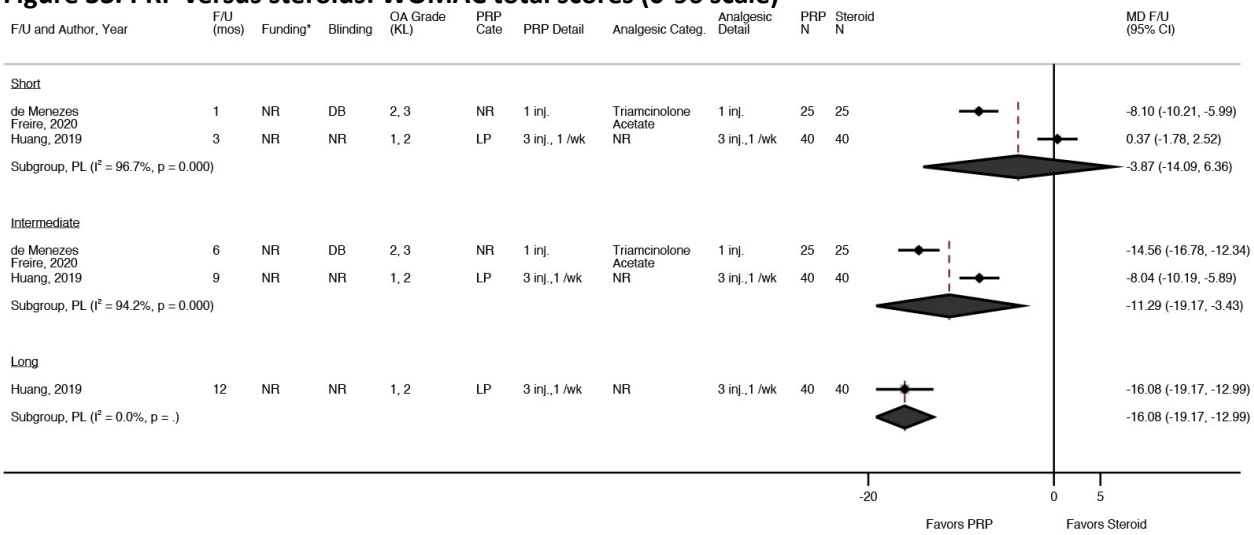
Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, N/A = Not applicable, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, VAS = Visual analog scale

5.2.1.3.3 Outcomes assessing multiple domains

WOMAC total scores

Three RCTs reported WOMAC total scores (0-96)[50,67,95] but only two contributed to the meta-analysis. One trial[95] reported WOMAC total scores that were incongruous with the score scale and could not be reconciled and therefore were excluded. In pooled analyses across the two trials (N=130), one fair[50] and one poor[67] quality, there was no difference between PRP and steroids short term, but PRP was associated with a moderate improvement in WOMAC total scores intermediate term (MD -11.29, 95% CI -19.17 to -3.43, I^2=94.2%). At both timepoints, pooled estimates were imprecise, and heterogeneity was substantial. Differences in treatment regimens (1 vs. 3 injections), timing of follow-up (1 vs. 3 and 6 vs. 9 months) or Kellgren-Lawrence grades (grades 1-2 vs. 2-3) may explain some of the heterogeneity. At long term, one poor-quality trial reported that PRP was associated with a moderate improvement in function (MD -16.08, 95% CI -19.17 to -12.99).[67]

Figure 33. PRP versus steroids: WOMAC total scores (0-96 scale)



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index

5.2.1.3.4 Need for secondary invasive procedures

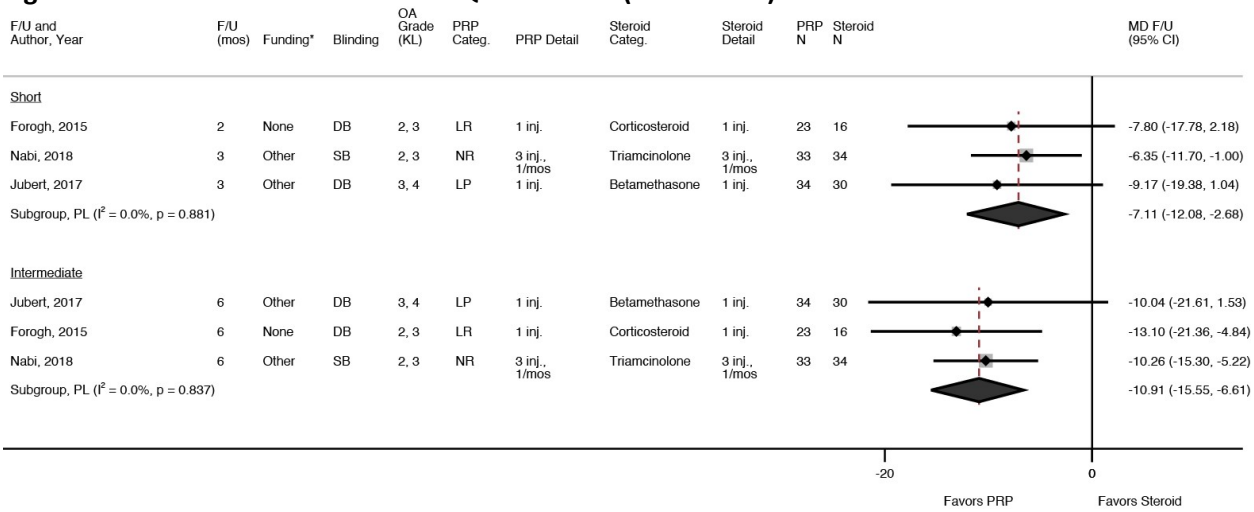
The need for secondary invasive procedures was not well reported by the included trials. One small, poor-quality RCT (N=40) reported that no patient in the PRP group received TKA during the 13-month study period (discontinued treatment) compared with three (15%) in the steroid group.[44]

5.2.1.3.5 Secondary Outcomes

Quality of Life

Three RCTs, one fair[71] and two poor[49,91] quality, reported **KOOS QoL scores** (0-100 scale) and reported a small improvement in quality of life with PRP short term (MD -7.11, 95% CI -12.08 to -2.68, I^2=0%) and a moderate improvement intermediate term (MD -10.91, 95% CI -15.55 to -6.61, I^2=0%) compared with steroids (Figure 34). The estimates were imprecise.

Figure 34. PRP versus steroids: KOOS QoL subscale (0-100 scale)



Categ. = Category CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index

Medication use

One fair-quality trial (N=64)[71] stated that no difference was found between a single injection of PRP versus betamethasone in dose or frequency of painkillers and NSAIDs (data not reported). No other trial reported medication use.

5.2.1.4 PRP vs. Oral Analgesics

Three RCTs compared PRP with oral analgesics for the treatment of knee OA (Appendix G).[24,114,127] Sample sizes ranged from 60 to 70 (total N=195). The average age was 56 (range, 53 to 57) years, 46% was female (range, 33% to 54%), and mean BMI (across 2 trials) was 27.83 kg/m^2 (range, 24.9 to 32.2 kg/m^2). Severity of OA was classified as grade 1 in 46% (range, 33% to 60%) across two trials,[24,127] grade 2 in 53% (range, 43% to 67%), and grade 3 in one trial (PRP: 57%, NSAIDs: 40%). Symptom duration was not reported in two trials,[24,127] and only mentioned as minimum 3 months for inclusion criteria in the other.[114] Patients in all three trials could have either unilateral or bilateral OA.[24,114,127]

Injection regimen varied as one trial each gave a single 5 mL injection,[24] two 3 mL injections (15 day intervals),[114] and three 3 mL injections (14 day intervals).[127] All[24,114,127] PRP injections were poor in leukocytes. Control groups consisted of 60 mg NSAIDs for 56 weeks in one trial,[24] 200 mg of celecoxib for 56 weeks in one trial,[114] and 500 mg of acetaminophen for 6 weeks in one trial.[127] Additional treatments varied, with one trial giving none,[114] one trial cold therapy,[127] and one trial omeprazole.[24] Follow-up ranged from 3 to 12 months with all trials reporting intermediate term results[24,114,127]; two trials[114,127] reported short-term results and two trials)[24,114] reported long-term results. One trial received non-industry funding[24], one trial did not receive funding,[114] and one trial did not report on funding.[127] Trials were located in Spain[24] and Mexico.[114,127]

Two trials[24,114] were considered fair quality and one[127] was considered poor quality. Common methodological limitations included unclear allocation concealment methods, as well as a lack of blinding (patients, outcome assessors, and care providers).

5.2.1.4.1 Function

Function "Success" (Responders)

One fair quality RCT[24] found that a single injection of PRP was associated with a substantially greater likelihood of a 20% improvement (i.e., a clinically important decrease) from baseline in **WOMAC Physical Function scores** compared with an NSAID (etoricoxib 60 mg., daily for 12 months) at intermediate and long term (Table 25). However, estimates were imprecise, especially at 12 months.

Table 25. PRP vs. NSAID: Proportion of patients achieving a ≥20% decrease in WOMAC Physical Function scores

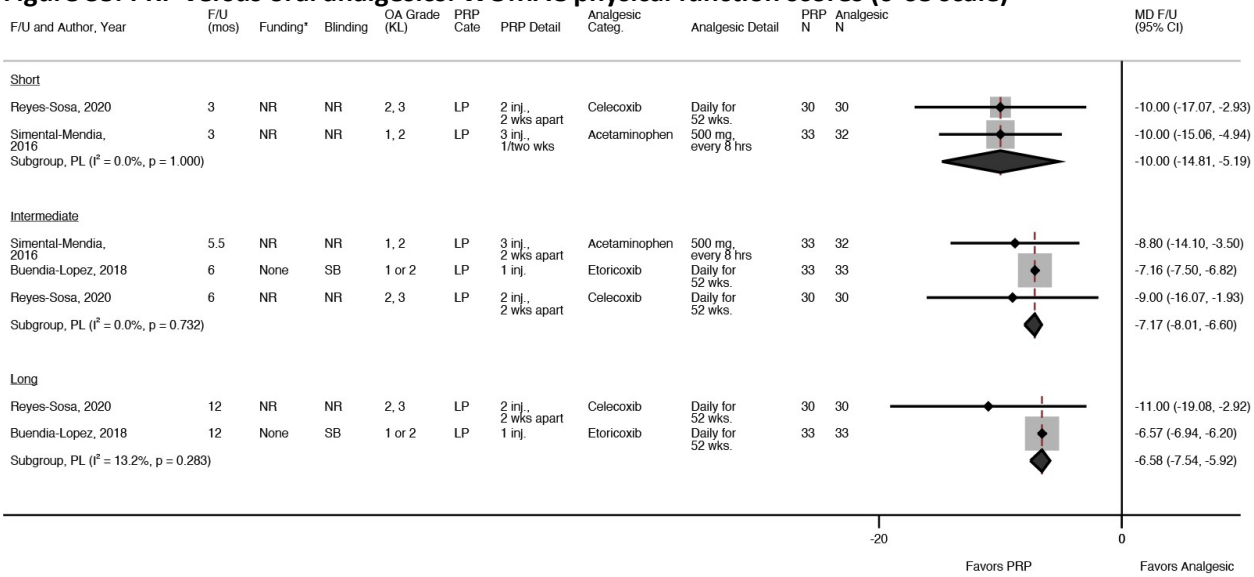
Author, Year Quality	Follow-up	PRP % (n/N)	Etoricoxib 60 mg. % (n/N)	RR (95% CI)
Buendia-Lopez, 2018 *Fair*	6 months	45.5% (15/33)	12.1% (4/33)	**3.75 (1.39 to 10.11)**
	12 months	24.2% (8/33)	0% (0/33)	16.00 (0.96 to 267.39)

CI = Confidence interval, mg. = Milligram, PRP = Platelet-rich plasma, RR = Risk ratio, SD = Standard deviation, WOMAC = Western Ontario and McMaster osteoarthritis index

WOMAC physical function scores

All three RCTs, two fair quality trials comparing PRP versus NSAIDs[24,114] and one poor quality trial comparing PRP versus acetaminophen,[127] reported WOMAC physical function scores (0-68 scale), Figure 35. PRP was associated with a moderate improvement in function at short (2 RCTs, MD -10.00, 95% CI -14.81 to -5.19, I^2=0%)[114,127] and intermediate term (3 RCTs, MD -7.17, 95% CI -8.01 to -6.60, I^2=0%)[24,114,127] and a small improvement at long term (2 RCTs, MD -6.58, 95% CI -7.54, I^2=13.2%).[24,114] Exclusion of the poor quality trial at short and intermediate term did not change the estimates.

Figure 35. PRP versus oral analgesics: WOMAC physical function scores (0-68 scale)



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SB = Single blind, Wks = Weeks, WOMAC = Western Ontario and McMaster osteoarthritis index

5.2.1.4.2 Pain

Pain "Success"

One fair quality RCT[24] found that a single injection of PRP was associated with a substantially greater likelihood of a 20% improvement (i.e., a clinically important decrease) from baseline in both **WOMAC Pain scores and VAS pain scores** compared with an NSAID (etoricoxib 60 mg., daily for 12 months) at intermediate term; results were similar long term for **WOMAC Pain scores** only, however the estimate was extremely imprecise (Table 26).

Table 26. PRP vs. NSAID: Proportion of patients achieving a ≥20% decrease in pain scores

Author, Year Quality	Outcome	Follow-up	PRP % (n/N)	Etoricoxib 60 mg. % (n/N)	RR (95% CI)
Buendia-Lopez, 2018 Fair	VAS Pain, 20% decrease	6 months	48.5% (16/33)	18.2% (6/33)	**2.67 (1.19 to 5.96)**
		12 months	15.2% (5/33)	6.1% (2/33)	2.50 (0.52 to 11.98)
	WOMAC Pain, 20% decrease	6 months	48.5% (16/33)	15.2% (5/33)	**3.20 (1.33 to 7.72)**
		12 months	30.3% (10/33)	0 % (0/33)	**20.00 (1.22 to 328.57)**

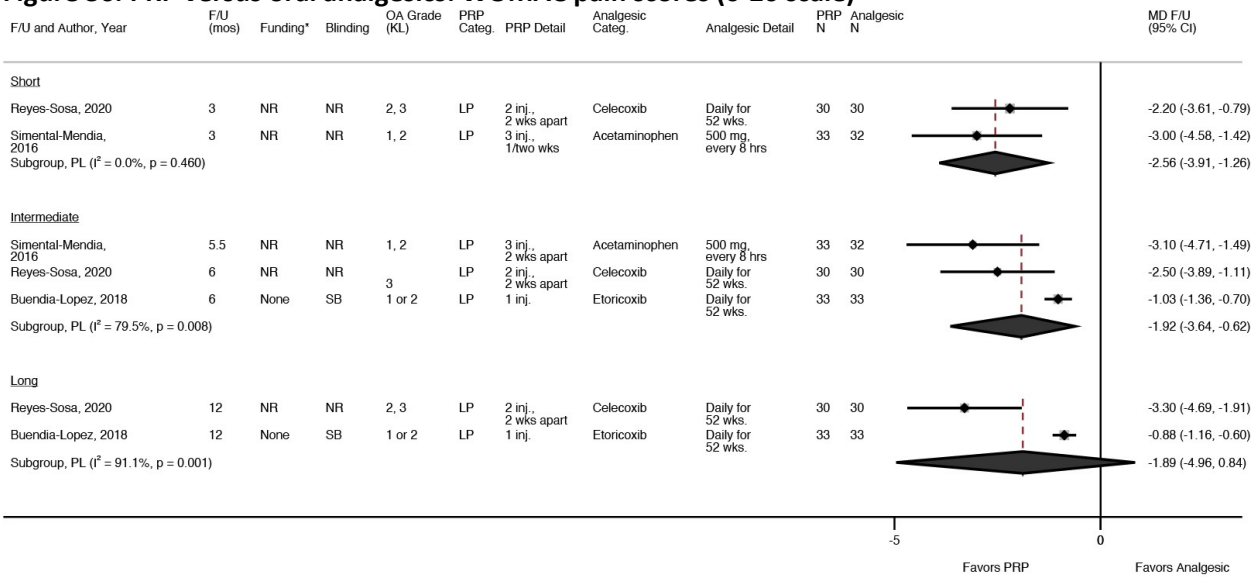
CI = Confidence interval, mg. = Milligram, PRP = Platelet-rich plasma, RR = Risk ratio, SD = Standard deviation, VAS = Visual analog score, WOMAC = Western Ontario and McMaster osteoarthritis index

WOMAC Pain Scores

All three RCTs, two fair quality trials comparing PRP versus NSAIDs[24,114] and one poor quality trial comparing PRP versus acetaminophen,[127] reported WOMAC pain scores (0-20 scale), Figure 36. PRP was

associated with a moderate improvement in pain at short term (2 RCTs, MD -2.56, 95% CI -3.91 to -1.26, I^2=0%)[114,127] and a small improvement intermediate term (3 RCTs, MD -1.92, 95% CI -3.64 to -0.62, I^2=79.5%).[24,114,127] Exclusion of the poor quality trial[127] at short and intermediate term resulted in slightly attenuated estimates but did not change conclusions or reduce heterogeneity at intermediate term. Long term, pooled analyses showed no difference in pain between groups (2 fair-quality RCTs, MD -1.89, 95% CI -4.96 to 0.84, I^2=91.1%), but heterogeneity was substantial.[24,114] Individually, both trials found that PRP was associated with improvement in pain; however, the estimate was below the threshold for a small effect in one trial (MD -0.88)[24] that compared a single PRP injection with daily etoricoxib while the other trial showed that PRP (2 injections given 2 weeks apart) was associated with a moderate improvement in pain (MD -3.30) compared with daily celecoxib. Difference in the severity of OA in these populations (1 or 2 vs. 2 or 3) or differences in treatments may explain some of the heterogeneity seen long term.

Figure 36. PRP versus oral analgesics: WOMAC pain scores (0-20 scale)



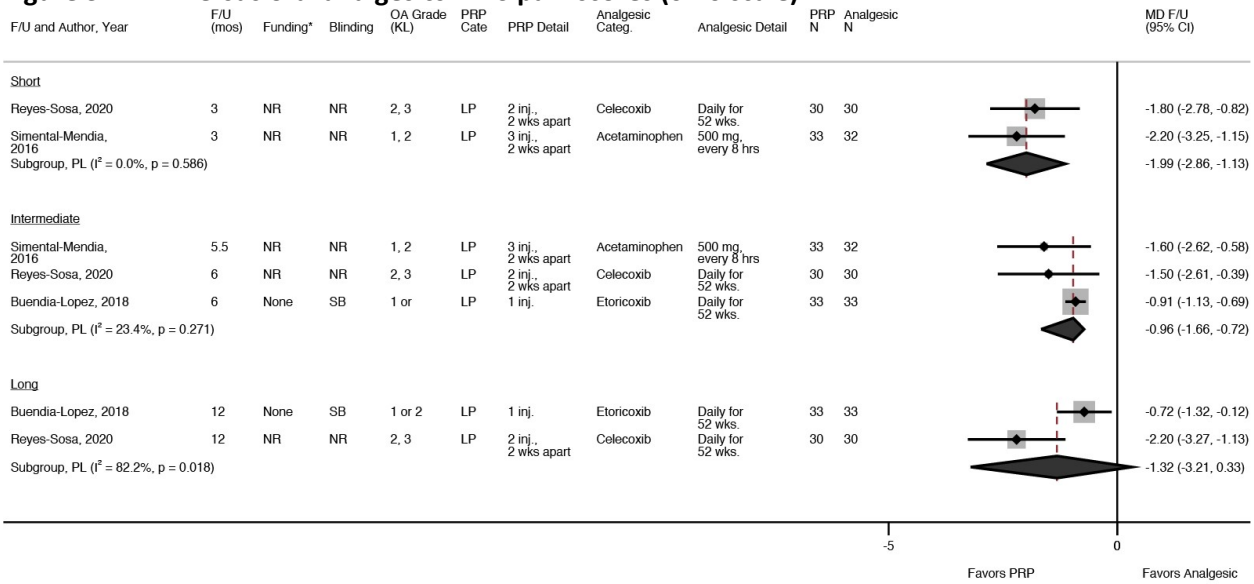
Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, Oral A. = Oral analgesic, PRP = Platelet-rich plasma, SB = Single blinded, WOMAC = Western Ontario and McMaster osteoarthritis index, Wks = Weeks

VAS Pain Scores

All three RCTs, two fair quality trials comparing PRP versus NSAIDs[24,114] and one poor quality trial comparing PRP versus acetaminophen,[127] reported VAS pain scores (0-10 scale), Figure 37. PRP was associated with a moderate improvement in pain at short term (2 RCTs, MD -1.99, 95% CI -2.86 to -1.13, I^2=0%)[114,127] and a small improvement intermediate term (3 RCTs, MD -0.96, 95% CI -1.66 to -0.72, I^2=23.4%).[24,114,127] Exclusion of the poor quality trial[127] at short and intermediate term resulted in slightly attenuated estimates but did not change conclusions. Long term, pooled analyses showed no difference in VAS pain scores between groups (2 fair-quality RCTs, MD -1.32, 95% CI -3.21 to 0.33, I^2=82.2%), but heterogeneity was substantial.[24,114] Individually, both trials found that PRP was associated with improvement in pain but the effect sizes differed: a small improvement (-0.72) in one trial[24] that compared a single PRP injection with daily etoricoxib and a large improvement in pain (MD -2.20) in the other trial that compared two injections of PRP (given 2 weeks apart) versus daily celecoxib. Differences

in treatments or difference in the severity of OA in these populations (1 or 2 vs. 2 or 3) may explain some of the heterogeneity seen long term.

Figure 37. PRP versus oral analgesics: VAS pain scores (0-10 scale)



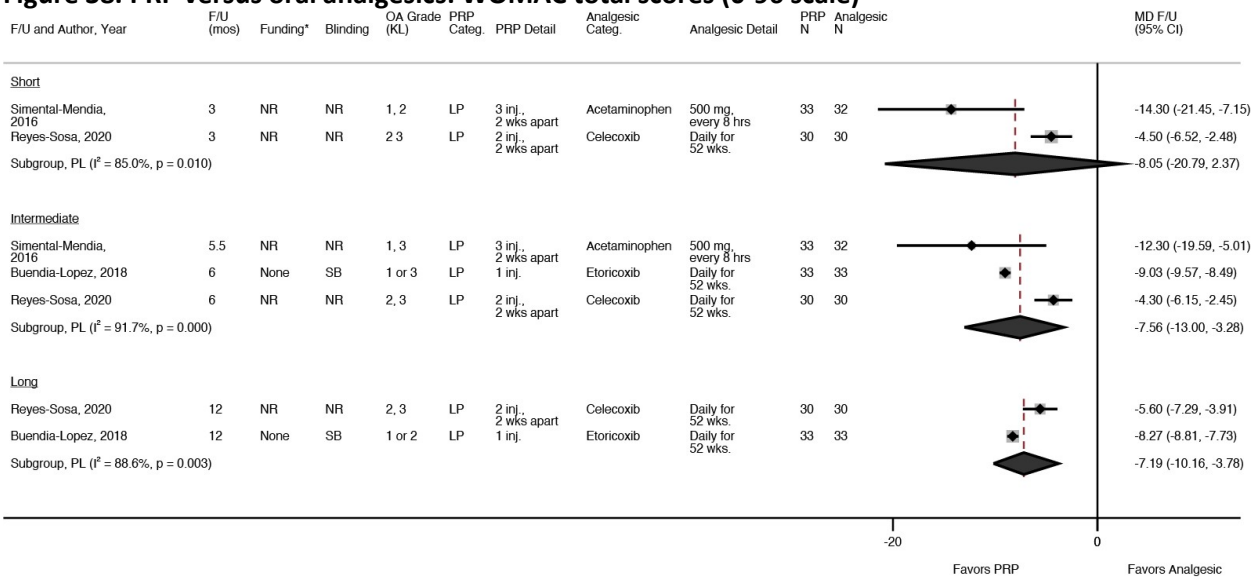
Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, Oral A. = Oral analgesic, PRP = Platelet-rich plasma, SB = Single blinded, VAS = Visual analog scale, Wks = Weeks

5.2.1.4.3 Outcomes assessing multiple domains

WOMAC total scores

All three RCTs, two fair quality trials comparing PRP versus NSAIDs[24,114] and one poor quality trial comparing PRP versus acetaminophen,[127] reported WOMAC total scores (0-96 scale), Figure 38. Short term, there was no difference between groups (2 RCTs, MD -8.05, 95% CI -20.79 to 2.37, I^2=85.0%)[114,127] but the estimate was very imprecise and the heterogeneity substantial. Individually, both trials found that PRP was associated with improvement in pain; however, the estimate was below the threshold for a small effect in the fair-quality trial (MD -4.5)[24] that compared a PRP (2 injections given 2 weeks apart) with daily celecoxib while the other, poor-quality trial showed that PRP (3 injections given 2 weeks apart) was associated with a moderate improvement in WOMAC total scores (MD -14.3) compared with daily acetaminophen. Difference in the severity of OA in these populations (1 or 2 vs. 2 or 3) or differences in treatments may explain some of the heterogeneity seen short term. PRP was associated with a small improvement intermediate term (3 RCTs, MD -7.56, 95% CI -13.00 to -3.28, I^2=91.7%)[24,114,127] and long term (2 RCTs, MD -7.19, 95% CI -10.16 to -3.78, I^2=88.6%)[24,114] compared with oral analgesics. Exclusion of the poor-quality trial intermediate term resulted in a slightly attenuated effect estimate (still small effect) and increased imprecision.

Figure 38. PRP versus oral analgesics: WOMAC total scores (0-96 scale)



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, Oral A. = Oral analgesic, PRP = Platelet-rich plasma, SB = Single blinded, WOMAC = Western Ontario and McMaster osteoarthritis index, Wks = Weeks

5.2.1.4.4 Need for secondary invasive procedures

No trial reported this.

5.2.1.4.5 Secondary Outcomes

Quality of Life

One small, poor-quality trial[127] reported that PRP was associated with primarily small improvements in quality of life based on the **SF-12 PCS and MCS scores** compared with an NSAID (Table 27).

Table 27. PRP vs. NSAID: SF-12 PCS and MCS scores

Author, Year Quality	Outcome*	F/U	PRP (n=33) Mean (SD)	Celecoxib 200 mg (n=32) Mean (SD)	MD (95% CI)
Simental-Mendia, 2016 Poor	SF-12 PCS (0-100, lower = better)	3 mos.	48.8 (7.9)	41 (10)	-7.8 (-12.19 to -3.41)
		6 mos.	49.9 (8.1)	41 (7)	-8.9 (-12.58 to -5.22)
	SF-12 MCS (0-100, lower = better)	3 mos.	55.9 (7.9)	45 (4.7)	-10.9 (-14.05 to -7.75)
		6 mos.	54.3 (7.6)	47 (3)	-7.3 (-10.09 to -4.51)

CI = Confidence interval, F/U = Follow-up, mg. = Milligram, Mos. = Months, PRP = Platelet-rich plasma, SD = Standard deviation, SF-12 MCS = Short form-12 Mental component score, SF-12 PCS = Short form-12 Physical component score

Medication use

One trial (N=60)[114] stated that no patient (PRP or NSAID) required another medication for pain control; no other information was provided.

5.2.1.5 PRP (w/ Exercise) vs. Exercise

Randomization by patient

Three RCTs[5,8,111] compared PRP with exercise for the treatment of knee OA (Appendix G). Sample sizes ranged from 52 to 65 (total N=179). The average age of participants was 59 (range, 55 to 62), 90% were female (range, 80% to 97%), and mean BMI was 29.89 kg/m^2 (range, 27.3 kg/m^2 to 33.6 kg/m^2). Severity of OA was poorly described. One trial[8] included patients with Kellgren-Lawrence grade 1, 2, and 3, but did not describe distribution; one trial[5] included only patients with grade 4 OA; and one trial[111] included patients with Kellgren-Lawrence grade 1 through 4, but did not report distribution. Mean symptom duration was reported in one trial[111], with 83% versus 74% having symptoms longer than 12 months; one trial[5] required patients to have symptoms longer than 3 months (inclusion criteria), and the third trial[8] did not report symptom duration.

In two trials[5,111], all patients were given home exercises, and those randomized to receive PRP also were given either two[111] injections (4 to 6 mL; interval details not reported) or three[5] injections (volume not reported; in 3 week intervals). In the third trial[8], PRP randomized patients received 6 mL of one injection, while controls received exercise and transcutaneous electrical nerve stimulation (TENS). PRP patients in all three trials[5,8,111] received leukocyte-rich PRP. All three trials allowed patients to receive additional treatments: paracetamol in all two[5,8], and acetaminophen (or acetaminophen-codeine if pain persists) in one[111]. Follow-up ranged from 3 (short-term) to 6 (intermediate) months; two trials reported short term results[5,8] and two trials[5,111] reported intermediate term results. No trials reported long term results. One trial reported non-industry funding[8] and the other two did not report on funding. Trials were located in Iran[8,111] and Turkey.[5]

All three[5,8,111] trials were considered fair quality. Common methodological limitations included unclear allocation concealment methods, as well as a lack of blinding (patients, outcome assessors, and care providers). There were also some concerns regarding imbalances in patient characteristics at baseline in two trials.[5,111]

Randomization by knee

One additional study[108] conducted in Iran compared PRP to exercise and randomized by knee rather than patient (Appendix G). While self-described as an RCT, for purposes of this report it is considered an observational cohort study (a nonrandomized study of interventions [NRSI]) since the randomization was done to two knees within the same patient. Patient factors may influence outcomes for both treatments. All patients had bilateral OA. Both knees were prescribed exercises three times a day; in addition, one knee was randomized to two leukocyte-rich PRP injections (volume not reported) in 4-week intervals. Patients were additionally allowed to take paracetamol and/or codeine if pain persisted. Mean age was 58 years, mean BMI was 28.49 kg/m^2, and all patients were female. The severity of OA was KL grade 1 in 26%, grade 2 in 53%, and grade 3 in 21% of patients. Inclusion criteria required symptom duration to be 3 months or longer. All patients were followed and reported results at 8 months (intermediate term). Funding was not reported.

This trial was rated poor. Despite authors describing it as double-blind, it is unclear how patient and provider blinding was possible when there was no mention of a placebo injection. The intervention and allocation of different treatments was poorly described.

5.2.1.5.1 Function

Function "Success"

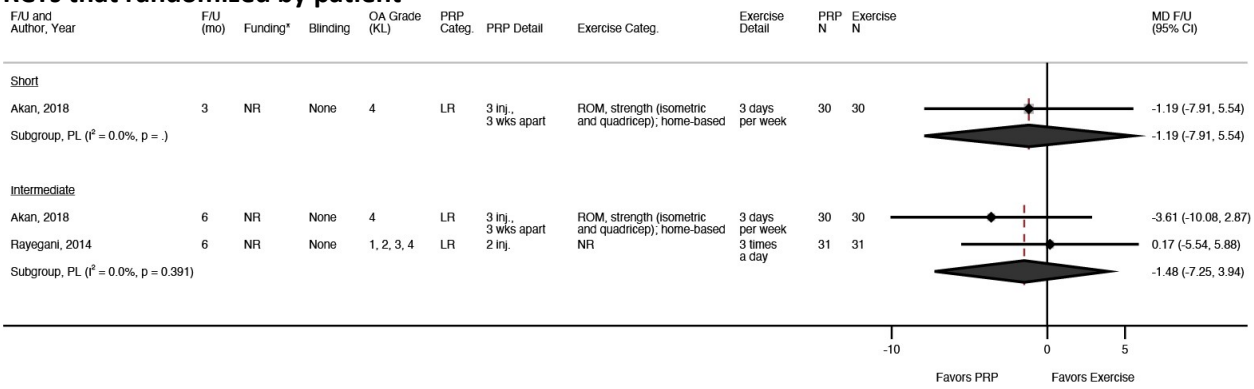
No trial reported on this.

WOMAC Physical Function Scores

Two small, fair-quality RCTs that randomized by patient reported WOMAC physical function scores (0-68) and found no difference between PRP plus exercise versus exercise alone at short term (1 RCT, N=60)[5] or intermediate term (2 RCTs, N=122),[5,111] Figure 39. Effect estimates were very imprecise.

One small poor-quality NRSI that randomized by knee (42 knees in 21 patients)[108] found no difference in WOMAC physical function scores at intermediate term (8 months) when PRP (2 injections, 1 month apart) was added to exercise versus exercise alone (MD -1.9, 95% CI -6.46 to 2.66).

Figure 39. PRP plus exercise versus exercise alone: WOMAC physical function scores (0-68 scale) in RCTs that randomized by patient



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index

KOOS ADL and Sports and Recreation Scores

One fair-quality trial[8] compared two injections of PRP (1 month apart) with 10 sessions of exercise and TENS and reported short term outcomes only. PRP was associated with a moderate improvement in function according to the KOOS ADL subscale but not the KOOS Sports and Recreation subscale (Table 28) compared with exercise and TENS; while the difference between groups for the latter outcome was statistically significant favoring the control group, the difference was below the threshold for a small effect (MD 4.1).

Table 28. PRP vs. exercise plus TENS: KOOS function outcomes

		Angoorani, 2015		
Outcome	**F/U**	**PRP (n=26) Mean (SD)**	**Exercise + TENS (n=24) Mean (SD)**	**MD (95% CI)***
KOOS ADL (0-100, lower = better)*	2 mos.	54.4 (3.35)	44.2 (4.36)	-10.2 (-12.37 to -8.03)
KOOS Sports and Recreation (0-100, lower = better)*	2 mos.	21.3 (4.33)	25.4 (5.31)	4.1 (1.40 to 6.80)

ADL = Function in daily living, CI = Confidence interval, F/U = Follow-up, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, PRP = Platelet-rich plasma, SD = Standard deviation, TENS = Transcutaneous electrical nerve stimulation

*The direction of the KOOS scale was flipped so that a lower score was better (typically for KOOS a higher score is better) in order to be consistent across measures.

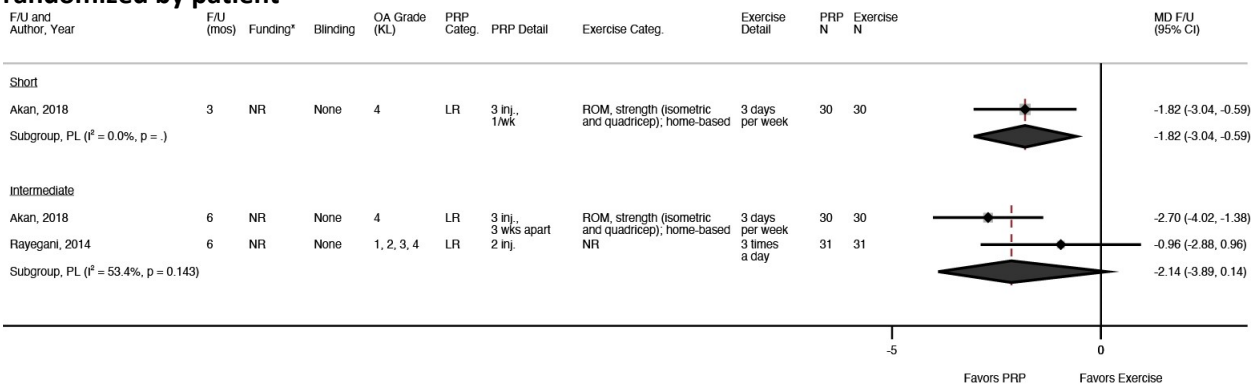
5.2.1.5.2 Pain

WOMAC Pain Scores

Two small RCTs that randomized by patient compared PRP plus exercise versus exercise alone and reported WOMAC pain scores (0-20).[5,111] In one trial, three weekly injections of PRP in addition to exercise were associated with a small improvement in pain short term (MD -1.82, 95% CI -3.04 to -0.59) and a moderate improvement intermediate term (MD -2.70, 95% CI -4.02 to -1.38) compared with exercise alone in patients with severe knee OA (KL grade 4).[5] The second trial enrolled patients with grades 2 and 3 OA primarily who received two PRP injections at 1 month intervals and reported no difference between treatment groups at intermediate term (MD -0.96, 95% CI -2.88 to 0.96).[111] When the trials were pooled at intermediate term, there was no difference in pain improvement between treatment groups (2 RCTs, MD -2.14, 95% CI -3.89 to 0.14, I^2=53.4%),[5,111] Figure 40. All reported estimates were imprecise.

One small poor-quality NRSI that randomized by knee (42 knees in 21 patients)[108] found no difference in WOMAC pain scores (0-20 scale, MD -0.19, 95% CI -1.98 to 1.60) at intermediate term (8 months) when PRP (2 injections, 1 month apart) was added to exercise versus exercise alone.

Figure 40. PRP plus exercise versus exercise alone: WOMAC pain scores (0-20 scale) in RCTs that randomized by patient



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, WOMAC = Western Ontario and McMaster osteoarthritis index.

KOOS Pain and VAS Pain Scores

One fair-quality trial[8] compared two injections of PRP (1 month apart) with 10 sessions of exercise and TENS and reported short term outcomes only. Compared with exercise and TENS, PRP was associated with a small improvement in pain based on the KOOS pain subscale but there was no difference between groups on the VAS pain scale (Table 28).

One small, poor-quality NRSI that randomized by knee (42 knees in 21 patients)[108] found no differences in VAS pain scores at intermediate term when PRP (2 injections, 1 month apart) was added to exercise versus exercise alone (Table 29).

Table 29. PRP vs. exercise: KOOS pain and VAS pain

Study Quality	Outcome	F/U	PRP (n=26) Mean (SD)	Exercise + TENS (n=24) Mean (SD)	MD (95% CI)*
Angoorani, 2015 *Randomized by patient* **Fair**	**KOOS Pain (0-100, lower = better)***	2 mos.	50.7 (3.24)	44.2 (3.88)	**-6.5 (-8.49 to -4.51)**
	VAS Pain (0-10, lower = better)	2 mos.	4.8 (2.07)	5.1 (1.84)	-0.3 (-1.38 to 0.78)
Study	**Outcome**	**F/U**	**PRP + exercise (n=21 knees) Mean (SD)**	**Exercise alone (n=21 knees) Mean (SD)**	**MD (95% CI)***
Raeissadat, 2020 *Randomized by knee* **Poor**	**VAS Pain (0-10, lower = better)**	8 mos.	2.76 (2.07)	3.42 (1.83)	-0.66 (-1.84 to 0.52)

CI = Confidence interval, F/U = Follow-up, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, PRP = Platelet-rich plasma, SD = Standard deviation, TENS = Transcutaneous electrical nerve stimulation, VAS = Visual analog score.
*The direction of the KOOS scale was flipped so that a lower score was better (typically for KOOS a higher score is better) in order to be consistent across measures.

5.2.1.5.3 Need for secondary invasive procedures

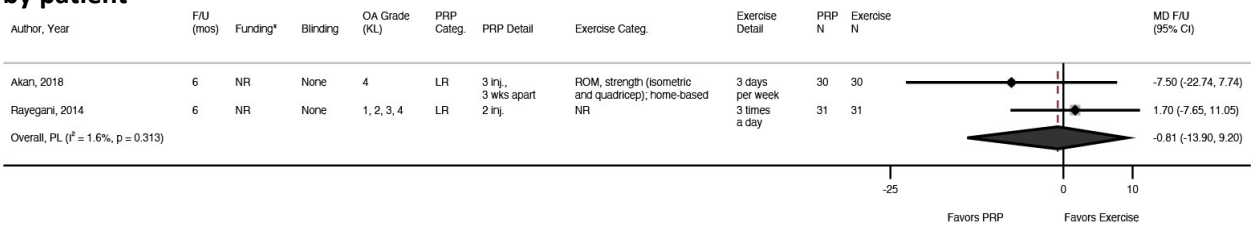
The need for secondary invasive procedures was not well reported by the included trials. One small, fair-quality RCT (N=60) reported that one patient (3.3%) in the PRP group underwent TKA after their first PRP injection compared with no patient in the exercise alone group.[5] The follow-up period was 12 months.

5.2.1.5.4 Secondary Outcomes

Quality of Life

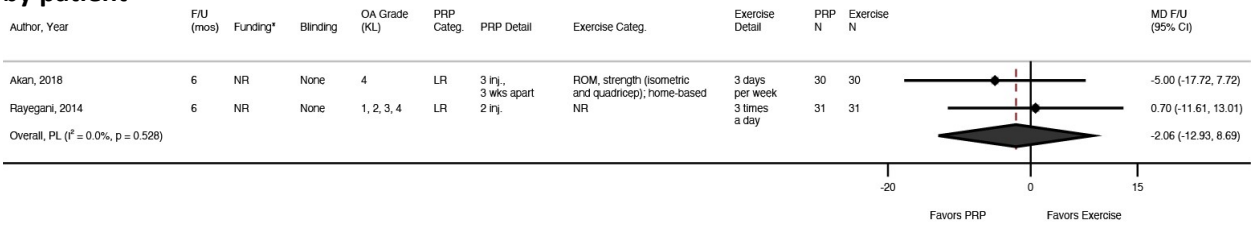
Across two small trials that compared PRP plus exercise with exercise alone,[5,111] there were no differences in **SF-36 PCS or MCS** scores between treatment groups at intermediate term (Figures 41 and 42). Effect estimates were very imprecise.

Figure 41. PRP plus exercise versus exercise alone: SF-36 PCS scores (0-100) in RCTs that randomized by patient



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SF-36 PCS = Short form-36 physical component score

Figure 42. PRP plus exercise versus exercise alone: SF-36 MCS scores (0-100) in RCTs that randomized by patient



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, PRP = Platelet-rich plasma, SF-36 PCS = Short form-36 mental component score

One fair-quality trial (N=50)[8] compared two injections of PRP (1 month apart) with 10 sessions of exercise and TENS and reported a small improvement in quality of life with PRP based on the **KOOS QoL subscale** (0-100, lower=better; mean -22.6 vs. -17.6, MD -5.0, 95% CI -6.41 to -3.59).

Medication use

One fair-quality trial (N=62)[111] reported that patients who received PRP plus exercise consumed significantly more acetaminophen (500 mg) over the 6 month study period: mean consumption was 64 ± 11.8 in the PRP group versus 31.5 ± 36.5 in the exercise only group (MD 32.55, 95% CI 19.04 to 46.06). According to the authors, the highest rate of consumption in the PRP group occurred around the time of injection, but in the exercise-only group acetaminophen use was fairly steady throughout the follow-up period.

5.2.1.6 PRP vs. PT

One trial[51] conducted in Egypt compared PRP to rehabilitation/physical therapy (PT) for the treatment of knee OA (Appendix G). Patients randomized to PRP received 2 injections (volume and leukocyte content not reported) in 2-week intervals. Control patients received infrared, TENS, and strength training three times per week for once a month. Sample size was 40 (20 in each group), mean age was 55 years, 75%

were female, and BMI was not reported. OA severity was KL grade 1 in 10%, grade 2 in 53%, and grade 3 in 37% if patients. Mean symptom duration was 5.3 years in the PRP group compared to 6.4 years in the PT group. All patients were followed for 3 months (short term). No funding was received. This trial was considered poor quality. Methods were poorly described, and blinding was not possible due to inherent differences in the interventions.

5.2.1.6.1 Function and Pain

One small, poor-quality trial found that PRP (2 injections, 2 weeks apart) was associated with substantial improvements in function (WOMAC physical function subscale) and pain (VAS pain scale) short term compared with 4 weeks of physical therapy/rehabilitation (Table 30).

Table 30. PRP vs. PT: Function and Pain outcomes

Study Quality	Outcome	F/U	PRP (n=20) Mean (SD)	PT (n=20) Mean (SD)	MD (95% CI)*
Gabella, 2019 Poor	**WOMAC Physical Function (0-68, lower = better)**	3 mos.	23 (8.5)	53.2 (7.4)	-30.2 (-35.14 to -25.26)
	VAS Pain (0-10, lower = better)	3 mos.	3.5 (0.9)	7.0 (1.0)	-3.5 (-4.09 to -2.91)

CI = Confidence interval, F/U = Follow-up, MD = Mean difference, Mos. = Months, PRP = Platelet-rich plasma, PT = Physical therapy, SD = Standard deviation, VAS = Visual analog score, WOMAC = Western Ontario and McMaster osteoarthritis index

No other outcomes of interest, to include the need for invasive procedures, were reported.

5.2.1.7 PRP vs. Prolotherapy

Two trials[104,110] compared PRP to prolotherapy for the treatment of knee OA (Appendix G). Sample sizes were 42 and 60 (total N=102). Mean age was 61 (range, 58 to 66) years, 50% were female (range 47% to 55%), and mean BMI was reported as 28.45 in one trial[110], while the other trial[104] reported patients as overweight (BMI 25.01 to 30: 43% versus 47%) and obese (BMI >30: 47% versus 57%) in PRP and prolotherapy groups respectively. One trial[104] reported OA severity as KL grade 2 (17% versus 23%), grade 3 (53% versus 40%), and grade 4 (30% versus 37%); the other trial[110] reported mean KL score as 2.47 versus 2.42. Mean symptom duration was not reported in either trial, though one trial[110] only included patients with symptoms for longer than 3 months.

Both trials[104,110] used two-injection regimen for PRP; one with weekly intervals[104] using leukocyte-poor PRP (volume not reported), and the other[110] with monthly injections (7 mL; leukocyte content not reported). Control patients in each trial received dextrose: in one trial[110] two 7 mL injections were given with 4 week intervals, and the other trial[104] gave three 5 mL (2 mL dextrose, 2 mL bacteriostatic water, 1 mL lidocaine) with 1 week intervals. Additional treatments were not reported for either trial. Follow-up ranged from 1 to 6 months; both trials[104,110] had short-term and intermediate follow-up results. One trial received non-industry[104] funding, the other[110] did not give funding details. Trials were conducted in Egypt[104] and Iran[110].

Both trials[104,110] were considered poor quality. One trial[104] was unable to achieve blinding, and neither trial[104,110] was clear in randomization and concealment methods. Additionally, neither trial included homogenous populations at baseline.

5.2.1.7.1 Function and Pain

PRP was associated with small improvements in function and pain short and intermediate term compared with prolotherapy across both RCTs; one trial reported WOMAC physical function and WOMAC pain scores[110] and the other trial reported VAS pain scores[104] (Table 31).

Table 31. PRP vs. Prolotherapy: Function and Pain outcomes

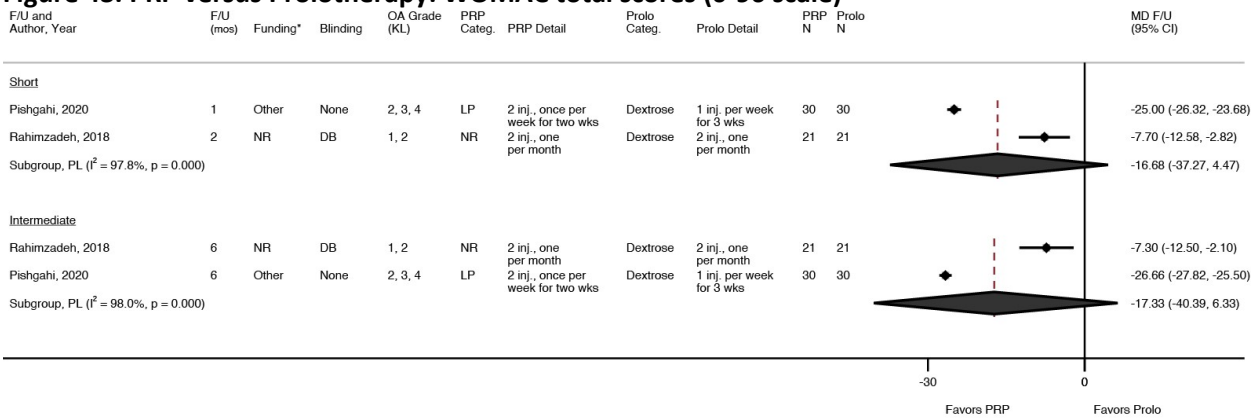
Study Quality	Outcome	F/U	PRP Mean (SD)	Prolotherapy Mean (SD)	MD (95% CI)*
Rahimzadeh, 2018 *Poor*	**WOMAC Physical Function (0-68, lower = better)**	2 mos.	19.6 (7.2) (n=21)	25 (5.5) (n=21)	-5.40 (-9.28 to -1.52)
		6 mos.	22.8 (7.9) (n=21)	27.8 (5.2) (n=21)	-5.00 (-9.05 to -0.95)
	WOMAC Pain (0-20, lower = better)	2 mos.	5.4 (1.8) (n=21)	7.1 (1.7) (n=21)	-1.70 (-2.76 to -0.64)
		6 mos.	6.2 (2.1) (n=21)	8.0 (1.6) (n=21)	-1.80 (-2.93 to -0.67)
Pishgahi, 2020 *Poor*	**VAS Pain (0-10, lower = better)**	2 mos.	5.63 (0.56) (n=30)	6.33 (0.56) (n=30)	-0.70 (-0.77 to -0.63)
		6 mos.	5.5 (1.24) (n=30)	6.33 (1.24) (n=30)	-0.83 (-0.92 to -0.74)

CI = Confidence interval, F/U = Follow-up, MD = Mean difference, Mos. = Months, PRP = Platelet-rich plasma, SD = Standard deviation, VAS = Visual analog score, WOMAC = Western Ontario and McMaster osteoarthritis index

5.2.1.7.2 Outcomes assessing multiple domains

Both trials reported the WOMAC total score[104,110]; this outcome assesses multiple domains that includes function, pain and stiffness. One trial (N=60)[104] that did not blind patients or providers, found that PRP was associated with a large improvement in at short (MD -25.00) and long term (MD -26.66) compared with prolotherapy while the other trial (N=42)[110] that did blind patients and providers, reported a small improvement with PRP at both timepoints (MD -7.70 and -7.30, respectively); when pooled, the differences between groups were not statistically significant at either timepoint due to extreme imprecision and heterogeneity (Figure 43). Both trials were small and poor quality.

Figure 43. PRP versus Prolotherapy: WOMAC total scores (0-96 scale)



Categ. = Category, CI = Confidence interval, F/U = Follow-up, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, Prolo = Prolotherapy, WOMAC = Western Ontario and McMaster osteoarthritis index.

5.2.1.7.3 Need for secondary invasive procedures

No trial reported on this.

5.2.1.8 PRP vs. PRP: Number of Injections

Six trials[55,73,81,100,143,161] compared PRP with different number of injections (Appendix G). Sample size ranged from 52 to 133 (total N=508). Mean age was 56 years (range, 52 to 66 years), mean BMI was 28.41 kg/m^2 (range, 24.9 to 31.09 kg/m^2), and 58% were female (range, 13% to 85%). Severity of OA varied widely. One trial[81] reported OA severity as Kellgren-Lawrence grade 0 in 6.1% of patients; two trials[81,161] reported grade 1 in 17% (range, 3.2% to 29.6%) and grade 2 in 57% (range, 48% to 69%). Two trials[73,161] reported grade 3, but distribution varied greatly; in one[161], proportions ranged from 19% to 37% between the two PRP groups, while the other trial[73] only included Kellgren-Lawrence grade 3. One trial[55] reported OA severity as early and advanced; 67% of patients were early OA (defined as Kellgren-Lawrence grade 0 to 3), while 33% were advanced OA (defined as Kellgren-Lawrence grade 4). Two trials[143] reported OA severity using the Ahback system, with 72%, 21%, and 4% of patients being reported as grade 1, 2, and 3 respectively reported in one trial[100], and another trial (reporting by knees) as 38% versus 30% and 63% versus 70% grade 1 and 2 respectively. Two trials[73,161] included patients with unilateral knee OA, two trials[100,143] with bilateral knee OA , and one trial[55] included patients with either unilateral or bilateral knee OA. One trial[81] did not give details. System duration was poorly reported, with only one trial[81] reporting mean symptom duration as 4.7 years. Two other trials reported the minimum number of months with symptoms as either 4[55] or 6[73,143] months in their inclusion criteria. No other trial reported on this.

All six trials included an arm for single injection[55,73,81,100,143,161]; in one trial, this single injection was combined with 2 injections of saline[81]. Three trials compared one PRP injection to two injections using 8 mL leukocyte-poor PRP[100], 4 to 6 mL of leukocyte-rich PRP[143], or an unspecified volume of leukocyte-rich PRP[73]. Four trials used three-injection regimens in 5 mL of leukocyte rich[55,161], 4 to 6 mL of leukocyte poor[81], or an unspecified volume of leukocyte-rich PRP[73]. Multi-injection schedules varied: two trials used weekly intervals[55,81], two trials used 2-week intervals[73,100], one trial used 3-week intervals[143], and one trial used monthly intervals[161]. Additional treatments likewise varied: two trials allowed paracetamol[55,161], one trial allowed acetaminophen[143], and one trial allowed acetaminophen with codeine[73]. One trial did not allow additional treatments[100] and one trial did not report[81]. Follow-up ranged from 3 (short term) to 24 months (long term); most trials reported short term[73,81,100,143,161] and intermediate[55,73,81,100,161] results. Two trials reported long term results[81,161] at 12 months, while one also included 24 month follow-up[161]. Three trials reported non-industry funding[81,100,143], and one reported no funding[161], others did not report. Trials were located in Turkey[55,73,161], Australia[81], Iran[143], and India[100].

One trial was considered good quality,[81] four trials were considered fair[55,73,100,161] and one trial[143] was considered poor. Allocation concealment methods were unclear in most trials. Other common methodological limitations included care providers not being blinded and the lack of an intention-to-treat analysis. The poor-quality trial[143] did not blind patients to the treatment received.

5.2.1.8.1 Function

Function "Success" (Responders)

One poor-quality trial[143] that compared a single PRP injection with two PRP injections at 3-week intervals reported short-term results for two response thresholds for the WOMAC physical function

subscale, a 30% and a 50% decrease. Patients who received a single PRP injection were moderately less likely to achieve a response using the 30% threshold compared with two PRP injections but there was no difference between groups using the 50% threshold (Table 32).

Table 32. One versus 2 PRP injections: Proportion of patients achieving response on the WOMAC Physical Function subscale

Author, Year Quality Follow-up	WOMAC Physical Function response threshold	PRP x 1 % (n/N)	PRP x 2 % (n/N)	RR (95% CI)
Tavassoli 2019 *Poor* 3 months	≥30% decrease	42.9% (12/28)	82.1% (23/28)	**0.52 (0.33 to 0.83)**
	≥50% decrease	3.6% (1/28)	17.9% (5/28)	0.20 (0.22 to 1.60)

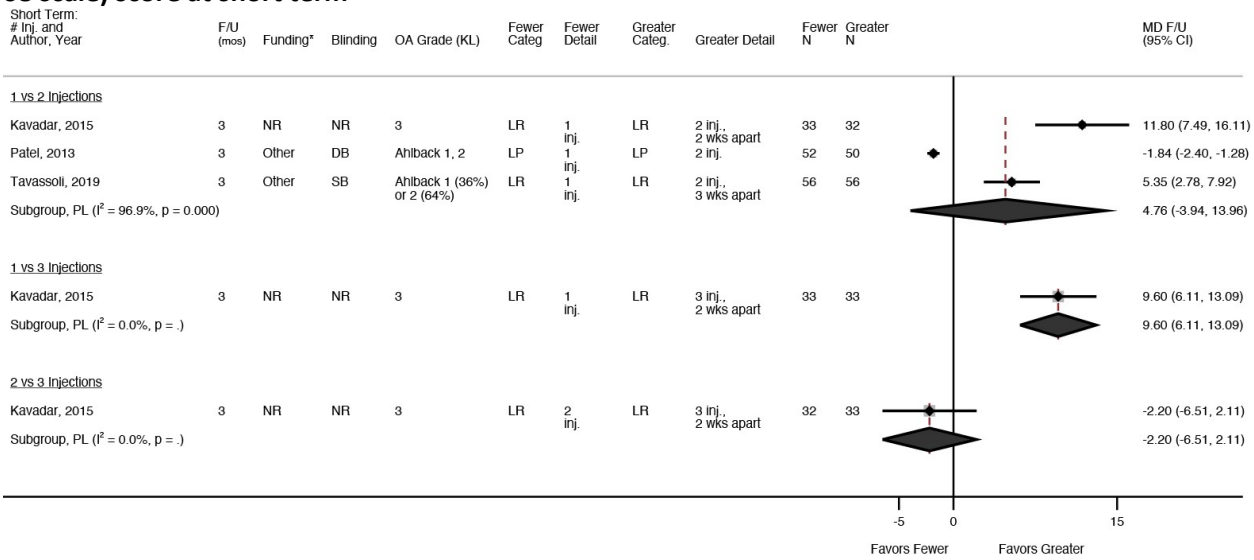
CI = Confidence interval, F/U = Follow-up, PRP = Platelet-rich plasma, RR = Risk ratio, WOMAC = Western Ontario and McMaster osteoarthritis index

WOMAC physical function scores

Three RCTs, two fair[73,100] and one poor[143] quality, reported WOMAC physical function scores. All three trials compared a single injection with two injections of PRP given at intervals of 2 weeks[73] or 3 weeks.[100,143] At short term, there was considerable inconsistency both in direction and magnitude of effect across the trials resulting in a pooled estimate that was not statistically significant (Figure 44). Two RCTs favored two versus one injection of PRP, one fair-quality trial (moderate improvement in function, MD 11.80, 95% CI 7.49 to 16.11)[73] and one poor-quality trial that reported results based on number of knees (small improvement in function, MD 5.35, 95% CI 2.78 7.92).[143] The third fair-quality trial,[100] which also reported results based on number of knees, favored a single injection of PRP but the difference was below the threshold for a small effect (MD -1.84). At intermediate term, across the two fair-quality trials[73,100] results were similar (Figure 45). The reason for the heterogeneity across trials is unclear.

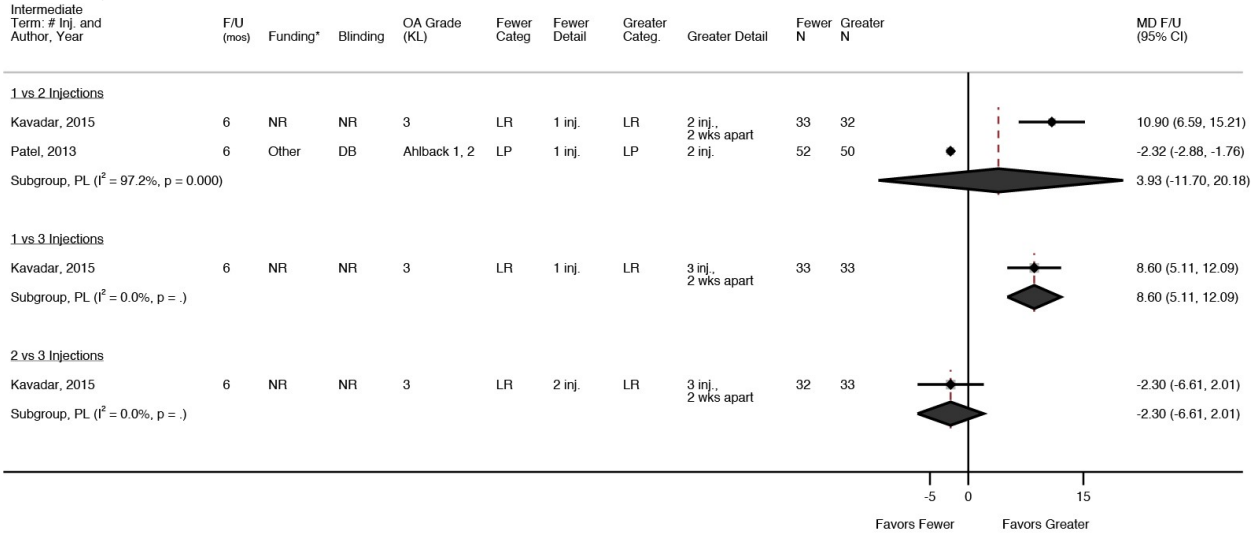
One trial had a third treatment arm that received three PRP injections and reported that three injections given at 2 week intervals were associated with moderate improvement in function at short and intermediate term compared with only one injection but there was no difference when compared with two injections (Figures 44 and 45).[73]

Figure 44. Single PRP injection versus Multiple PRP injections: WOMAC physical function subscale (0-68 scale) score at short term



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded, WOMAC = Western Ontario and McMaster osteoarthritis index

Figure 45. Single PRP injection versus Multiple PRP injections: WOMAC physical function subscale (0-68 scale) score at intermediate term



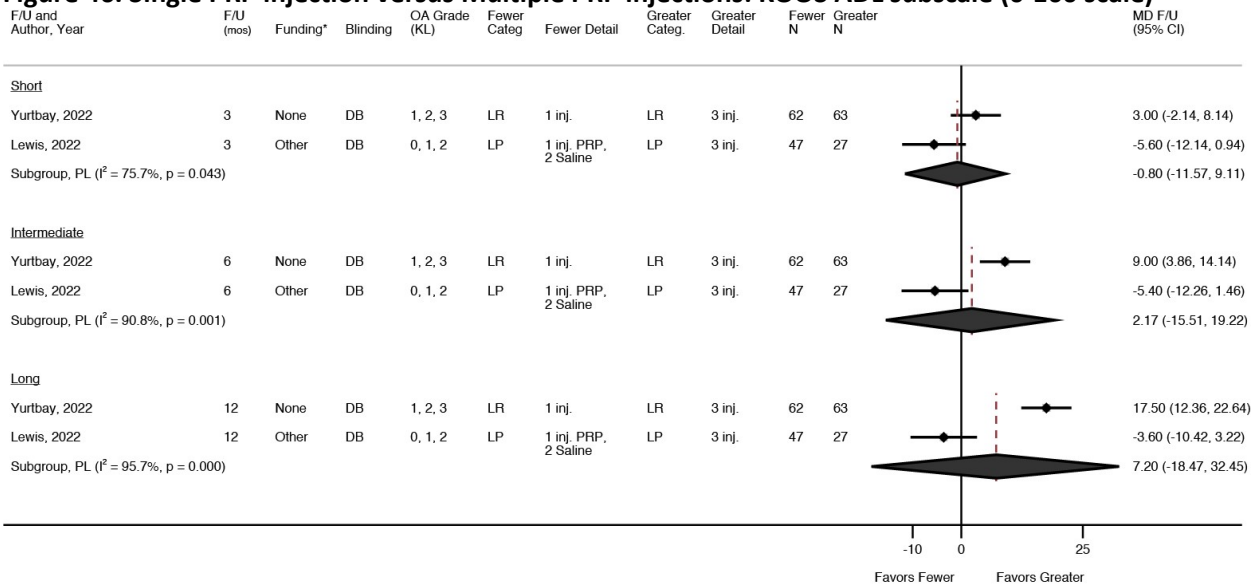
Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, WOMAC = Western Ontario and McMaster osteoarthritis index

KOOS ADL and Sports and Recreation subscales

Two trials (one good and one fair quality)[81,161] that compared one versus three PRP injections reported function using the **KOOS ADL and Sports and Recreation subscales** (0-100). The pooled estimates at short, intermediate and long term showed no difference between groups; the individual trial estimates

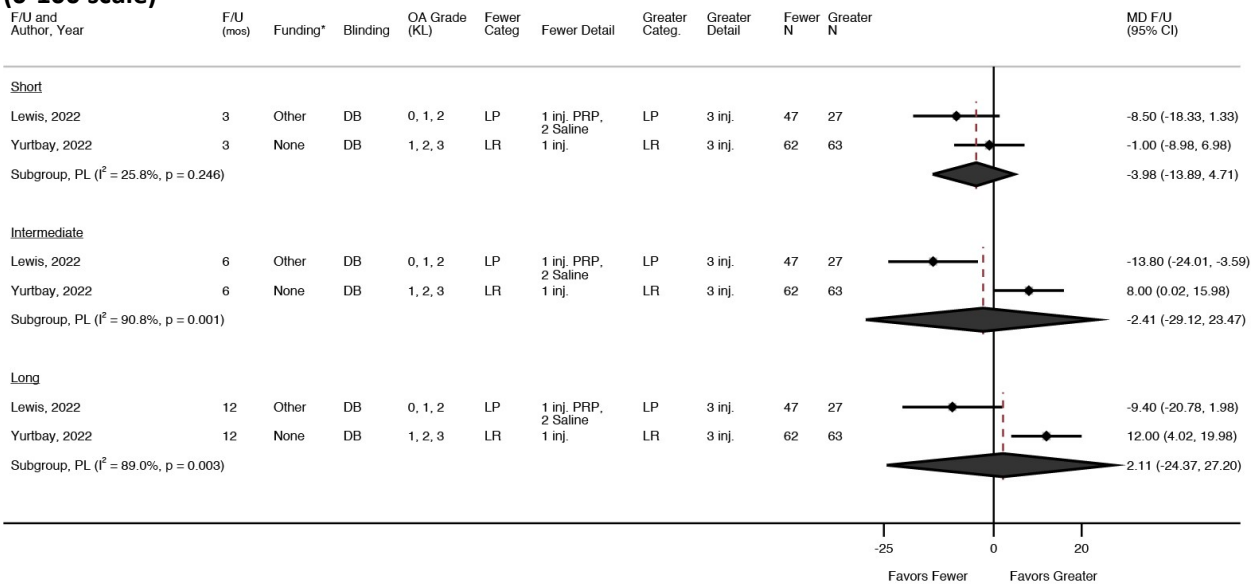
went in opposite directions and heterogeneity was substantial (Figures 46 and 47). The good quality trial[81] that compared a single injection of PRP (followed by two injections of saline) versus three injections of PRP found no difference between groups on either functional measure at any timepoint and the estimates tended to favor the single PRP regimen. Conversely, the fair-quality trial[161] consistently favored the three injection regimen with small improvements in function seen at intermediate term (**ADL:** MD 9.00, 95% CI 3.86 to 14.14; **Sports and Recreation:** MD 8.0, 95% CI 0.02 to 15.98) and moderate improvements long term (**ADL:** MD 17.50, 95% CI 12.36 to 22.64; **Sports and Recreation:** MD 12.0, 95% CI 4.02 to 19.98) compared with a single injection (no placebo injections). In the latter fair-quality trial, the three injections were given at one month intervals while in the good-quality trial they were given at one week intervals, which may partially explain the difference in results.

Figure 46. Single PRP injection versus Multiple PRP injections: KOOS ADL subscale (0-100 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, KOOS ADL= Knee injury and osteoarthritis outcome score function in daily living, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis

Figure 47. Single PRP injection versus Multiple PRP injections: KOOS Sports and Recreation subscale (0-100 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, KOOS = Knee injury and osteoarthritis outcome score, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis

IKDC

One fair-quality trial (N=83)[55] compared one injection of PRP followed by two injections of saline versus three injections of PRP, all at 1 week intervals. Three injections of PRP were associated with a moderate improvement in function at intermediate term on the IKDC (0-100) compared to a single injection (mean 60.8 vs. 50.2, MD 10.6, 95% CI 6.94 to 14.26).

5.2.1.8.2 Pain

Pain "Success" (Responders)

One poor-quality trial[143] that compared a single PRP injection with two PRP injections at 3-week intervals reported short-term results for two response thresholds for the WOMAC pain subscale (30% and 50% decrease) and one for the VAS pain scale (50% decrease), Table 33. There was no difference between treatment groups using the 30% threshold though two injections of PRP tended to be favored. When the 50% threshold was applied, patients who received a single PRP injection were substantially less likely to achieve a response on both the WOMAC and the VAS pain scales compared with two PRP injections.

Table 33. One versus two PRP injections: Proportion of patients achieving response on the WOMAC Pain subscale and the VAS scale

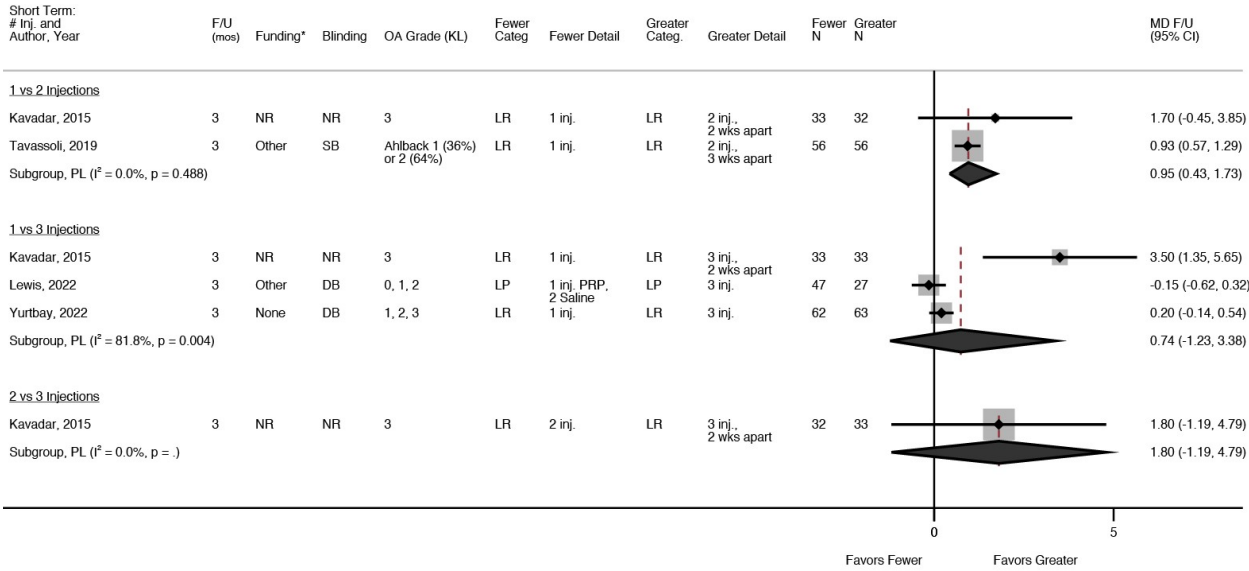
Author, Year Quality Follow-up	Outcome	Threshold	PRP x 1 % (n/N)	PRP x 2 % (n/N)	RR (95% CI)
Tavassoli 2019 *Poor* 3 months	WOMAC Pain	≥30% decrease	85.7% (24/28)	100% (28/28)	0.86 (0.74 to 1.00)
		≥50% decrease	21.4% (6/28)	57.1% (16/28)	0.38 (0.17 to 0.82)
	VAS Pain	≥50% decrease	7.1% (2/28)	60.7% (17/28)	0.12 (0.03 to 0.46)

CI = Confidence interval, F/U = Follow-up, PRP = Platelet-rich plasma, RR = Risk ratio, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

VAS pain scores

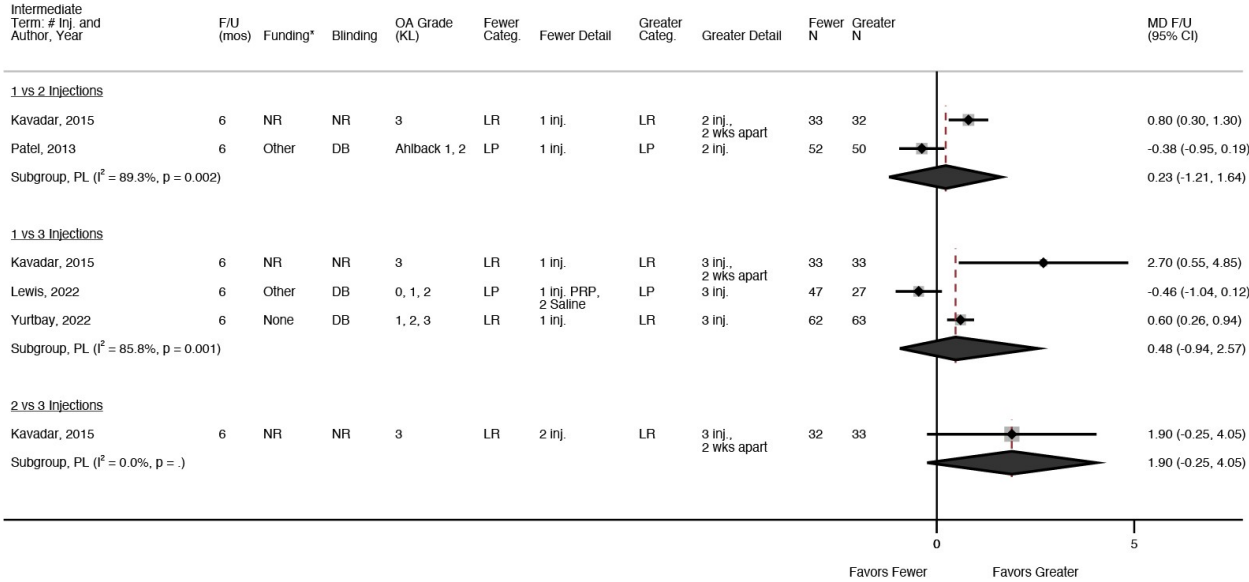
Five trials that compared PRP regimens based on the number of injections given (fewer vs. greater) reported VAS pain scores[73,81,100,143,161]: single injection versus two (3 RCTs)[73,100,143] or three injections (3 RCTs)[73,81,161] and two versus three injections (1 RCT).[73] In pooled analyses, only the difference at short term across two trials, one fair-[73] and one poor-quality,[143] comparing one versus two PRP injections was statistically significant and showed a small improvement in VAS pain with two injections given three weeks apart (Figure 48); there were no differences between groups in pooled analyses at other timepoints or for any other comparisons (1 vs. 3 injections, 2 vs. 3 injections) (Figures 48-50). One fair-quality trial[73] that had three PRP arms (1 vs. 2 vs. 3 injections with multiple injections given at 2 week intervals) was a consistent outlier at short and intermediate term in favor of a greater number of PRP injections, especially three versus a single injection. Exclusion of this trial did not change conclusions but tended to drive the point estimate closer to the null. At long term, one good quality trial[81] reported no difference between one injection of PRP (plus 2 injections of saline) versus three injections of PRP while a second fair-quality trial[161] found a moderate improvement in pain on VAS with three versus one injection of PRP. The reason for the inconsistency and heterogeneity across the trials is unclear.

Figure 48. Single PRP injection versus Multiple PRP injections: VAS pain (0-10 scale) scores at short term



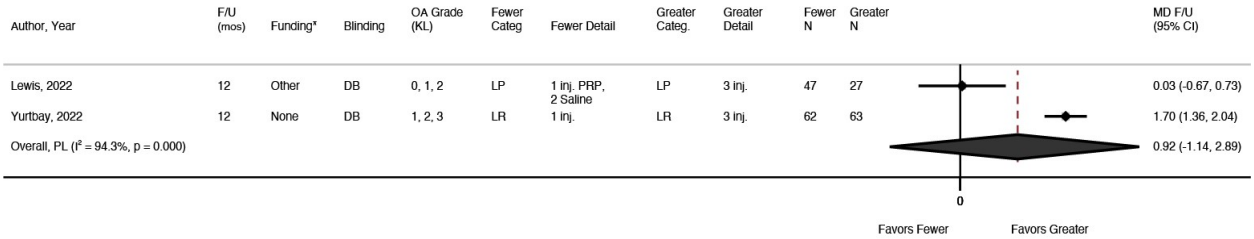
Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded, VAS = Visual analog scale

Figure 49. Single PRP injection versus Multiple PRP injections: VAS pain (0-10 scale) scores at intermediate term



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, VAS = Visual analog scale

Figure 50. Single PRP injection versus Multiple PRP injections: VAS pain (0-10 scale) scores at long term



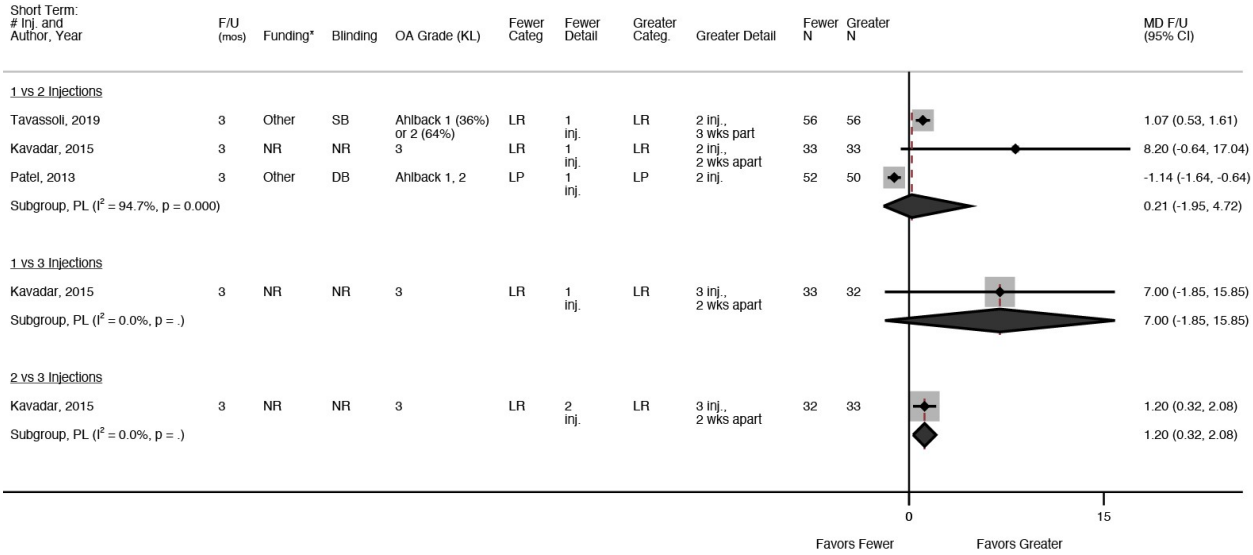
Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, VAS = Visual analog scale

WOMAC pain scores

Three RCTs, two fair[73,100] and one poor[143] quality, reported WOMAC pain scores. All three trials compared a single injection with two injections of PRP given at intervals of 2 weeks[73] or 3 weeks.[100,143] At short term, there was considerable inconsistency both in direction and magnitude of effect across the trials resulting in a pooled estimate that was not statistically significant (Figure 51). Two RCTs[73,143] favored two versus one injection of PRP, but only the poor-quality trial that reported results based on number of knees was statistically significant (small improvement in pain, MD 1.07, 95% CI 0.53 1.61).[143] Conversely, the third fair-quality trial[100] which also reported results based on number of knees, reported a small improvement with a single PRP injection compared with two injections (MD -1.14, 95% CI -1.64 to -0.64). At intermediate term, both fair-quality trials[73,100] reported a small improvement in pain but in opposite directions (Figure 52). The reason for the heterogeneity across trials is unclear.

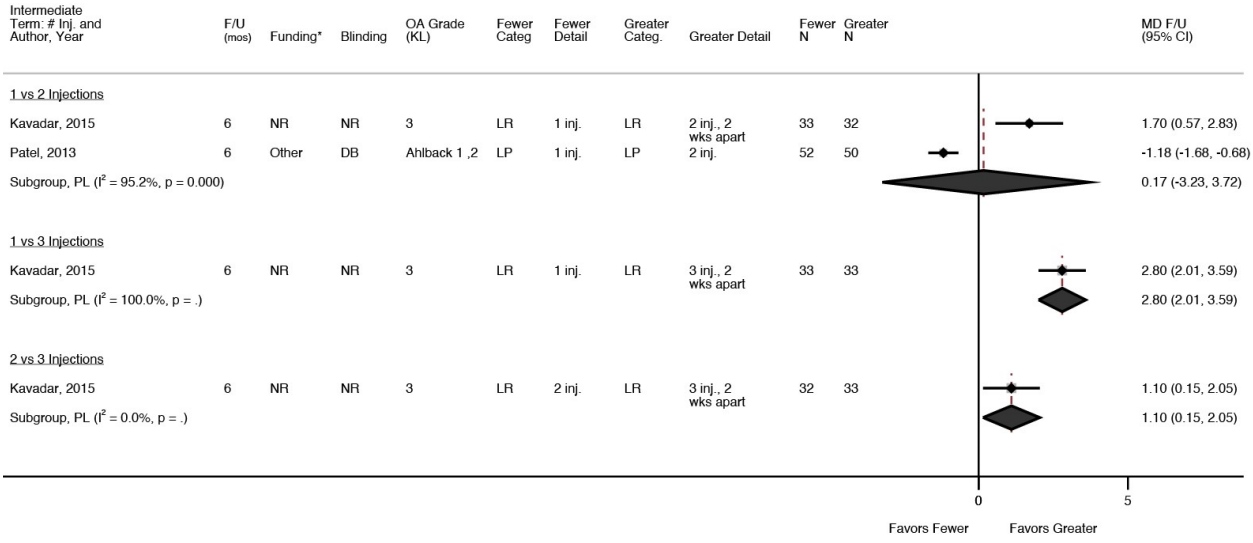
One trial had a third treatment arm that received three PRP injections and reported that three injections given at 2 week intervals were associated with a small improvement in function at short and intermediate term compared with two injections (2 week interval); compared with one injection, only the difference at intermediate term was significant (moderate improvement in pain with 3 injections) (Figures 51 and 52).[73]

Figure 51. Single PRP injection versus Multiple PRP injections: WOMAC pain subscale (0-20 scale) score at short term



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded, WOMAC = Western Ontario and McMaster osteoarthritis index

Figure 52. Single PRP injection versus Multiple PRP injections: WOMAC pain subscale (0-68 scale) score at intermediate term

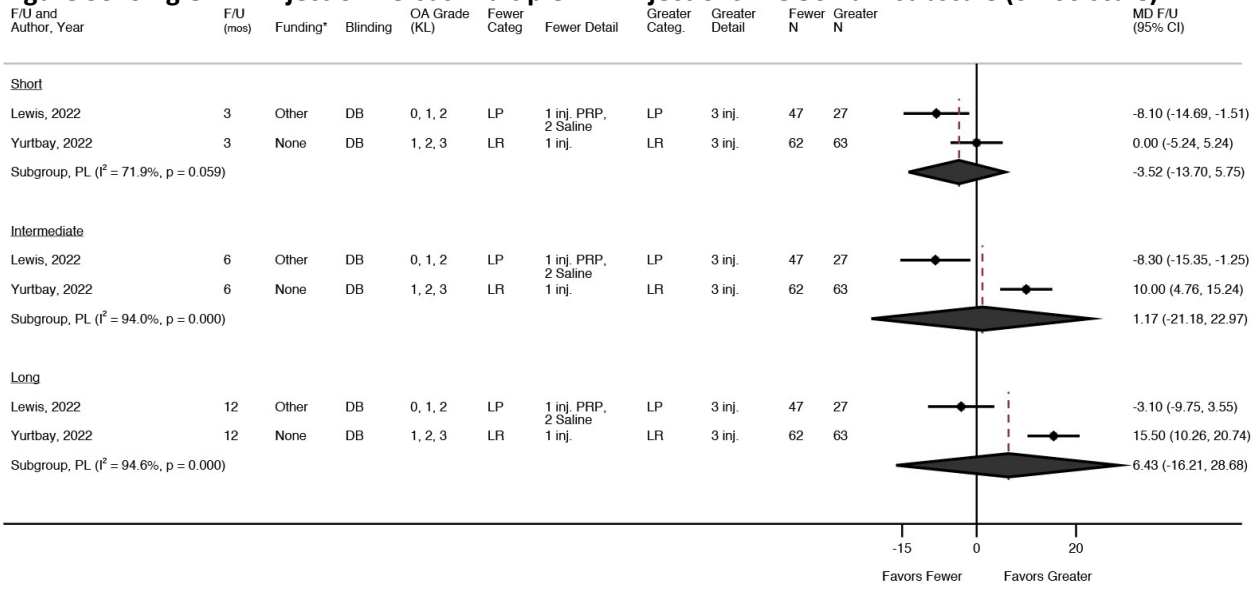


Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, WOMAC = Western Ontario and McMaster osteoarthritis index

KOOS Pain

Two trials (one good and one fair quality)[81,161] that compared one versus three PRP injections reported pain using the **KOOS Pain subscales** (0-100). The pooled estimates at short, intermediate and long term showed no difference between groups; the individual trial estimates went in opposite directions and heterogeneity was substantial (Figure 53). The good quality trial[81] found that a single injection of PRP (followed by two injections of saline) was associated with a small improvement in pain versus three injections of PRP at short (MD -8.10, 95% CI -14.69 to -1.51) and intermediate term (MD -8.30, 95% CI -15.35 to -1.25); there was no difference between groups at long term. Conversely, in the fair-quality trial,[161] three injections of PRP were associated with moderate improvement in pain at intermediate term (MD 10.0, 95% CI 4.76 to 15.24) and long term (MD 15.5, 95% CI 10.26 to 20.74) compared with a single injection (no placebo injections); there was no difference between treatment regimens short term. In the latter fair-quality trial, the three injections were given at one-month intervals while in the good-quality trial they were given at one-week intervals, which may partially explain the difference in results.

Figure 53. Single PRP injection versus Multiple PRP injections: KOOS Pain subscale (0-100 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, KOOS = Knee injury and osteoarthritis outcome score, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis,

5.2.1.8.3 Outcomes assessing multiple domains

Responders: WOMAC total

One poor-quality trial[143] that compared a single PRP injection with two PRP injections at 3-week intervals reported short-term results for two response thresholds for the WOMAC total score, a 30% and a 50% decrease. Patients who received a single PRP injection were much less likely to achieve a response using both thresholds (Table 34).

Table 34. One versus 2 PRP injections: Proportion of patients achieving response on the WOMAC Total

Author, Year Quality Follow-up	WOMAC Total response threshold	PRP x 1 % (n/N)	PRP x 2 % (n/N)	RR (95% CI)
Tavassoli 2019 *Poor* 3 months	≥30% decrease	60.7% (17/28)	85.7% (24/28)	0.71 (0.51 to 0.99)
	≥50% decrease	0% (0/28)	25.0% (7/28)	NC, p<0.05

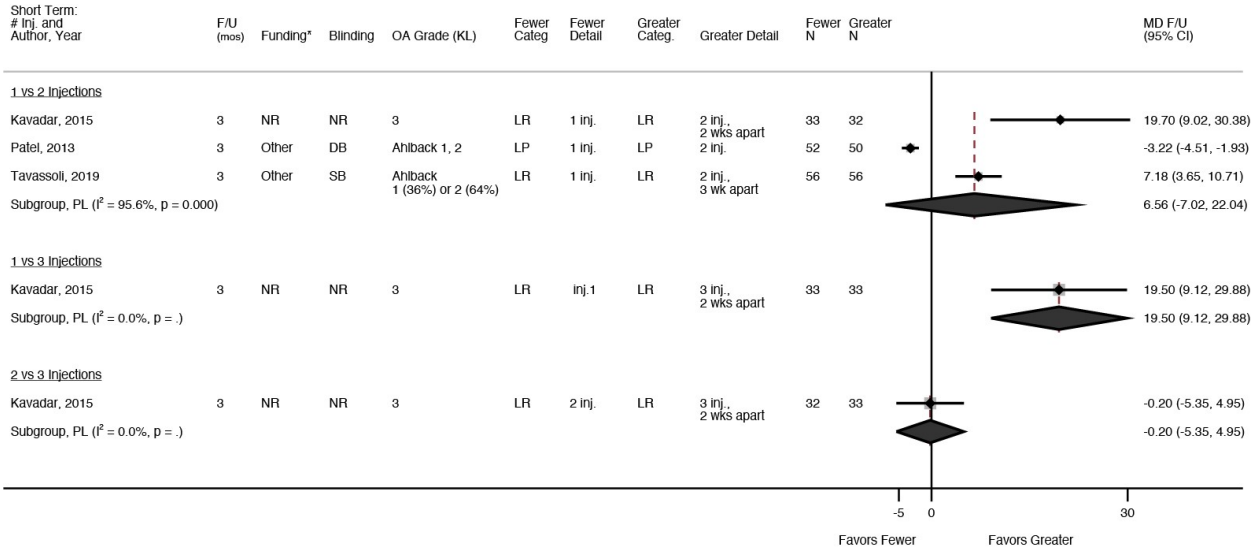
CI = Confidence interval, F/U = Follow-up, PRP = Platelet-rich plasma, RR = Risk ratio, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

WOMAC total scores

Three RCTs, two fair[73,100] and one poor[143] quality, reported WOMAC total scores. All three trials compared a single injection with two injections of PRP given at intervals of 2 weeks[73] or 3 weeks.[100,143] At short term, there was considerable inconsistency both in direction and magnitude of effect across the trials resulting in a pooled estimate that was not statistically significant (Figure 54). Two RCTs favored two versus one injection of PRP, one fair-quality trial (large improvement, MD 19.70, 95% CI 9.02 to 30.38)[73] and one poor-quality trial that reported results based on number of knees (small improvement, MD 7.18, 95% CI 3.65 to 10.71).[143] The third fair-quality trial,[100] which also reported results based on number of knees, favored a single injection of PRP but the difference was below the threshold for a small effect (MD -3.22). At intermediate term, across the two fair-quality trials[73,100] results were similar (Figure 55). The reason for the heterogeneity across trials is unclear.

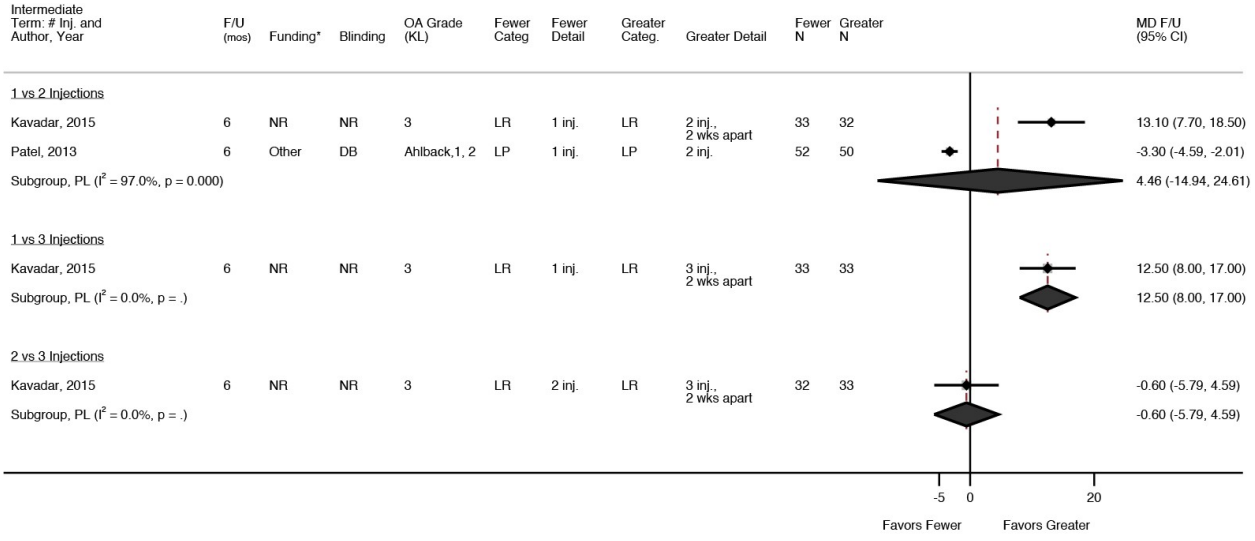
One trial had a third treatment arm that received three PRP injections and reported that three injections given at 2 week intervals were associated with a large improvement short term and moderate improvement intermediate term compared with only one injection but there was no difference when compared with two injections (Figures 54 and 55).[73]

Figure 54. Single PRP injection versus Multiple PRP injections: WOMAC total (0-96 scale) score at short term



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, SB = Single blinded, WOMAC = Western Ontario and McMaster osteoarthritis index

Figure 55. Single PRP injection versus Multiple PRP injections: WOMAC total score (0-96 scale) score at intermediate term



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, Inj. = Injection, KL = Kellgren-Lawrence grade, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, WOMAC = Western Ontario and McMaster osteoarthritis index

5.2.1.8.4 Need for secondary invasive procedures

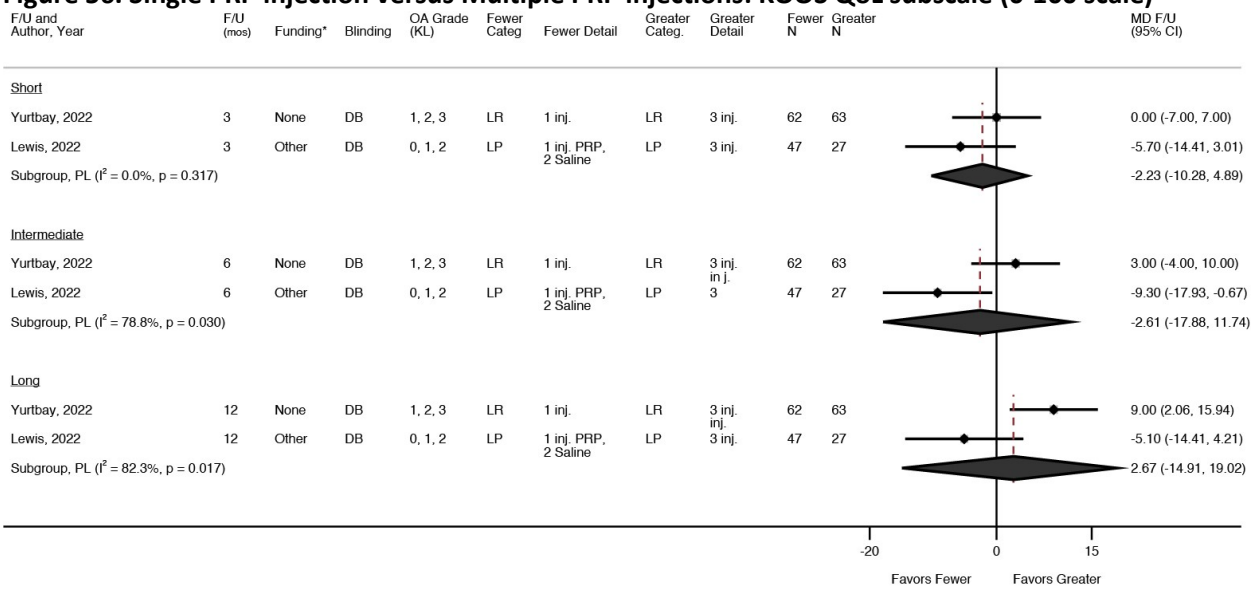
No trial reported on this.

5.2.1.8.5 Secondary Outcomes

Quality of Life

Two trials (one good and one fair quality)[81,161] that compared one versus three PRP injections reported quality of life using the **KOOS QoL subscale** (0-100). The pooled estimates at short, intermediate and long term showed no difference between groups; the individual trial estimates went in opposite directions and heterogeneity was substantial (Figure 56). The good quality trial[81] found that a single injection of PRP (followed by two injections of saline) was associated with a small improvement in quality of life intermediate term (MD -9.30, 95% CI -17.93 to -0.67) versus three injections of PRP. Conversely, the fair-quality trial[161] consistently favored three PRP injections over a single injection (no placebo injections) and showed a small improvement in quality of life with more injections long term (MD 9.0, 95% CI 2.06 to 15.94). There were no differences between PRP treatment regimens at other timepoints across the trials. In the latter fair-quality trial, the three injections were given at one-month intervals while in the good-quality trial they were given at one-week intervals, which may partially explain the difference in results.

Figure 56. Single PRP injection versus Multiple PRP injections: KOOS QoL subscale (0-100 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, KOOS QoL = Knee injury and osteoarthritis outcome score quality of life, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis

One fair-quality trial[55] compared one injection of PRP (followed by two injections of saline) versus 3 injections of PRP, all at 1-week intervals. The multiple injection regimen was associated with a small improvement in quality of life at intermediate term on the **EQ-VAS (0-100, lower = better)** compared to a single injection of PRP (mean -71.4 vs. -62, MD -9.4, 95% CI -13.27 to -5.53).

5.2.1.9 PRP vs. PRP: Leukocyte Poor vs. Leukocyte Rich

Two RCTs[159,164] compared leukocyte-poor (LP)- with leukocyte-rich (LR)-PRP (Appendix G). Sample sizes were 60 and 70 (total N=130). The average age was 61 (range, 59 to 62) years, mean BMI was 28.71 kg/m^2 (range, 25.45 to 32.53), and 81% were female (range, 70% to 90%). OA severity was poorly reported; one trial enrolled participants with KL grade 2 or 3, though they did not report distribution[159]. Mean symptom duration was not reported in either trial, though one required a minimum of 3 months according to their inclusion criteria[164]. Both trials gave three injections to all participants, one[159] in weekly intervals (volume not reported), and the other[164] in 2-week intervals (5 mL). Additional treatments included NSAIDs in one trial[159], and the other[164] did not allow any cointerventions. Follow-up ranged from 2 to 12 months, with both trials[159,164] reporting short, intermediate, and long-term results. Both trials were funded by non-industry sources, and were conducted in Turkey[159] and China[164].

One trial[164] was considered good quality and the other[159] was considered fair quality. Common methodological limitations were the lack of an intention-to-treat analysis; the fair quality study[159] was unclear in whether care providers were blinded and patient characteristics at baseline were not robust.

5.2.1.9.1 Function

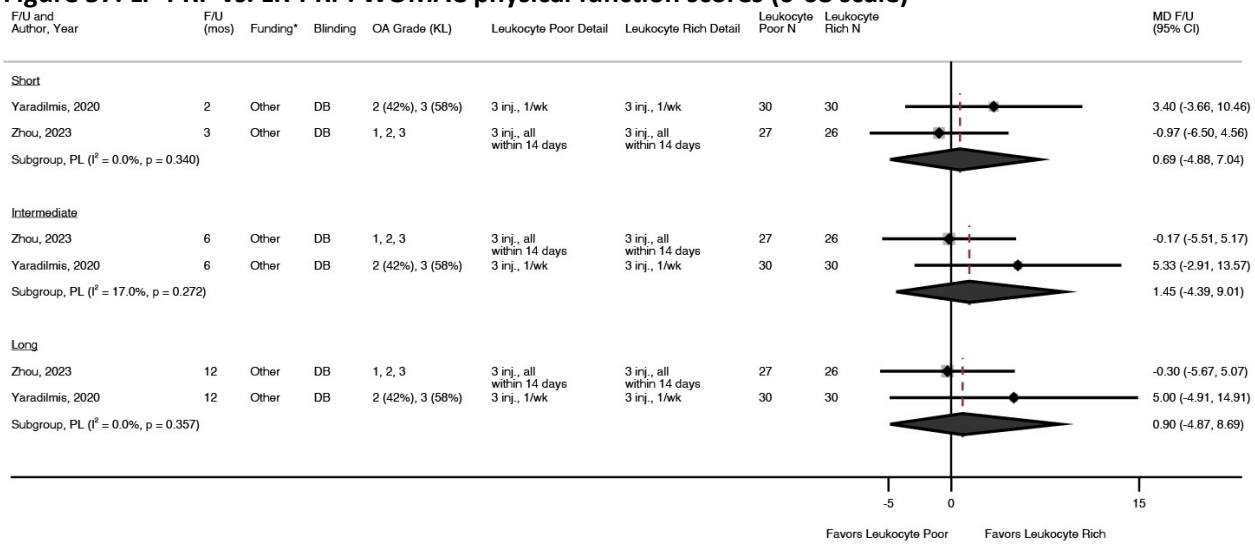
Function "Success" (Responders)

No trial reported on this.

Function Scores

There were no differences in **WOMAC physical function scores** (0-68 scale) at short, intermediate or long term between LP-PRP and LR-PRP across both RCTs[159,164]; estimates were very imprecise, Figure 57.

Figure 57. LP-PRP vs. LR-PRP: WOMAC physical function scores (0-68 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, WOMAC = Western Ontario and McMaster osteoarthritis index

5.2.1.9.2 Pain

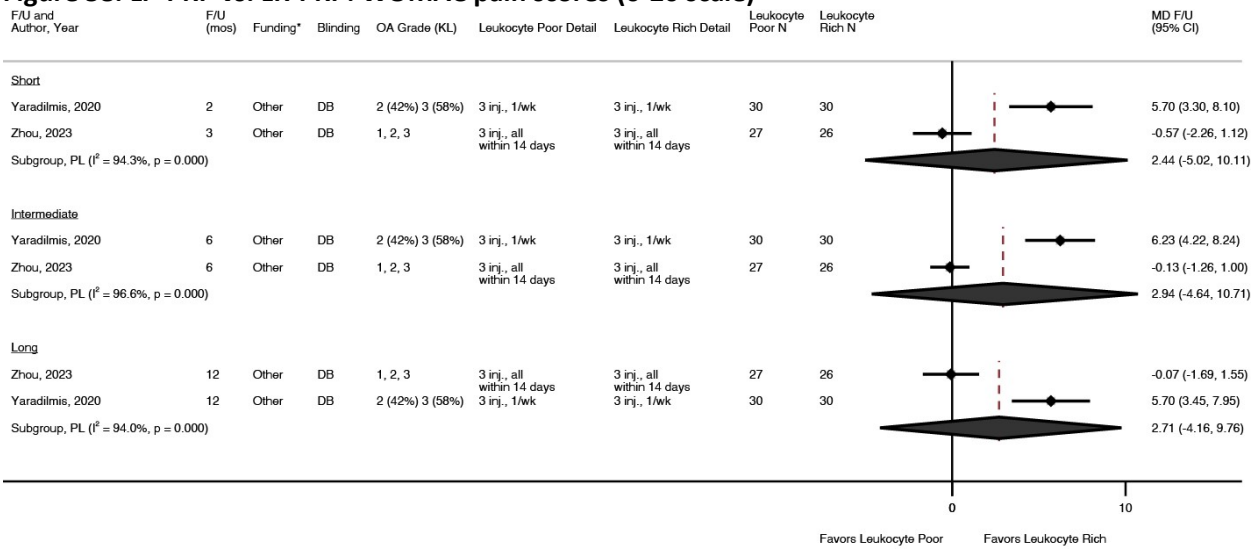
Pain "Success" (Responders)

No trial reported on this.

Pain Scores

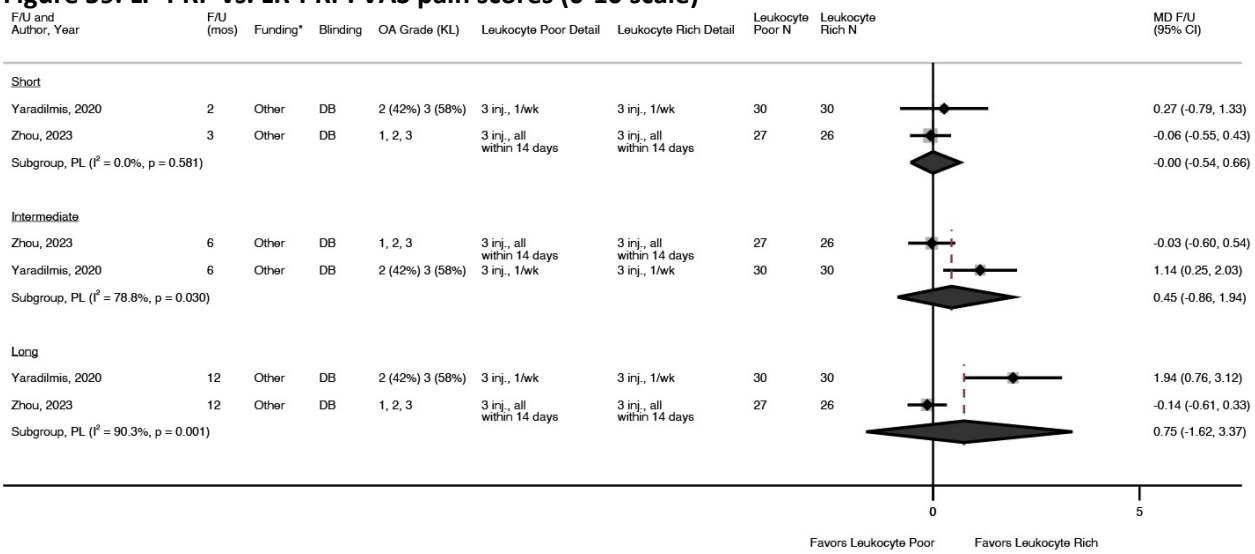
Both trials that compared LP-PRP versus LR-PRP reported **WOMAC pain** (Figure 58) and **VAS pain** (Figure 59) scores at short, intermediate and long term.[159,164] There were no differences between treatment groups in pain improvement on either measure at any timepoint in pooled analyses; however, except for VAS pain short term, the individual trial estimates were in opposite directions and heterogeneity was substantial. The good quality trial reported no differences between groups (with MDs close to zero) for both WOMAC and VAS pain across all timepoints.[164] Conversely, the fair-quality trial found that LR-PRP was associated with large improvements in WOMAC pain scores at all time points (MD range, 5.70 to 6.23) and moderate improvements in VAS pain scores at intermediate term (MD 1.14) and long term (MD 1.94); there were no differences short term in this trial and estimates were imprecise.[159] Possible explanations for some of the heterogeneity include differences in PRP injection protocols (both trials used 3 injections of PRP but one trial injected on a weekly basis while the other completed all 3 injections within 14 days), differences in the concentration of leukocytes and/or the concentration of platelets and differences in Kellgren-Lawrence OA grade between the two populations.

Figure 58. LP-PRP vs. LR-PRP: WOMAC pain scores (0-20 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, WOMAC = Western Ontario and McMaster osteoarthritis index

Figure 59. LP-PRP vs. LR-PRP: VAS pain scores (0-10 scale)



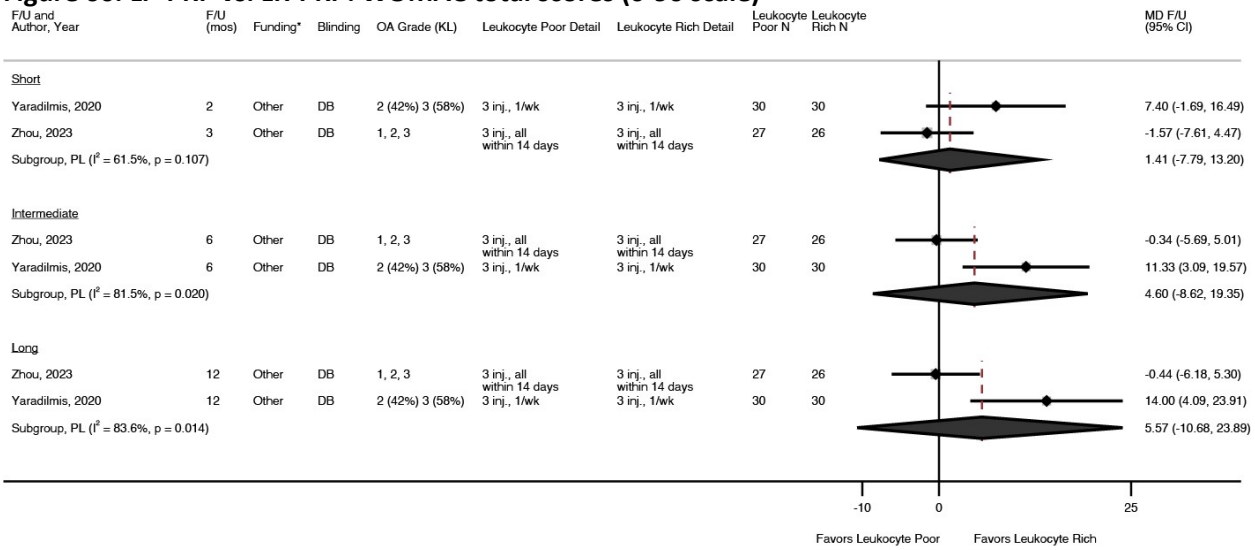
Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, VAS = Visual analog scale

5.2.1.9.3 Outcomes assessing multiple domains

WOMAC total scores

Both trials that compared LP-PRP versus LR-PRP reported **WOMAC total scores** (Figure 60) at short, intermediate and long term.[159,164] There were no differences between treatment groups in functional improvement at any timepoint in pooled analyses; however, the individual trial estimates were in opposite directions and heterogeneity was substantial. The good quality trial reported no differences between LP-PRP and LR-PRP (with MDs close to zero) for both at all timepoints.[164] Conversely, the fair-quality trial found that LR-PRP was associated with moderate improvements in WOMAC total scores at intermediate term (MD 11.33) and long term (MD 14.00); though LR-PRP tended to be favored short term, the difference did not reach statistical significance.[159] All estimates in this latter trial were imprecise. Possible explanations for some of the heterogeneity include differences in PRP injection protocols (both trials used 3 injections of PRP, but one trial injected on a weekly basis while the other completed all 3 injections within 14 days), differences in the concentration of leukocytes and/or the concentration of platelets and differences in Kellgren-Lawrence OA grade between the two populations.

Figure 60. LP-PRP vs. LR-PRP: WOMAC total scores (0-96 scale)



Categ. = Category, CI = Confidence interval, DB = Double blinded, F/U = Follow-up, KL = Kellgren-Lawrence grade, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, NR = Not reported, OA = Osteoarthritis, WOMAC = Western Ontario and McMaster osteoarthritis index

5.2.1.9.4 Need for secondary invasive procedures

The need for secondary invasive procedures was not well reported by the included trials. One small, good-quality RCT (N=53) reported that no patient in the LP-PRP group received TKA during the 6-month follow-up compared with one (3.8%) in the LR-PRP group.[164]

5.2.1.9.5 Secondary outcomes

Symptom recurrence

Symptom recurrence (e.g., persistent, or increased pain, reduced function) resulting in need for additional injection of PRP or placebo within 2 months after protocol completion was not reported by included RCTs. One small, fair-quality trial[159] reported symptom recurrence at 12 months (defined as reduction in function back to baseline levels and request for re-injection) which did not differ significantly between groups, respectively: 20% (6/30) versus 10% (3/30), RR 2.0 (95% CI 0.55 to 7.27).

5.2.2 Key Question 2b: Harms and Complications (Safety) of PRP for Knee OA

Harms, complications and adverse events related to PRP use were poorly reported across the included studies. Study sample sizes were small. There was substantial heterogeneity with regard to the types of adverse events, how they were categorized and how they were reported. Some trials provided a definition of what constituted a serious adverse event, others merely stated that there were no serious adverse events but provide no definitions.

A total of 14 RCTs[5,8,19,35,43,44,71,73,91,95,100,104,158,164] and one NRSI[53] that randomized by knee reported information related to adverse events (Table 34).

5.2.2.1 Serious adverse events

Nine RCTs[8,19,35,43,44,73,100,104,164] and one NRSI[53] reported information on serious AEs (Table 35). One RCT compared different leukocyte concentrations in PRP and reported that three patients (11.5%) who received leukocyte-rich (LR)-PRP experienced severe swelling and mild fever (not beyond 37.5 C) compared with no patient in the leukocyte-poor (LP)-PRP arm.[164] One of these patients required arthroscopic debridement after symptoms persisted for 1 week; the other two patients' symptoms resolved after 3 days without special intervention. The NRSI reported one case of severe inflammation with swelling and stiffness immediately post-injection in the knee randomized to 8ml of leukocyte-poor (LP)- PRP (5%; 1/20 knees); symptoms persisted for 2 weeks and then improved. There were no serious events reported in the placebo (saline) group. The remaining eight RCTs reported that no serious treatment-related AEs or serious AEs occurred in either the PRP or control group (i.e., placebo, prolotherapy, exercise, steroid, multiple PRP injections). An additional two trials (comparing PRP vs. placebo and vs. steroid) [91,158] reported that no treatment-related AEs occurred but it was unclear if these were serious or not.

5.2.2.2 Non-serious AEs

Nine RCTs[5,8,43,44,71,95,100,158,164] reported on other non-serious AEs (Table 35). Mild and transient events were somewhat more frequent following PRP versus comparator treatments but there were no statistically significant differences between groups, but sample sizes were small. Mild pain and/or swelling was common after PRP injections, ranging from 11.5% to 33.3% across four RCTs, three that treated patients with a series of three injections[5,19,43] and one that used a single injection regimen[8]; the range in the placebo groups was 0% to 15% in three of these trials[5,19,43] and 4.2% in the exercise arm of one trial.[8] A fifth small RCT that compared different leukocyte concentrations in PRP reported a higher frequency of mild pain and swelling following three injections of LR-PRP (30.8%) versus LP-PRP (14.8%).[164] One RCT reported knee stiffness in 3.6% of patients following PRP injections (3 injections weekly) versus no patient after saline injection.[19] One small trial reported that 78.9% of patients in the PRP group (single 8 ml injection of LP-PRP) experienced mild synovitis within the first week after treatment versus no patient in the steroid group[44]; all cases resolved spontaneously. One trial that compared different numbers of PRP injections to each other and to placebo found a higher frequency of mild events (e.g., dizziness, headache, tachycardia) in the multiple injection arm versus the single injection arm (44% vs. 23%); there were no events in the placebo (saline) arm.[100]

Table 35. Adverse events reported in patients with knee OA comparing PRP to other treatments.

Adverse event	Study	Comparison	PRP % (n/N)	Control % (n/N)	RR (95% CI)
Serious AEs					
Serious treatment related AEs[*]	Bennell, 2021	PPR vs. Placebo	0% (0/138)	0% (0/140)	-
	Pishgahi, 2020	PRP vs. Prolotherapy	0% (0/30)	0% (0/30)	-
Serious AEs	Chu, 2022[†]	PRP vs. Placebo	0% (0/308	NR	-
	Elik, 2020[‡]	PRP vs. Placebo	0% (0/30)	0% (0/27)	-
	Ghai, 2019[§]	PRP vs. Placebo	5% (1/20 knees)	0% (0/20 knees)	-
	Patel, 2013[**]	PRP (1 injection) vs. Placebo	0% (0/26)	0% (0/23)	-
		PRP (2 injection) vs. Placebo	0% (0/25)	0% (0/23)	-
		PRP (1 injection) vs. PRP (2 injection)	0% (0/26)	0% (0/25)	-
	Elksnins-Finogejevs, 2020[**]	PRP vs. Steroid	0% (0/19)	0% (0/17)	-
	Angoorani, 2015[**]	PRP vs. Exercise	0% (0/26)	0% (0/24)	-
	Kavadar, 2015[**]	PRP (1 injection) vs. PRP (2 injection)	0% (0/34)	0% (0/34)	-
		PRP (1 injection) vs. PRP (3 injection)	0% (0/34)	0% (0/34)	-
		PRP (2 injection) vs. PRP (3 injection)	0% (0/34)	0% (0/34)	-
	Zhou, 2023[††]	P-PRP vs. L-PRP	0% (0/27)	11.5% (3/26)	-
Treatment-related AEs	Wu, 2018	PRP vs. Placebo	0% (0/20 knees)	0% (0/20 knees)	-
	Nabi, 2018	PRP vs. Steroid	0% (0/33)	0% (0/34)	-
Other AEs					
Mild pain	Bennell, 2021	PPR vs. Placebo	18.1% (25/138)	15.0% (21/140)	1.21 (0.71 to 2.05)
	Elik, 2020	PRP vs. Placebo	16.7% (5/30)	11.1% (3/27)	1.5 (0.4 to 5.69)
	Akan, 2018	PRP vs. Exercise	33.3% (7/30)	NR	-
Swelling	Bennell, 2021	PRP vs. Placebo	2.2% (3/138)	0% (0/140)	-
Swelling & pain	Angoorani, 2015	PRP vs. Exercise	11.5% (3/26)	4.2% (1/24)	2.77 (0.31 to 24.85)
	Akan, 2018	PRP vs. Exercise	20.0% (6/30)	NR	-
	Zhou, 2023[†††]	P-PRP vs. L-PRP	14.8% (4/27)	30.8% (8/26)	0.48 (0.16 to 1.41)
Knee stiffness	Bennell, 2021	PRP vs. Placebo	3.6% (5/138)	0% (0/140)	-
Mild synovitis	Elksnins-Finogejevs, 2020	PRP vs. Steroid	78.9% (15/19)	0% (0/17)	-
Other mixed or undefined	Bennell, 2021[‡‡]	PRP vs. Placebo	22.5% (31/138)	16.4% (23/140)	1.37 (0.84 to 2.22)

	Nunes-Tamashiro, 2022	PRP vs. Placebo	0% (0/34)	0% (0/33)	-
		PRP vs. Steroid	0% (0/34)	0% (0/33)	
	Patel, 2013[§§]	PRP (1 injection) vs. Placebo	23.1% (6/26)	0% (0/23)	-
		PRP (2 injection) vs. Placebo	44% (11/25)	0% (0/23)	-
		PRP (1 injection) vs. PRP (2 injection)	23.1% (6/26)	44% (11/25)	0.52 (0.23 to 1.20)
	Wu, 2018	PRP vs. Placebo	0% (0/20 knees)	0% (0/20 knees)	-
	Jubert, 2017	PRP vs. Steroid	0% (0/40)	0% (0/40)	-
	Akan, 2018[***]	PRP vs. Exercise	0% (0/30)	NR	-

AE = adverse event; CI = confidence interval; NR = not reported; L-PRP = leukocyte-rich PRP; P-PRP = pure PRP; PRP = platelet-rich plasma; RR = risk ratio.
* Defined as any untoward medical occurrence that resulted in death, was life threatening, required hospitalization, resulted in significant disability, or required medical or surgical intervention.
† Defined as fever, infection, deep vein thrombosis, hematoma, tissue hypertrophy, marked muscle atrophy, adhesion formation.
‡ Defined as Septic infection, long-term pain, bleeding.
§ Defined as Severe inflammation with swelling and stiffness post injection.
** Undefined.
†† Defined as Serious swelling and fever not beyond 37.5 C.
‡‡ Other lower limb musculoskeletal symptoms
§§ Included syncope, dizziness, headache, nausea, gastritis, sweating, tachycardia; 30 min duration or less and subsided on their own.
*** hypotension, vasovagal reaction, hematomas, and infections.
†††Defined as mild swelling, local pain, serious swelling and mild fever (≤37.5C).

5.2.3 Key Question 2c: Differential Efficacy and Safety of PRP for Knee OA

None of the new trials identified by the update search reported subgroup analyses or did formal tests for interaction to evaluate heterogeneity of treatment effect for knee OA. One trial included in the prior 2016 PRP report that was carried over to this report, reported subgroup analyses based on severity of OA (early vs. advanced).[55] The results from the prior 2016 report have been verified and checked for accuracy and are repeated below.

Studies included

One small trial (N=123)[55] reported subgroup analyses for **PRP versus saline injections**, however no formal evaluation of differential efficacy via test for interaction was reported. Authors do not state if subgroup analysis was planned *a priori* or conducted post hoc.

Results

Based on our calculation of effect sizes and evaluation of the extent to which subgroup confidence intervals overlapped, stage of OA may modify the effect of treatment, such that PRP patients with early OA reported better function as evaluated by the patient-reported IKDC measure as well as better quality of life as evaluated by the patient-reported EQ-VAS scale compared with those with advanced OA following PRP (Table 36). This is based on the observation that the MD estimates are different for the early and advanced OA groups and there is little or no overlap in the confidence intervals, suggesting that these groups may respond differently. Future studies are needed to confirm and explore this further.

Table 36. Knee OA: Differential Efficacy for PRP vs. Placebo (Saline)

RCT	F/U	Outcome, F/U	Subgroup	PRP* Mean ± SD	Saline Mean ± SD	MD (95% CI)†
Gormeli 2017	6 mos.	**IKDC** (0-100 (best))	Early OA	59.7 ± 6.0 (n=56)	36.6 ± 5.4 (n=27)	23.1 (20.4, 25.7)
			Advanced OA	47.1 ± 4.4 (n=27)	36.3 ± 3.5 (n=13)	10.8 (7.9, 13.6)
		Quality of life (EQ-VAS) (0-100 (best))	Early OA	71.5 ± 5.3 (n=56)	48.4 ± 5.1 (n=27)	23.1 (20.6, 25.5)
			Advanced OA	57.1 ± 4.64 (n=27)	47.2 ± 5.0 (n=13)	9.9 (6.6, 13.2)

EQ-VAS: EuroQol visual analog scale; f/u: follow-up; IKDC: International Knee Documentation Committee Subjective Knee Form; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

*Two PRP groups were combined (3 vs. 1 PRP injection) to create a single PRP group.

†Calculated by AAI (nee Spectrum Research, Inc.) to compare effect sizes and overlap of confidence intervals for early and advanced OA groups.

5.2.4 Key Question 2d: Cost-Effectiveness of PRP for Knee OA

No full economic studies comparing PRP to conventional, conservative care were identified for knee OA. One U.S. based study compared PRP vs. HA.[123] Results for this study can be found in section **5.1.4 Key Question 1d** above for the comparison of HA vs. PRP for knee OA.

6 Hip Osteoarthritis

6.1 Key Question 1: Hyaluronic Acid (HA)/Viscosupplementation for Hip OA

6.1.1 Key Question 1a: Efficacy and Effectiveness of HA for Hip OA

A total of three RCTs evaluating HA for treatment of hip OA versus various other intervention met the inclusion criteria. Two RCTs compared HA with a saline placebo[23,106]; one of them also compared HA with steroid[106]. The third trial compared HA versus PRP[150].

The two RCTs comparing HA with saline included a range of 69 to 357 participants (total N=426). The average age was 63 years (range, 60 to 65 years), 60% were female (range, 58% to 61%), and mean BMI (reported in one trial) was 30 kg/m^2. Severity of OA was poorly reported in one trial[106], with 50% (HA) versus 65% (placebo) of participants entering with either grade 1 or 2 OA, and 50% (HA) versus 35% (placebo) being grade 3 or 4. In the other trial[23] 38% were Kellgren-Lawrence grade 2, 62% were grade 3, and 27% were grade 4. Comorbidities (including fibromyalgia, back pain, intervertebral disc degeneration, disc protrusion, lumbar spinal stenosis, neuropathy, and sciatica) were reported in one trial[23], and both groups were similar at baseline (Appendix G). Symptom duration was not reported in either trial. HA was given as either 6 mL of Hylan G-F 20 in a single injection, or 2 mL of Hyalgan given in three bi-monthly injections with ultrasound guidance[23,106] or fluoroscopy[23]. Placebo injections were given in the same volume and regimen in compliance with blinding protocol. Additional treatments included acetaminophen and NSAIDs[23], or other normal analgesic consumption[106].

The trial[106] that also compared HA with steroid randomized 65 patients to three 2 mL bi-monthly injections of Hyalgan or a single injection of 1 mL of Depomedrol. In the HA and steroid groups respectively, mean age was 65 versus 69 years, 61% versus 72% were female, OA severity was graded as 1 or 2 in 50% versus 54% of hips (details not reported), and grade 3 or 4 in 50% versus 46% (details not reported).

One final trial[150] compared Hialano G-F (Synvisc-One) given in a single 6 mL injection to 6 mL of PRP in a single injection. All injections were guided via ultrasound, and additional treatments were not reported. The average age was 61 versus 51 years, 47% versus 63% were female, and BMI was similar (28.4 versus 28.6 kg/m^2) for the HA and PRP groups respectively. At baseline, participant OA severity was graded as Kellgren Lawrence grade 1 (26% versus 37%), grade 2 (53% versus 47%), or a combined grade 3 or 4 (11% versus 16%). Symptom duration was not reported, though patients were only included if they had been symptomatic for at least 6 months.

All three trials[23,106,150] were considered fair quality. The main consistent limitation across all three was a lack of clarity on concealment allocation. . In one trial, it was also unclear how randomization occurred, if care providers were blinded or analyses were based on intention-to-treat principle[150]. In one trial comparing HA to placebo, care providers were not blinded, and 25.2% of participants were lost to follow-up, but were included in the intention-to-treat analysis[23]. The main flaw in the final trial comparing HA to placebo and steroid was a differential loss to follow-up across treatment groups[106]. Funding was reported as industry in one trial[23], and non-industry in the other two[106,150]. Trials were located in Spain[150], Denmark[106], and the USA & Canada[23].

6.1.1.1 HA versus Placebo

Two fair-quality RCTs compared HA with a saline placebo[23,106]. HA was given as either 6 mL of Hylan G-F 20 in a single injection, or 2 mL of Hyalgan given in three bi-monthly injections with ultrasound guidance[23,106] or fluoroscopy[23]. Placebo injections were given in the same volume and regimen in compliance with blinding protocol. Additional treatments included acetaminophen and NSAIDs[23], or other normal analgesic consumption[106].

Results are summarized in Table 37.

6.1.1.1.1 Function

Function "Success"

Neither trial reported this

Function: scores

The two trials reported different measures of function. The largest trial (N=357) found no difference between HA and placebo in WOMAC Function using a 0-10 NRS version of this measure at either short or intermediate term based on change scores[23]. Similarly, the other trial (N=69) found no difference between the groups based on the Lequesne score (0-24 scale) at short term.[106]

6.1.1.1.2 Pain

Pain "Success" and Pain Scores

One trial found no difference in likelihood of achieving a ≥2 point decrease in WOMAC pain while walking (0-10 NRS) between HA and saline placebo at either short or intermediate term.[23] The two trials reported different measures of pain. There was no difference between HA and placebo based on WOMAC Pain (0-10 NRS) at short or intermediate term in one trial[23] or on VAS pain (0-100) while walking in the other.[106]

6.1.1.1.3 Outcomes assessing multiple domains

One trial reported on two measures that evaluated multiple domains. There was no difference between groups on the **WOMAC Total** score. More HA than placebo recipients met criteria for **OARSI responder** (criteria not described) at short term, but data were insufficient to calculate effect sized (53% vs. 44%).

Additional invasive procedures: One trial reported that no HA patients were lost to follow up for having arthroplasty compared with one patient in the saline group.[106]

6.1.1.1.4 Secondary Outcomes

Symptom recurrence: Persistent, or increased pain, reduced function resulting in need for additional injection of HA or PRP within 2 months after protocol completion was not reported by included RCTs.

Quality of Life: Not reported.

Medication use: The larger of the two trials reported similar proportions of patients using NSAIDS since the prior study visit.[23] Similar proportions were reported for HA and placebo at short and intermediate term.

Return to normal activities: Not reported.

Table 37. Summary of results: HA versus placebo injection for hip OA

Outcome	Study	F/U	HA Mean ± SD or 95% CI or median (range)	Placebo (saline) Mean ± SD or 95% CI or median (range)	Effect size (95% CI)
Function					
WOMAC Function (0-10 NRS scale)	Brander 2019 (N=357)	3 months	Change from baseline -1.94 (-2.30 to -1.57)	Change from baseline -2.28 (-2.65 to -1.90)	MD (change scores) -0.34 (-0.17 to 0.85)
		6 months	Change from baseline -2.09 (-2.50 to 1.68)	Change from baseline -2.13 (-2.55 to -1.71)	MD (change scores) 0.05 (-0.53 to 0.63)
Lequesne (1-24 scale)*	Qvistgaard 2016 (N= 69)	3 months	8.9 (NR)	9.1 NR	MD -0.2 (-1.73 to 1.33)
Pain					
Response WOMAC Pain (walking) ≥2 point decrease in 0-10 NRS	Brander 2019 (N=357)	3 months	46.7%	50.29%	OR 0.78 (0.49 to 1.23)
		6 months	40.7%	42.29%	OR 0.81 (0.49 to 1.33)
WOMAC Pain- (0-10 NRS)	Brander 2019 (N=357)	3 months	Change from baseline -2.12 (-2.48 to -1.76)	Change from baseline -2.44 (-2.81 to -2.07)	MD (change scores) 0.32 (-0.19 to 0.83)
		6 months	Change from baseline -2.23 (-2.65 to -1.82)	Change from baseline -2.30 (-2.72 to -1.87)	MD (change scores) 0.06 (-0.52 to 0.65)
VAS Pain 0-100 scale (walking)	Qvistgaard 2016 (N= 69)	3 months	graph estimate 36 (NR)	graph estimate 38 (NR)	MD (graph estimate) -2.0 (-13.43 to 9.43) SMD (author report) 0.4 (-0.1 to 0.9)
Other outcomes					
WOMAC total (0-96)	Qvistgaard 2016 (N= 69)	3 months	graph estimate 36 (NR)	graph estimate 38 (NR)	MD 1.0 (-4.71 to 6.71)
OARSI responders (not specified)	Qvistgaard 2016 (N= 69)	3 months	53% (30% to 70%	44% (28% to 61%)	NR
Invasive procedures (arthroplasty)	Qvistgaard 2016 (N= 69)	3 months	0%	2.8% (1/36)	NC
Secondary outcomes					
NSAID use since last visit	Brander 2019 (N=357)	3 months	20% (37/180)	19.4% (34/172)	OR 1.04 (0.69 to 1.58)
		6 months	18.5% (33/180)	21.0% (37/172)	OR 0.85 (0.56 to 1.30)

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index.
* Estimated from graph; MD calculated.

6.1.1.2 HA versus PRP

One trial[150] compared Hialano G-F (Synvisc-One) given in a single 6 mL injection to 6 mL of PRP in a single injection in patients who had not responded to symptomatic treatment. All injections were guided via ultrasound.

Authors report median values and interquartile ranges for continuous variables, and do not provide numbers of patients for dichotomous outcomes precluding estimates of effect size.

Results are summarized in Table 38.

6.1.1.2.1 Function and pain

There were no differences in functional improvement between HA and PRP based on WOMAC functions scores at short or long term. Authors report medians and interquartile ranges; calculation of effect size was not possible.

6.1.1.2.2 Additional invasive procedures

Arthroplasty was reported in 2 patients in the HA group (5.6%) and 4 patients in the PRP group (10.5%); RR 0.53, 955CI 0.10 to 2.71)

6.1.1.2.3 Outcomes assessing multiple domains

There were no differences between HA and PRP in **WOMAC Total scores** (0-100) at either short or long-term. There was similarly no difference in **Harris Hip Score** (0-100 scale, clinician-based measure) short term, but long-term PRP may be associated with improvement (higher score) compared with HA (p= 0.050). Authors report medians and interquartile ranges; calculation of effect size was not possible.

Authors report treatment on OARSI responders based on the following criteria: Improvement ≥50% in pain or function or absolute change >20 points or who meet 2/3 of the following criteria: pain, function, or overall patient assessment ≥20% or absolute change of >10 points. There were consistently fewer HA recipients who met the criteria for response at short (69.4% vs. 81.6%), intermediate (58.3% vs. 73.7%) and long term 44.1% vs. 64.7%), however authors indicate that differences were not statistically significant; the numbers of patients for each group were not reported, precluding calculation of effect size.

6.1.1.2.4 Secondary Outcomes

Symptom recurrence: Persistent, or increased pain, reduced function resulting in need for additional injection of HA or PRP within 2 months after protocol completion was not reported by included RCTs.

Quality of Life: Not reported.

Medication use: Authors report that fewer HA recipients experienced a drop in analgesic use relative to baseline than PRP recipients but that results were not statistically significant (62.9% vs. 84.2%, p> 0.05)

Return to normal activities: Not reported.

Table 38. Summary of results: HA versus PRP injection for hip OA

Outcome	Study	F/U	HA Median (IQR)	PRP Median (IQR)	p-value
Function					
WOMAC Function	Villanova-Lopez 2020 N= 74	1 month	21.5 (14.2-45.8)	21 (16.7-36)	0.480
		12 months	28 (20.2-48.7)	23.5 (13.7-58)	0.260
Pain					
WOMAC Pain (0-20)	Villanova-Lopez 2020 N= 74	1 month	6 (2-10)	5 (2-7.2)	0.470
		12 months	9.5 (3.75-15)	7 (1.75-11)	0.190
VAS Pain 0-100 scale		1 month	4.5 (2-7)	4 (2-6)	0.570
		12 months	6 (2.7-8)	5 (1.7-7.3)	0.150
Outcomes assessing multiple domains					
WOMAC total (0-100)	Villanova-Lopez 2020 N= 74	1 month	29.5 (14.2-45.8)	28.5 (16.7-36)	0.410
		12 months	40.5 (27.2-70.7)	33 (13.7-58)	0.270
Harris Hip Score (0-100)	Villanova-Lopez 2020 N= 74	1 month	64.8 (55-81.13)	69.5 (62-84)	0.140
		12 months	**60.2 (43-74.2)**	**70.9 (57.2-89)**	**0.050**
OARSI responders*	Villanova-Lopez 2020 N= 74	1 month	69.4%	81.6%	>0.05
		6 months	58.3%	73.7%	>0.05
		12 months	44.1%	64.7%	>0.05
Additional procedures					
Invasive procedures (arthroplasty)	Villanova-Lopez 2020 N= 74	Any time	5.6% (2/36)	10.5% (4/38)	RR 0.53 (0.10 to 2.71
Secondary outcomes					
Drop in analgesic use vs. baseline	Villanova-Lopez 2020 N= 74	12 months	62.9%	84.2%	>0.05

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index

6.1.1.3 HA versus Steroid Injection

One fair quality trial[106] which had three treatment arms randomized patients to three 2 mL bi-monthly injections of Hyalgan or a single injection of 1 mL of Depomedrol. Data for the outcomes of interest for this review were not well reported in this study and most data were estimated from graphs, making it difficult to draw firm conclusions. All data were for short-term follow-up Results are summarized in Table 39.

Based on estimates from graphs provided, there do not appear to be differences between HA and steroid injections for function based on **the Lequesne Index** or in **VAS pain** during walking. Similarly, no difference in **WOMAC Total score** was apparent. Fewer HA recipients were classified as **OARSI responders** compared with those who received steroid injections (53% vs. 66%). No one in the HA group had arthroplasty compared with one steroid recipient had hip arthroplasty.

Secondary Outcomes were not reported in this trial.

Table 39. Summary of results: HA versus steroid injection for hip OA

Outcome	Study	F/U	HA e.g., Mean ± SD or 95% CI or median (range)	Steroid Mean ± SD or 95% CI or median (range)	Effect size (95% CI)
Function					
Lequesne (1-24 scale)*	Qvistgaard 2016 (N= 68)	3 months	8.9 (NR)	8.9 (NR)	NR
Pain					
VAS Pain 0-100 scale (walking)	Qvistgaard 2016 (N= 68)	3 months	graph estimate 36 (NR)	graph estimate 36 (NR)	NR
Other outcomes					
WOMAC total (0-96)	Qvistgaard 2016 (N= 68)	3 months	graph estimate 35 (NR)	graph estimate 32(NR)	MD (graph estimate 3 (-3.93 to 9.93)
OARSI responders (not specified)	Qvistgaard 2016 (N= 68)	3 months	53% (30% to 70%)	66% (49% to 82%)	NR
Invasive procedures (arthroplasty)	Qvistgaard 2016 (N= 68)	3 months	0%	3.1% (1/32)	NC

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index.
* Estimated from graph; MD calculated.

6.1.2 Key Question 1b: Harms and Complications (Safety) of HA for Hip OA

All three RCTs evaluating HA for Hip OA reported adverse events.

6.1.2.1 HA vs. Placebo

The largest RCT[23] report that treatment related adverse events were more common the HA group (13.9% versus 8.7%) including those at the target hip (12.8% vs. 7.0%, RR 1.47, 95% CI 0.79 to 2.7) and that serious adverse events (SAEs) were less common in the HA versus the placebo group (5.6% vs. 8.7%, RR 0.63, 95% CI 0.29 to 1.3), however results were not statistically significant. Authors considered only one of the SAEs was considered treatment-related (arthralgia in the saline group). Further information is not provided. Authors list the following as treatment-emergent events occurring in >2% at the target

hip: Arthralgia (12.2% vs. 12.2%), injection site joint pain (4.4 % vs. 1.7%), injection site pain (2.2% vs. 0.6%), groin pain (2.2% vs. 0%) and osteoarthritis. For osteoarthritis, authors report that nine of the 10 events were judged to not be related to treatment; the one event (in the HA group judged to be treatment related) was a self-limited post-injection flare. Authors do not report any life-threatening events. Similar proportions of patients from each group discontinued due to any adverse event (5.5% vs. 5.7%).

6.1.2.2 HA vs. Placebo and HA vs. Steroid

One RCT with three arms (HA, placebo, steroid) reported that there were no serious adverse events, hip infections or withdrawals due to injection-related pain.[106] Transient flare of hip pain occurred in three patients but to not provide information regarding group assignment for these. Minor transient discomfort at the injection site occurred (number of patients not reported

6.1.2.3 HA vs. PRP

One RCT reported that no adverse events occurred.[150]

6.1.3 Key Question 1c: Differential Efficacy and Safety of HA for Hip OA

6.1.3.1 HA vs. Placebo and HA vs. Steroid

One fair quality trial (N=101) of three treatment arms (**HA, saline placebo and steroid**) explored the potential impact of hip OA severity on treatment effects by dichotomizing Kellgren-Lawrence grades (1 or 2 versus 3 or 4) and by presence of intra-articular effusion.[106] At baseline 57% of participants had grade 1 or 2 and 21% had effusion. Evaluations were done to explore the impact of these factors on treatment effects with change in walking pain scores as the outcome of interest. Authors present data graphically and provide p-values for interaction, but no other data. All tests for interaction were not statistically significant. The study may not have been sufficiently powered to detect effect modification and evidence is insufficient.

6.1.4 Key Question 1d: Cost-Effectiveness of HA for Hip OA

One U.S.-based study compared HA with conservative care in patient with hip OA.[90] Results for this trial can be found under section **5.1.4** above (Knee OA cost-effectiveness section).

6.2 Key Question 2: Platelet Rich Plasma (PRP) for Hip OA

One RCT that evaluated PRP for treatment of hip OA met the inclusion criteria and compared PRP with HA.[150] Results for this trial can be found in the following sections above (i.e., HA vs. PRP for hip OA): **KQ 2a – efficacy** (section **6.1.1.2**) and **KQ 2b – Safety** (section **6.1.2.3**).

No studies were identified that evaluated **differential efficacy or safety** (**KQ 2c**) or conducted formal **cost-effectiveness** analyses (**KQ 2d**) of PRP for the treatment of hip OA.

7 Strength of Evidence (SOE)

The following strength of evidence (SOE) summaries have been based on the highest quality of studies available across the totality of the evidence identified from the prior report and this update report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by time frame and/or comparator. Details of other outcomes are available in the report.

Notes: Only primary outcomes (function, pain, need for secondary invasive intervention, serious adverse events) were rated for SOE

7.1 Strength of Evidence Summary: Results for HA/Viscosupplementation

7.1.1 Strength of Evidence Summary: HA vs. Placebo (Saline) for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
Function: WOMAC physical function scores (0-68 lower score = better function)	Short term (3 mos.)	4 RCTs (N = 1152) Petterson, 2019 Arden, 2014 Strand, 2012 Hangody, 2018	No	No	No	Yes (-1)	**Pooled MD:** -4.34, 95% CI -8.96 to -0.64, I^2=53.4% Conclusion: HA was associated with a small improvement in function.	⊕⊕⊕◯ MODERATE
	6 mos.	2 RCTs (N=569) Strand, 2012 Hangody, 2018	No	No	No	Yes (-1)	**Pooled MD:** -3.25, 95% CI -11.38 to 3.94, I^2=58.3% Conclusion: No difference	⊕⊕⊕◯ MODERATE
Other functional scores:	3 mos.	1 RCT (N =134) Farr, 2019 Gomoll, 2021	Yes (-2)	Unknown	No	Yes (-1)	**KOOS ADL** MD-0.98, 95% CI -0.51 to 3.14 **KOOS Sport/Rec** MD 1.16, 95% CI -4.59 to 6.61 Conclusion: No difference	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
KOOS ADL and KOOS Sport, Recreation (0-100, lower= better function	6 mos.		Yes (-2)	Unknown	No	Yes (-1)	**KOOS ADL** MD -5.19, 95% CI -13.24 to 2.86) **KOOS Sport/Rec** MD -7.18, 95%CI 18.41 to 4.05 Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
	12 mos.						**KOOS ADL** MD -2.1, 95% CI -10.71 to 6.51 **KOOS Sport/Rec** MD 1.33, 95% CI 1-0.69 to 13.35 Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
Pain "success" (responders) WOMAC Pain	Short term 1.5 mos 3 mos.	1.5 months 1 RCT (N=218) Arden, 2014 3 months 1 RCT (N=365) Petterson, 2019	No	Unknown	No	Yes (-1)	**1.5 mos**, 40% reduction w absolute improvement ≥ 5 points RR 1.16 (0.76 to 1.77) **3 mos**, > 50% improvement from baseline and > 20 mm absolute improvement from baseline RR 1.00 (0.82 to 1.21) Conclusion: No difference; estimates are below the threshold for small or not statistically significant.	⊕⊕⊕◯ MODERATE
	Intermediate 6 mos.	1 RCT (N=365) Petterson, 2019 1 RCT (N=438)	No	Unknown	No	Yes (-1)	> 50% improvement from baseline and > 20 mm absolute improvement from baseline RR 1.04 (0.85 to 1.28)	⊕⊕⊕◯ MODERATE

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
		Ke, 2021					>2-point improvement from baseline in WOMAC A1 (Pain with walking) NRS (clinically important reductions) RR 0.98 (0.86 to 1.12) Conclusion: No difference; estimates are below the threshold for small or not statistically significant	
Pain Scores **WOMAC (0-20)** **VAS (0-10 scale)**	3 mos.	**WOMAC Pain** 4 RCTs (N=827) Bao, 2018 Hangody, 2018 Strand, 2012 Arden, 2014 **VAS Pain†** 3 RCTs (N=604) Bao, 2018 Farr, 2019 Ke, 2021 (N=438)	No	No	No	Yes (-1)	**WOMAC Pain (0-20)** **All RCTS**: MD -1.15, 95% CI -1.80 to -0.26, I^2=60.8% **3 low ROB RCTs** MD -0.90, 95% CI -1.75 to 0.11, I^2=65.2% **VAS Pain (0-10)†** **ALL RCTS (3 RCTs)** MD – 0.23, 95%CI -1.37 to 0.94, I^2=89.3% **1 low ROB RCT** (Ke, N=438) MD 0.03, 95% CI -1.37 to 0.94 Conclusion: No difference between HA and placebo based on highest quality trials	⊕⊕⊕◯ MODERATE
	Intermediate (6 mos.)	**WOMAC Pain** 1 RCT (N=219) Hangody, 2018 **VAS Pain**	No	Consistent	No	Yes (-1)	**WOMAC (0-20)** -0.88 95% CI -1.50 to -0.26 **VAS Pain (0-10)**	⊕⊕⊕◯ MODERATE

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
		2 RCTs (N=1247) Ke, 2021 Gel-200 SSED, 2016					MD -0.03, 95%CI -0.20 to 0.09, I^2=0%) [excludes 1 small poor-quality trial, Farr 2019] Conclusion: No difference between HA and placebo; WOMAC Pain scores effect estimate are below threshold for small effect; no difference in VAS	
	Long term 12 mos.	**VAS Pain** 1 RCT (N=32) Gomoll, 2021	Yes (-2)	Unknown	No	Yes (-1)	VAS Pain MD 0.12, 95% CI -1.24 to 1.48 Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
OMERACT-OARSI Responder (assesses multiple domains)	3 mos.	1 RCT (N=375) Strand, 2012	No	Unknown	No	Yes (-1)	RR 1.12, 95% CI 0.92 to 1.38 Conclusion: No difference	⊕⊕◯◯ LOW
	6 mos.	1 RCT (N=33) Farr, 2019	Yes (-2)	Unknown	No	Yes (-1)	RR 0.92, 95% CI 0.40 to 2.09 Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
	12 mos.	1 RCT (N=29) Gomoll, 2021	Yes (-2)	Unknown	No	Yes (-1)	RR 0.84, 95% CI 0.34 to 2.09 Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
Secondary Invasive interventions	---	None	---	---	---	---	NONE REPORTED	---
KQ 1b: Safety								
Serious Treatment Related AEs‡	Any	1 RCT (N=132) Gomoll, 2021 1 RCT (N=84) Gormeli, 2017 4 RCTs (N=935) Hangody, 2018	1 RCT (Yes -2) 4 RCTs (Yes -1)	Unknown	No	Yes (-2)	1 RCT: 1.55% (1/64) vs. 0% - Knee stiffness and pain (pseudo-septic reaction) 1 RCT: 4.3% (2/46) vs. 4.4% (2/45), RR 1.0 (0.15, 6.80) – withdrawal due to treatment intolerance	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
		Ke, 2021 Arden, 2014 Bao, 2018					4 RCTs: report that there were no serious treatment related AEs **Conclusion**: These may be rare; studies are likely underpowered to detect rare events; authors do not define specific AEs to be considered or identified	
Serious AEs‡	Any	7 RCTs (N=2,327) Hangody, 2018 Petterson, 2019 Strand, 2012 GEL 200 SSED, 2016 Gormeli, 2017 Ke, 2021 Bao, 2018	Yes (-1)	Unknown	No	Yes (-2)	Hangody: Arthralgia, peripheral edema, rash 1.5% (2/135) vs. 3.2% (5/63), RR 0.47 (00.47 (0.07, 3.24).07, 3.24) Petterson: NR; 4.3% (8/184) 4.3% (8/184) vs. 2.7% (5/185), RR 1.61 (0.54, 4.83) Strand: NR; 3.2% (8/249) vs. 0% GEL SSED: 1.7% (7/404) vs. 1.5% (6/410) **3 RCTs** (Ke, Bao, Gormeli): Report no events in either group **Conclusion**: These may be rare; studies are likely underpowered to detect rare events or compare treatments; authors do not define specific AEs to be	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
							considered or identified except as noted above	
Treatment-Related AEs‡	Any	**8 RCTs (9 publications) (N=1,863): No specifics of AEs** Hangody, 2018 Petterson, 2019 Strand, 2012/ Strand, 2016 Arden, 2014 Ke, 2021 Bao, 2018 Gormoll, 2021 Gormeli, 2017 **1 Fair RCT (N=814); AEs specified** GEL 200 SSED, 2016	Yes (-1)	Unknown	No	Yes (-1)	**Range across RCTs that don't describe AEs** (rang of study Ns, 60 to 438) Range of reported events: HA vs. Placebo (saline) HA (0% to 26.9) vs. 0% to 25.8%); **Significant difference between HA and saline in one RCT** (Arden, AEs not described); estimate is imprecise. 15.7% (17/108) vs. 5.5% (6/110), RR 2.89 (1.18, 7.04) **1 RCT that specified**: (N= 814) Arthralgia, joint swelling, joint effusion: 6.2% (25/404) vs. 6.6 (27/401) **<u>Conclusions:</u>** There was a wide range of reported frequencies for treatment-related AEs. There were no differences between HA and saline in all but 1 trial (AEs were not described). The only trial that specified AEs was also the largest (N=814)	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
							and found no difference between HA and saline	
Other AEs (not categorized)‡	Any	**6 RCTs (N=2,196): describing AEs** Hangody, 2018 Petterson, 2019 Strand, 2012 Strand, 2016 Ke, 2021 Gel 200 SSED, 2016 **3 RCTs (N=390): did not describe** Arden, 2014 Bao, 2018 Gomoll, 2021	Yes (-1)	Unknown	No	Yes (-1)	**6 RCTs with AEs descriptions** Hangody: Headache, arthralgia, spinal pain, back pain, nasopharyngitis: 24.7% (33/135) vs. 17.4% (11/63), RR1.40 (0.76, 2.59) Petterson: includes joint stiffness 49.5% (91/184) vs. 54.1% (100/185), RR0.91 (0.75, 1.11) Strand 2012: includes joint stiffness 19.7% (49/249) vs. 16.4% (21/128), RR 1.20 (0.75, 1.91) Strand 2016: Includes joint effusion, upper respiratory infection: 17.6% (22/125) vs. 21.7% (23/106) RR 0.81 (0.48, 1.37) Ke 2021: Includes pyrexia, axillary pain, chest discomfort, peripheral edema, chills, malaise, and thirst 41.7% (91/218) vs. 48.6% (107/220), RR 0.86 (0.70, 1.06)	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
							GEL 200 SSED: Includes arthralgia, joint swelling, joint effusion 37.9% (153/404 vs. 40.0% (164/410), RR 0.95 (0.80, 1.12) **AEs not specified:** (Ns ranged from 60 to 438) Range HA (0% to 49.5%) vs. Saline (0% to 54.1%) Not rial found a difference between HA and saline **Conclusions:** There was a wide range of reported frequencies for treatment-related AEs. There were no differences between HA and saline in any trial	
Swelling‡	Any	3 RCTs (4 publications) (N=1,184) Petterson, 2019 Strand, 2012 Strand, 2016 Ke, 2021	Yes (-1)	Unknown	No	Yes (-1)	Ns ranged from 231 to 442 Ranges HA (1.1% to 17.6%) vs. Saline (0.5% to 12.3%) Conclusion: there was no difference between HA and saline	⊕⊕◯◯ LOW

ADL = Function in daily living, CI = Confidence interval, HA = Hyaluronic acid, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, mm = Millimeter, Mos. = Months, NRS = Numerical rating scale, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, RCT = Randomized controlled trial, ROB = Risk of bias, RR = Risk ratio, SoE = Strength of evidence, SSED = Summary of safety and effectiveness data, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).
†Bao and Farr are HIGH ROB - focus SOE on Ke, the largest, only high-quality RCT.
‡Adverse events are detailed in the full report (Table 19) and in data abstraction.

7.1.2 Strength of Evidence Summary: HA vs. PRP for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
Function Response (success) WOMAC Physical Function	Short term	1 RCT (N=83) Tavassoli, 2019	Yes (-2)	Unknown	No	Yes (-1)	**HA vs. PRP** **30% decrease in score** 0% vs. 62.5% **50% decrease in score** 0% vs. 10.7% **Conclusion:** No HA recipient met thresholds for treatment response: more PRP recipients met thresholds for response. Evidence was considered insufficient.	⊕◯◯◯ INSUFFICIENT
	Intermediate term	1 RCT (N=65) Buendia-Lopez, 2018	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** **20% decrease in score** 14.2% vs. 45% RR 0.34, 95% CI 0.14 to 0.84 **Conclusion:** HA was associated with lower likelihood of treatment response versus PRP	⊕⊕◯◯ LOW
	Long term	1 RCT (N=65) Buendia-Lopez, 2018	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** **20% decrease in score** 0% vs. 24% **Conclusion:** HA was associated with lower likelihood of treatment response versus PRP	⊕⊕◯◯ LOW
Function: WOMAC physical function scores (0-68 lower score	Short term	4 RCTs (N=287) Raeissadat, 2021 Lisi, 2018 Lana, 2016 Louis, 2018	Yes (-1)	No	No	Yes (-1)	MD 3.24, 95% CI -0.18 to 6.72 I^2=51.3%) [excluding poor-quality outlier]† <u>Conclusion</u>: No difference between HA and PRP (estimate	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
= better function)							below threshold for small effect)	
	Intermediate term	4 RCTs (N=292) Buendia-Lopez, 2018 Raeissadat, 2021 Lisi, 2018 Lana, 2016	Yes	Yes (-1)	No	Yes (-1)	4 RCTs, MD 4.72, 95% CI 1.89 to 8.65, I^2=71.9%) Conclusion: Small improvement in function with PRP vs. HA	⊕⊕◯◯ LOW
	Long term	4 RCTs (N=359) Buendia-Lopez, 2018 Raeissadat, 2021 Lisi, 2018 Raeissadat, 2015	Yes (-1)	No	No	Yes (-1)	MD 6.42, 95% CI 5.68 to 6.95, I^2=0%) [excludes outlier trial, Lana 2016] Conclusion: Small improvement in function with PRP vs. HA	⊕⊕◯◯ LOW
Other functional measures IKDC (0-100) Lysholm (0-100)	Short term	**IKDC** 2 RCTs (N=288) Cole, 2017 Sdeek, 2021 **Lysholm** 2 RCTs (N=155) Lisi, 2018 Raeissadat, 2021	Yes (-1)	No	No	Yes (-1)	**IKDC** MD 2.24, MD -8.39 to 14.51, I^2=69.5% **Lysholm** MD 0.09, 95% CI -0.71 to 1.07, I^2=0% **Conclusion**: No difference between HA and PRP for either measure	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
	Intermediate term	**IKDC** 3 RCTs (N=410) Gormeli, 2017 Cole, 2017 Sdeek, 2021 **Lysholm** 2 RCTs (N=155) Lisi, 2018 Raeissadat, 2021	Yes (-1)	No (IKDC) Yes (Lysholm)	No	Yes (-1)	**IKDC** 3 RCTs, MD 6.47, 95% CI 3.67 to 9.21, I^2= 0% **Lysholm** MD 2.07, 95% CI 0.59 to 3.93 I^2=71.4% **Conclusion**: IKDC: small functional improvement with PRP vs. HA Lysholm: No difference between HA and PRP; estimate is below the threshold for a small effect.	⊕⊕◯◯ LOW
	Long term	**IKDC** 2 RCTs (N=288) Cole, 2017 Sdeek, 2021 **Lysholm** 2 RCTs (N=155) Lisi, 2018 Raeissadat, 2021	Yes (-1)	No	No	Yes (-1)	**IKDC** 9.75, 95% CI 3.05 to 16.81, I^2=0%) **Lysholm** MD 1.11, 95%CI 0.18 to 2.57, I^2=43.3%) **Conclusion**: No difference between HA and PRP; estimates for both measures are below the threshold for a small effect.	⊕⊕◯◯ LOW
Pain "success" (responders) WOMAC Pain (0-20)	Short term	1 RCT (N=83) Tavassoli, 2019	Yes (-2)	Unknown	No	Yes (-1)	**HA vs. PRP** **WOMAC Pain** **30% decrease in score** 0% vs. 92.8% **50% decrease in score** 0% vs. 39.3%	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
VAS Pain (0-10)							**VAS Pain** **50% decrease in score** 0% vs. 33.9% **Conclusion:** No HA recipient met thresholds for treatment response: more PRP recipients met thresholds	
	Intermediate term	1 RCT (N=65) Buendia-Lopez, 2018	Yes (-1)	Unknown	No	Yes (-1)	**WOMAC Pain** 20% decrease in score 21.9% vs. 48.5% RR 0.45, 95% CI 0.21 to 0.95 **VAS Pain** 20% decrease in score 25% vs. 48.5% RR 0.52, 95% CI 0.26 to 1.03) **Conclusion:** Substantially more PRP recipients achieved 20% decrease in pain scores than HA recipients	⊕⊕◯◯ LOW
Pain Scores **WOMAC (0-20)** **VAS (0-10 scale)**	Short term	**WOMAC Pain** 5 RCTs (N=480) Louis, 2018 Tavassoli, 2019 Raeissadat, 2021 Lisi, 2019 Cole, 2017 **VAS Pain** 6 RCTs (N=589) Raeissadat, 2021	Yes (-1)	Yes (WOMAC) No (VAS)	No	Yes (-1)	**WOMAC Pain (0-20)** (5 RCTs, MD 1.87 95% CI 0.16 to 3.45, I^2=93.4%) [excludes outlier trial, Lana 2016]‡ **VAS Pain (0-10)** 6 RCTs MD 0.33, 95% CI 0.07 to 0.63, I^2=0%) [excludes two outlier trials]§ Conclusion: Small improvement in pain favoring	⊕⊕◯◯ LOW That PRP may provide small pain improvement

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
		Lisi, 2018 Cole, 2017 Louis, 2018 Sdeek, 2021 Wang, 2022					PRP over HA based on WOMAC but estimate is below threshold for VAS	
	Intermediate term	**WOMAC Pain** 4 RCTs (N=319) Buendia-Lopez, 2018 Raeissadat, 2021 Lisi,2018 Cole, 2017 **VAS Pain** 6 RCTs (N=608) Buendia-Lopez, 2018 Lisi, 2018 Cole, 2017 Raeissadat, 2021 Sdeek, 2021 Wang, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	**WOMAC (0-20**) 4 RCTs, MD 1.16, 95% CI -0.01 to 2.47, I^2= 81.3 [excludes extreme outlier trial, Lana 2016] **VAS Pain (0-10)** (6 RCTs, MD 0.49, 95 % CI 0.04 to 1.04). <u>Conclusion</u>: Small improvement in pain favoring PRP over HA	⊕⊕◯◯ LOW
	Long term	**WOMAC Pain** 5 RCTs (N=458) Raeissadat, 2015 Buendia-Lopez, 2018 Raeissadat, 2021 Lisi, 2018 Cole, 2017	Yes (-1)	No	No	Yes (-1)	**WOMAC (0-20**) 5 RCTs, MD 1.15, 95% CI 0.90 to 1.57, I^2=36.2%) [excludes extreme outlier trial, Lana 2016] **VAS Pain (0-10)** (6 RCTs, MD 0.88, 95% CI 0.57 to 1.24, I^2=29.9%). <u>Conclusion</u>:	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
		VAS Pain 6 RCTs (N=564) Buendia-Lopez, 2018 Raeissadat, 2021 Lisi, 2018 Cole, 2017 Sdeek, 2021 Wang, 2022					Small improvement in pain favoring PRP over HA	
WOMAC Total scores Response (success)	Short term	Single HA and PRP injection 1 RCT (N=46) Louis, 2018 Multiple PRP injections 1 RCT (N=83) Tavassoli, 2019	Single injection No Multiple injections Yes (-2)	Unknown	No	Yes (-1)	**HA vs. PRP** Single injection (good quality study) **>5 point or 40% improvement in total score** 45.8% vs. 72.7 % RR 0.63 95%CI 0.38 to 1.04 **Conclusion:** The likelihood of response was lower following HA versus PRP Multiple HA injections protocols (poor quality) **30% decrease in score** 0% vs. 73.2% **50% decrease in score** 0% vs 0% **Conclusion:** No HA recipient met thresholds for treatment response. More PRP recipients achieved a 30% decrease in	Single injection ⊕⊕◯◯ LOW Multiple HA injections ⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
							scores for response. Evidence was considered insufficient.	
	Intermediate term	Single injection HA 1 RCT (N=34) Louis, 2018	No	Unknown	No	Yes (-1)	**HA vs. PRP** Single injection (good quality study) **>5 point or 40% improvement in total score** 58.8% vs. 52.9%, RR 1.11, 95% CI 0.61 to 2.02 **Conclusion:** No difference between HA and PRP	⊕⊕◯◯ LOW (single injection)
Invasive procedures	Any time to 78.9 months	1 RCT (N=85) Wang, 2022	Yes (-2)	Unknown	No	Yes (-1)	HA vs. PRP AKS or TKA: 30.2% vs. 11.9% RR 2.54, 95% CI 0.99 to 6.5) <u>Conclusion</u>: HA was associated with substantial increased risk of receiving AKS or TKA	⊕◯◯◯ INSUFFICIENT
KQ 1b: Safety								
Serious Treatment-related AEs**	Any	2 RCTs (N=272) Tavassoli, 2019 Sdeek, 2021	Yes (-2)	Unknown	No	Yes (-2)	2 poor-quality RCTs report that no major adverse events occurred. <u>**Conclusions:**</u> These may be rare; studies are likely underpowered to detect rare events	⊕◯◯◯ INSUFFICIENT
Withdrawal due to AE**	Any	2 RCTs (n=157) Gormeli, 2017 Buendia-Lopez, 2018	Yes (-1)	Unknown	No	Yes (-1)	Gormeli: 2 patients in each group (HA and PRP) withdrew early because they were unable to tolerate injection	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
							Buendia-Lopez: 2 HA recipients withdrew due to pain and swelling within 2 weeks of injection. No PRP patients withdrew **Conclusions:** Data are insufficient to draw conclusions	

AKS=arthroscopic knee surgery, CI = Confidence interval, HA = Hyaluronic acid, IKDC = International knee documentation committee, MD = Mean difference, mm = Millimeter, Mos. = Months, NRS = Numerical rating scale, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, PRP = Platelet rich plasma, RCT = Randomized controlled trial, RR = Risk ratio, SoE = Strength of evidence, TKA= total knee arthroplasty, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).
†Exclusion of one poor-quality outlier RCT which reported results based on numbers of knees, not patients: Tavassoli 2019.
‡Excludes one extremer outlier, Lana 2016; there were substantial baseline differences between groups and study reported medians and range.
§Excludes two outliers: Lana 2016 (baseline differences, estimated variation) and Tavassoli 2019 (reports results for numbers of knees)
**Adverse events are detailed in the full report (Table 19) and in data abstraction.

7.1.3 Strength of Evidence Summary: HA vs. Steroid for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
Function: WOMAC physical function scores and KOOS ADL and KSS function	Short term (3 mos.)	**WOMAC, KOOS** 1 RCT (N=140) Askari, 2016 **KSS function** 2 RCTs (N=160) Campos, 2017 Viashya, 2017	Yes -1	Unknown (different measures)	No	Yes (-1)	**WOMAC Physical Function** 0.25 (-3.69 to 4.19) **KOOS ADL** 0.37 (-5.42 to 6.61) **KSS** Pooled MD-2.63 (-17.4 to 12.40), I^2=61.6% Conclusion: No difference between HA and steroid based across measures in the good quality RCT (WOMAC, KOOS) or in pooled KSS analyses across 2 poor quality RCTs	⊕⊕◯◯ LOW
KSS Function	Intermediate (6 months)	**KSS function** 2 RCTs (N=160) Campos, 2017 Viashya, 2017	Yes (-2)	Yes (-1)	No	Yes (-1)	Pooled MD -6.63 (-22.6 to 9.73), I^2=67.1% Conclusion: No difference between HA and steroid	⊕◯◯◯ INSUFFICIENT
Pain Scores **WOMAC (0-20)** **VAS (0-10 scale)**	3 mos.	**WOMAC Pain** 2 RCTs (N=526) Askari, 2016 Leighton, 2014 **VAS Pain** 4 RCTs (N=471) Tammachote, 2016	WOMAC No VAS Yes (-1)	No	No	Yes (-1)	**WOMAC Pain (0-20)** MD 0.40 95%CI -1.17 to 1.80, I^2=0% **VAS Pain (0-10)** MD – 0.47, 95 % CI -1.7 0 to 0.77, I^2=90.1% [excludes poor-quality outlier, Bisicchia 2016] **3 RCTs,** MD 0.09, 95% CI -0.52 to 0.66, I^2=23.8	⊕⊕⊕◯ MODERATE

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
		Askari, 2016 Vaishya, 2017 Bisicchia, 2016					Conclusion: No difference between HA and steroids for pain improvement	
	Intermediate (6 mos.)	**WOMAC Pain** 1 RCT (N=386) Leighton, 2014 **VAS Pain** **3 RCTs (N= 317)** Tammachote, 2016 Vaishya, 2017 Bisicchia, 2016	WOMAC No VAS Yes (-1)	WOMAC Unknown VAS No	No	Yes (-1)	**WOMAC (0-20**) MD -0.75, 95%CI -3.41 to 1.91 **VAS Pain (0-10)** MD -0.48, 95% CI -1.29 to 00.47 Conclusion: No difference between HA and steroids for pain improvement	⊕⊕⊕◯ MODERATE
	Long term 12 mos.	VAS Pain 1 RCT (N=136) Bisicchia, 2016	Yes (-2)	Unknown	No	Yes (-1)	VAS Pain MD -0.60, 95% CI -1.34 to 0.14 Conclusion: No difference between HA and steroids for pain improvement	⊕◯◯◯ INSUFFICIENT
Additional invasive procedures	Anytime	1 RCT (N=136) Bisicchia, 2016	Yes (-2)	Unknown	No		HA vs. steroid 1.3% (1/75) vs. 2.7% (2.75)	⊕◯◯◯ INSUFFICIENT
KQ 1b: Safety								
Serious AEs†	Any	1 RCT (N=442) Leighton, 2014 3 RCTs (N=272) reported no events	Yes (-1)	Unknown	No	Yes (-2)	1 RCT: 4.1% (9/221) vs. 2.7% (6/221) RR 1.50 (0.54, 4.14) 3 RCTs reported no events	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
		Campos, 2017 Vaishya, 2018 Tammachote, 2016					**Conclusions:** These may be rare; studies are likely underpowered to detect rare events; authors do not define specific AEs to be considered or identified	
Treatment-Related AEs†	Any	1 RCT (N=442) Leighton, 2014	Yes (-1)	Unknown	No	Yes (-1)	AEs not specified 21.7% (48/221) vs. 6.8% (15/221), RR 3.20 (1.85, 5.54) **Conclusions:** Treatment related AEs were substantially more common with HA versus steroid	⊕⊕◯◯ LOW
Other AEs (not categorized)† Unclear if treatment related	Any	2 RCTs (N=260), described AEs Bissichia, 2016 Tammachote, 2016 2 RCTs (N=524), did not describe AEs Leighton, 2014 Vaishya, 2018	Yes (-1)	Unknown	No	Yes (-1)	**Trials Describing AEs** Bissichia (N= 150) Includes sensation of heaviness, pruritus 6.6% (5/75) vs. 5.3% (4/75) Tammachote (N=110): knee pain and swelling, 0% vs. O% **Trials not describing** Leighton (N=442): 54.3% (120/221) vs. 64.3% (142/221), RR 0.85 (0.72, 0.99) Vaishya (N=82); 2.4% (1/42) vs. 2.5% (1/40) **Conclusions:** The largest trial suggests that non-treatment related AEs were less common with HA vs.	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
							steroid but types of AEs are not described. Three other RCTs find no difference between HA and steroid.	
Swelling or pain and swelling†	Any	Swelling 1 RCT (N=442) Leighton, 2014 Pain and swelling 1 RCT (N=110) Tammachote, 2016	Yes (-1)	Unknown	No	Yes (-2)	Swelling 2.3 % vs. 0.5%, RR 5.00 (0.59, 42.45) Pain and swelling 0.2% (1/55) vs. 0% **Conclusions:** No difference between HA and steroid.	⊕◯◯◯ INSUFFICIENT

CI = Confidence interval, HA = Hyaluronic acid, KOOS ADL = Knee injury and osteoarthritis outcome score function in daily living, KSS = Knee society score, MD = Mean difference, mm = Millimeter, Mos. = Months, NRS = Numerical rating scale, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, RCT = Randomized controlled trial, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).
†Adverse events are detailed in the full report (Table 19) and in data abstraction.

7.1.4 Strength of Evidence Summary: HA vs. NSAID for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. NSAID Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
WOMAC physical function success; ≥20% decrease in score	6 months 12 Months	1 RCT (N=66) Buendia-Lopez, 2018 (oral NSAID)	Yes -1	Unknown	No	Yes (-1)	**HA vs. NSAID** **6 months** 15.7% vs. 12.2% RR 1.29 (0.38, 4.37) **12 months** **0% vs. 0 %** Conclusion: No difference	⊕⊕◯◯ LOW
WOMAC Physical Function Scores (0=68)	6 months	1 RCT (N=65) Buendia-Lopez, 2018 (oral NSAID)	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. NSAID** MD -4.07 (-4.48, -3.66) Conclusion: Small functional improvement with HA versus NSAID	⊕⊕◯◯ LOW
	12 Months		Yes (-1)	Unknown	No	Yes (-1)	**HA vs. NSAID** MD -0.13 (-0.48, 0.22) Conclusion: No difference	⊕⊕◯◯ LOW
Pain Success ≥20% decrease in score **WOMAC** **VAS**	6 months	1 RCT (N=65) Buendia-Lopez, 2018 (oral NSAID)	Yes -1	Unknown	No	Yes (-1)	**HA vs. NSAID** **WOMAC** 21.5% vs.15.2% RR 1.44 (0.51, 4.08) **VAS** 25% vs. 18.2% RR 1.38 (0.54, 3.52) Conclusion: No difference	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. NSAID Effect estimate (95% CI) Conclusion	Quality (SoE)
	12 Months		Yes -1	Unknown	No	Yes (-1)	**HA vs. NSAID** **WOMAC** 0% vs. 0 % **VAS** 0% vs.6% RR 0.26 (0.01, 5.50) <u>Conclusion</u> No difference	⊕⊕◯◯ LOW
WOMAC Pain scores (0-20)	6 months	1 RCT (N=65) Buendia-Lopez, 2018 (oral NSAID)	Yes -1	Unknow	No	Yes (-1)	MD -4.07, 95% CI -4.48 to -3.66 <u>Conclusion:</u> Moderate improvement in pain favoring HA vs. NSAID	⊕⊕◯◯ LOW
	12 Months		Yes -1	Unknow	No	Yes (-1)	MD -0.13 (-0.48, 0.22) <u>Conclusion</u>: No difference	⊕⊕◯◯ LOW
Pain Scores **VAS (0-10 scale)**	6 months	2 RCTs (N=126) Guner, 2016 (IM NSAID) Buendia-Lopez, 2018 (oral NSAID)	Yes -1	Unknow	No	Yes (-1)	**Pooled MD** -0.57, 95% CI -0.88 to -0.07, I^2=0% **Guner**: MD -0.19, 95%CI -1.08 to 0.07 **Buendia-Lopez**: MD -0.60, 95% CI -0.85 to -0.35) <u>Conclusion:</u> Small improvement in pain favoring HA vs. NSAID in pooled analysis and in one RCT (HA vs. etoricoxib); No difference in the RCT (HA vs. IM etofenamate)	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. NSAID Effect estimate (95% CI) Conclusion	Quality (SoE)
	12 Months		Yes -1	Unknown	No	Yes (-1)	**Pooled** MD 0.49, 95 CI 0.01 to 0.78 **Guner**: **Buendia-Lopez**: Conclusion: Small improvement in pain favoring **NSAID** vs. HA in one RCT (HA vs. etoricoxib) and when studies are pooled but no difference between HA vs. IM etofenamate in the other RCT	⊕◯◯◯ INSUFFICIENT
WOMAC Total score (0-100)	6 months	1 RCT (N=126) Guner, 2016 (IM NSAID) Buendia-Lopez, 2018 (oral NSAID)	Yes -1	Unknown	No	Yes (-1)	**HA vs. NSAID** **Pooled MD** -5.27, 95%CI -6.19 to -3.67, I^2=34.2% **Guner**: MD 0.64, 95%CI -8.78 to 10.06 **Buendia-Lopez:** -5.29, 95%CI -5.83 to -4.75) Conclusion: Small improvement in WOMAC total favoring NSAID vs. HA in one RCT (HA vs. etoricoxib) and when studies pooled but no difference in one RCT (HA vs. IM etofenamate)	⊕◯◯◯ INSUFFICIENT
	12 Months		Yes (-1)	Unknown	No	Yes (-1)	**HA vs. NSAID** Pooled MD -0.13, 95% CI -1.1 to 0.81) I^2=0% Conclusion: No difference between HA and NSAID in either	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. NSAID Effect estimate (95% CI) Conclusion	Quality (SoE)
							pooled estimates or for individual studies	
KQ 1b: Safety								
Any AE†	Any	1 RCT (N=59) Guner, 2016 (IM NSAID)	Yes (-1)	Unknown	No	Yes (-2)	Authors report no AEs in either group; AEs considered were not specified Conclusions: No firm conclusions are possible	⊕◯◯◯ INSUFFICIENT

CI = Confidence interval, HA = Hyaluronic acid, IM = Intramuscular, MD = Mean difference, NSAID = Non-steroidal anti-inflammatory drug, OA = Osteoarthritis, RCT = Randomized controlled trial, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).
†Adverse events are detailed in the full report (Table 19) and in data abstraction.

7.1.5 Strength of Evidence Summary: HA vs. Usual Care for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Usual Care Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
KOOS ADL (0-100 (best))	3, 9 and 12 months	1 RCT (N=156) Hermans, 2019	Yes (-2)	Unknown	No	Yes (-2)	MD (graph estimate) 3months -5.7 6 months -3.8 12 months -4.0 Conclusion: No difference; all estimates below the threshold for a small effect; authors don't provide sufficient data to determine CIs; they report a p-value of 0.010 across the study period.	⊕◯◯◯ INSUFFICIENT
Pain Scores VAS (0-10 scale), with activity	3, 9 and 12 months	1 RCT (N=156) Hermans, 2019	Yes (-2)	Unknown	No	Yes (-2)	MD (graph estimate) 3months 6 months 12 months Conclusion: No difference; all estimates below the threshold for a small effect; authors don't provide sufficient data to determine CIs; they report a p-value of 0.06 across the study period.	⊕◯◯◯ INSUFFICIENT
OMERACT-OARSI Responder	312months	1 RCT (N=156) Hermans, 2019	Yes (-2)	Unknown	No	No	**HA vs. usual care** 57% vs. 34%, RR 1.67, 95% CI 1.16 to 2.40) Conclusion: HA was associated with a slightly higher likelihood of meeting OMERACT-OARSI response versus usual care	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Usual Care Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1b: Safety								
Treatment related AE†	Any	1 RCT (N=156) Hermans, 2019	Yes (-1)	Unknown	No	Yes (-1)	Knee flare, gastro-intestinal AE, other 45.0% (35/77) vs. 18% (14/79) 2.56 (1.50, 4.38) Conclusions: Treatment related AEs were substantially more likely with HA vs. usual care	⊕⊕◯◯ LOW
Other AEs (assumed not treatment related) †‡	Any	1 RCT (N=156) Hermans, 2019	Yes (-1)	Unknown	No	Yes (-1)	9.1% (7/77) vs. 7.6% (6/79), RR 1.20 (0.42, 3.40) Conclusions: There were no differences in non-treatment AEs between HA and usual care	⊕⊕◯◯ LOW

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP); for this trial, data was estimated from graph; MD calculated where possible

† Adverse events are detailed in the full report (Table 19) and in data abstraction

‡ Included: Removal of tibia staple, radius fracture, fibroadenoma, abducens nerve paresis, peroneal tendon ganglion, rib fracture, neurofibromatosis, gout, spondylolisthesis, removal of sebhorric verruca, partial parotidectomy due to atypical Whartin tumor, dermatological flebectomy, actinic keratosis

7.1.6 Strength of Evidence Summary: HA vs. Physical Therapy for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PT Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
KOOS ADL (0-100)	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknown	No	Yes (-1	HA vs. PT Means (SD were NR) 36.5 vs. 42.7 MD 6.2 (-0.81, 13.21) Conclusion: No difference	⊕⊕◯◯ LOW
KOOS Sport & Recreation (0-100)	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknown	No	Yes (-1	HA vs. PT Means (SD were NR) 12.0 vs. 17.3 MD 5.3 (4.32, 6.28) Conclusion: A small improvement in this measure favoring PT over HA	⊕⊕◯◯ LOW
VAS Pain scores (0-10)	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknown	No	Yes (-1)	HA vs. PT Means (SD were NR) 5.75 vs. 3.9 MD 1.85 (1.36, 2.34) Conclusion: A moderate improvement in pain favoring PT over HA	⊕⊕◯◯ LOW
KOOS Pain (0-100 (best))	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknow	No	Yes (-1)	HA vs. PT Means (SD were NR) 22.3 vs. 30.5 MD 8.2 (5.10, 11.30) Conclusion: A small improvement in pain favoring PT over HA	⊕⊕◯◯ LOW
KQ 1b: Safety								
NR	---	No evidence	---	---	---	---	---	---

ADL = Function in daily living, CI = Confidence interval, HA = Hyaluronic acid, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, OA = Osteoarthritis, PT = Physical therapy, RCT = Randomized controlled trial, SoE = Strength of evidence, VAS = Visual analog scale

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.1.7 Strength of Evidence Summary: HA vs. Prolotherapy for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Prolotherapy Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
KOOS ADL (0-100 scale)	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknown	No	Yes (-2)	HA vs. prolotherapy Means (SD were NR) 35.6 vs. 61.8 MD 25.3 (17.98, 32.62) Conclusion: A large improvement in function favoring prolotherapy over HA	⊕◯◯◯ INSUFFICIENT
KOOS Sport and Recreation (0-100 scale)	3 months		Yes -1	Unknown	No	Yes (-1)	HA vs. prolotherapy Means (SD were NR) 12.0 vs. 17.7 MD 5.7 (4.67 to 6.73) Conclusion: A small improvement in function favoring prolotherapy over HA	⊕⊕◯◯ LOW
KOOS Pain (0-100 (best))	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknown	No	Yes (-1)	HA vs. prolotherapy Means (SD were NR) 22.3 vs. 33.1 MD 10.8 (4.67, 6.73) Conclusion: A small improvement in pain favoring prolotherapy over HA	⊕⊕◯◯ LOW
VAS Pain scores (0-10)	3 months	1 RCT (N=55) Rezasoltani, 2020	Yes -1	Unknown	No	Yes (-1)	HA vs. prolotherapy Means (SD were NR 5.75 vs. 2.5 MD 3.25 (2.70, 3.80)	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Prolotherapy Effect estimate (95% CI) Conclusion	Quality (SoE)
							Conclusion: A large improvement in pain favoring prolotherapy over HA	
KQ 1b: Safety								
NR	---	No evidence	---	---	---	---	---	---

ADL = Function in daily living, CI = Confidence interval, HA = Hyaluronic acid, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, NR = Not reported, OA = Osteoarthritis, RCT = Randomized controlled trial, SoE = Strength of evidence, VAS = Visual analog scale

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.1.8 Strength of Evidence Summary: HA vs. Exercise for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Exercise Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
WOMAC Function (0-1700(worst))	3 months	1 RCT (N=104) Saccomano, 2016	Yes (-2)	Unknown	No	Yes (-2)	MD 89.2 (-34.26, 212.66) Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
	6 months		Yes (-2)	Unknown	No	Yes (-2)	72.9 (-56.91, 202.71) Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
WOMAC Pain Scores (0-500(worst))	3 months	1 RCT (N=104) Saccomano, 2016	Yes (-2)	Unknown	No	Yes (-2)	MD 23.1 (-13.91, 60.11) Conclusion No difference	⊕◯◯◯ INSUFFICIENT
	6 months		Yes (-2)	Unknown	No	Yes (-2)	MD 19.9 (-16.28, 56.08) Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
KQ 1b: Safety								
NR	---	No evidence	---	---	---	---	---	---

CI = Confidence interval, HA = Hyaluronic acid, MD = Mean difference, OA = Osteoarthritis, RCT = Randomized controlled trial, SoE = Strength of evidence, WOMAC = Western Ontario and McMaster osteoarthritis index.

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.1.9 Strength of Evidence Summary: HA vs. HA for Knee OA

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA (Artz) vs. HA (Durolane)* Effect estimate (95% CI)† Conclusion	Quality (SoE)
KQ 1a: Efficacy								
WOMAC Physical Function (0-68) Scores	6 mos.	1 RCT (N=319) Zhang, 2015	Yes (-1)	Unknown	No	Yes (-1)	Difference in change scores MD −0.58 (−1.69 to 0.53) **Conclusion**: No difference in function between the two HA products	⊕⊕◯◯ LOW
WOMAC Pain (0-20) Success†	6 mos.		Yes (-1)	Unknown	No	Yes (-1)	**Pain:** 81.6% (129/158) 78.9% (127/161) OR 0.96 (0.65 to 1.41) **Conclusion**: No difference between HA products in the likelihood of response based the full WOMAC pain score	⊕⊕◯◯ LOW
WOMAC Pain (0-20) Scores	6 mos.		Yes (-1)	Unknown	No	Yes (-1)	Difference in change scores MD −0.10 (−0.56 to 0.37) **Conclusion**: No difference in WOMAC pain scores	⊕⊕◯◯ LOW
OMERACT-OARSI† Responder	6 mos.		Yes (-1)	Unknown	No	Yes (-1)	148 (93.7%) vs 151 (93.8%) OR 1.12 (0.63 to 2.05) **Conclusion**: No difference between HA products in the likelihood of response.	⊕⊕◯◯ LOW
KQ 1b: Safety								
Severe (not specified if treatment related)	Anytime	1 RCT (N=350) Zhang, 2015	Yes (-1)	Unknown	No	Yes (-1)	4.6% (8/174) vs. 3.4% (6/ 175) RR 1.34, (0.48 to 3.78) **Conclusion**: No difference between HA products	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA (Artz) vs. HA (Durolane)* Effect estimate (95% CI)† Conclusion	Quality (SoE)
Serious (not treatment related)	Anytime		Yes (-1)	Unknown	No	Yes (-1)	3.4% (6/174) vs. 1.7% (3/175) RR 2.01 (0.51 to 7.9) **Conclusion**: No difference between HA products	⊕⊕◯◯ LOW
All treatment related AEs (Severity NR)	Anytime		Yes (-1)	Unknown	No	Yes (-1)	9.8% (17/174) vs. 13.1% (23/175) RR 0.74 (0.41 to 1.34) **Conclusion**: No difference between HA products	⊕⊕◯◯ LOW
Patients with ≥1 treatment emergent AE (not specified)	Anytime		Yes (-1)	Unknown	No	Yes (-1)	42.5% (74/174) vs. 47.4% (83/175) RR 0.90 (0.71 to 1.13) **Conclusion**: No difference between HA products	⊕⊕◯◯ LOW

CI = Confidence interval; HA = Hyaluronic acid; MD = Mean difference; mos. = months; OA = Osteoarthritis; OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative OR = odds ratio; RCT = Randomized controlled trial; SoE = Strength of evidence; WOMAC = Western Ontario and McMaster osteoarthritis index.

*Four injections of the animal-derived HA (Artz®; molecular weight 620-1,170 kDa) were administered in one group; a single injection of the nonanimal (bacterial fermentation) HA formulation (Durolane®; molecular weight 100,00 kDa) followed by and three subcutaneous sham injections using an empty syringe were administered in the other group.

† authors only report per-protocol results from missed effects repeated measures analyses.

7.1.10 Strength of Evidence Summary: HA vs. Placebo for Hip OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
Function: WOMAC physical function scores (0-68 lower score **or Lequesne** (1-24 scale)	Short term (3 mos.)	**WOMAC** 1 RCT (N=357) Brander, 2019 **Lequesne** 1 RCT (N=69) Qvistgaard, 2016	Yes (-1)	No	No	Yes (-1)	**WOMAC** MD (change scores) -0.34 (-0.17 to 0.85) **Lequesne** MD -0.2 (-1/73 to 1.33) Conclusion: No difference between HA and placebo	⊕⊕◯◯ LOW
	6 mos.	**WOMAC** 1 RCT (N=357) Brander, 2019	Yes (-1)	Unknown	No	Yes (-1)	**WOMAC** MD (change scores) 0.05 (-0.53 to 0.63) Conclusion: No difference between HA and placebo	⊕⊕◯◯ LOW
WOMAC Pain (walking) ≥2 point decrease in 0-10 NRS)	3 mos.	**WOMAC** 1 RCT (N=357) Brander, 2019	Yes (-1)	Unknown	No	Yes (-1)	46.7% vs. 50.29% Odds Ratio 0.78 (0.49 to 1.23) Conclusion: No difference between HA and placebo	⊕⊕◯◯ LOW
	6 mos.		Yes (-1)	Unknown	No	Yes (-1)	40.7% vs. 42.49% Odds Ratio 0.81 (0.49 to 1.33) Conclusion: No difference between HA and placebo	⊕⊕◯◯ LOW
Pain Scores **WOMAC (0-10 NRS)**	3 mos.	**WOMAC Pain** 1 RCT (N=357) Brander, 2019 **VAS Pain** 1 RCT (N=69)	Yes (-1)	Consistent	No	Yes (-1)	**WOMAC Pain (0-10 NRS)** MD (change scores) 0.32 (-0.19 to 0.83 **VAS Pain (0-100)** MD (graph estimate) -2.0 (-13.43 to 9.43)	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
VAS (0-100 scale), walking		Qvistgaard, 2016					SMD (author report) 0.4 (-0.1 to 0.9) <u>Conclusion:</u> No difference between HA and placebo	
	Intermediate (6 mos.)	**WOMAC Pain** 1 RCT (N=357) Brander, 2019	Yes (-1)	Consistent	No	Yes (-1)	**WOMAC (0-10 NRS**) MD (change scores) 0.06 (-0.52 to 0.65 <u>Conclusion</u>: No difference between HA and placebo	⊕⊕◯◯ LOW
WOMAC Total score (0-96) (assesses multiple domains)	3 mos	1 RCT (N=69) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-1)	MD (graph estimate) 1.0 (-4.71 to 6.71) <u>Conclusion</u>: No difference between HA and placebo	⊕◯◯◯ INSUFFICIENT
OMERACT-OARSI Responder (assesses multiple domains)	3 mos.		Yes (-1)	Unknown	No	Yes (-2)	% (95% CI) 53% (30% to 70%) vs.44% (28% to 61%) Effect size: 9% (no CI), p-value: NR <u>Conclusion:</u> A higher proportion of HA vs. placebo recipients met response criteria; statistical significance is not reported.	⊕◯◯◯ INSUFFICIENT
Invasive procedures (arthroplasty)	Any time	1 RCT (N=69) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-2)	0% (0/38) vs. 2.8% (1/36) <u>Conclusion</u>: No firm conclusions can be drawn; this appears to be a rare event.	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1b: Safety								
Serious adverse events (SAE)	Any time	1 RCT (N=357) Brander, 2019	Yes (-1)	Unknown	No	Yes (-1)	HA vs. placebo 5.6% (10/182) vs. 8.7% (15/172 RR 0.63, 95% CI 0.29 to 1.3 Conclusion: No difference between HA and placebo; Authors only considered one of the events (arthralgia in the saline group) to be treatment-related; definition of SAE was not provided	⊕◯◯◯ INSUFFICIENT
Treatment-related AEs at target hip	Any time	1 RCT (N=357) Brander, 2019	Yes (-1)	Unknown	No	Yes (-1)	HA vs. Placebo (saline) 12.8% vs. 8.7% RR 1.47, 95% CI 0.79 to 2.7 Conclusion: No difference between HA and placebo	⊕⊕◯◯ LOW
Withdrawal due to an AE	Any time	1 RCT (N=357) Brander, 2019	Yes (-1)	Unknown	No	Yes (-1)	HA vs. Placebo (saline) 5.5% vs. 5.7	⊕⊕◯◯ LOW

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index
*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.1.11 Strength of Evidence Summary: HA vs. PRP for Hip OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
Function: WOMAC physical function scores (0-68 lower score)	1 month	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value 21.5 [14.2-45.8] vs. 21 [16.7-36], p=0.480 Conclusion: No difference between HA and PRP	⊕⊕◯◯ LOW
	12 mos		Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value 28 [20.2-48.7] vs. 23.5 [13.7-58], p=0.260 Conclusion: No difference between HA and PRP	⊕⊕◯◯ LOW
Pain Scores **WOMAC (0-20)** **VAS (0-100 scale)**	1 month	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value **WOMAC** 6 [2-10] vs. 5 [2-7.2], 0.470 **VAS** 4.5 [2-7] vs. 4 [2-6], 0.570 Conclusion: No difference between HA and PRP	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
	12 mos		Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value **WOMAC** 9.5 [3.75-15] vs. 7 [1.75-11], 0.190 **VAS** 6 [2.7-8] vs. 5 [1.7-7.3], 0.150 <u>Conclusion</u>: No difference between HA and PRP	⊕⊕◯◯ LOW
WOMAC Total score (0-100) (assesses multiple domains)	1 month	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value 29.5 [14.2-45.8] vs. 28.5 [16.7-36], 0.410 <u>Conclusion</u>: No difference between HA and PRP	⊕⊕◯◯ LOW
	12 mos		Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value 40.5 [27.2-70.7] vs.33 [13.7-58], 0.270 <u>Conclusion</u>: No difference between HA and PRP	⊕⊕◯◯ LOW
Harris Hip Score (0-100, higher scores better) (assesses multiple domains)	1 month	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value 64.8 [55-81.13] vs. 69.5 [62-84], p=0.140	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
							Conclusion: No difference between HA and PRP	
	12 mos		Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** Medians [Interquartile range], p-value 60.2 [43-74.2] vs. 70.9 [57.2-89], p=0.050 Conclusion: PRP may be associated with improvement (higher score) compared with HA (p 0.050). Authors report medians and interquartile ranges; calculation of effect size was not possible.	⊕⊕◯◯ LOW
OMERACT-OARSI Responder (assesses multiple domains)	1 mos.	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** 69.4% vs. 81.6%, p>0.05 Conclusion: Although fewer in the HA group met criteria those in the PRP group, authors report no difference	⊕⊕◯◯ LOW
	6 mos.		Yes (-2)	Unknown	No	Yes (-1)	**HA vs. PRP** 58.3% vs. 73.7, p>0.05 Conclusion: Although fewer in the HA group met criteria those in the PRP group, authors report no difference	⊕⊕◯◯ LOW
	12 mos.		Yes (-2)	Unknown	No	Yes (-1)	**HA vs. PRP** 44% vs 64.7% p>0.05 Conclusion: Conclusion: Although fewer in the HA group met	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
							criteria those in the PRP group, authors report no difference	
Invasive procedures (arthroplasty)	Anytime	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. PRP** 5.6% (2/36) vs. 10.5% (4/38) RR 0.53 (0.10 to 2.71) Conclusion: No difference between HA and PRP	⊕⊕◯◯ LOW
KQ 1b: Safety								
Serious treatment related adverse events	Anytime	1 RCT (N=74) Villanova-Lopez, 2020	Yes (-1)	Unknown	No	Yes (-1)	Study only reports that no adverse events occurred**.**	⊕◯◯◯ INSUFFICIENT

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index
*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.1.12 Strength of Evidence Summary: HA vs. Steroids for Hip OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Steroids Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 1a: Efficacy								
Lequesne (1-24 scale)†	3 months	1 RCT (N=68) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. steroid** Mean (SD) graph estimates 8.9 (NR) vs. 8.9 (NR) Conclusion: No difference between HA and steroid	⊕◯◯◯ INSUFFICIENT
Pain Scores VAS (0-100 scale), walking	3 months	1 RCT (N=68) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. steroid** Mean (SD) graph estimates 36 (NR)vs. 36 (NR) Conclusion: No difference between HA and steroid	⊕◯◯◯ INSUFFICIENT
WOMAC Total score (0-100) (assesses multiple domains)	3 months	1 RCT (N=68) Qvistgaard, 2016					**HA vs. steroid** Mean (SD) graph estimates 8.9 (NR) vs. 8.9 (NR) Conclusion: No difference between HA and steroid graph estimates	⊕◯◯◯ INSUFFICIENT
OMERACT-OARSI Responder (assesses multiple domains)	3 months	1 RCT (N=68) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-1)	HA vs. steroid Proportion (95% CI) 53% (30% to 70%) vs. 66% (49% to 82%) Effect size NR Conclusion: Fewer HA vs. steroid recipients met response criteria; no statistical testing reported	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HA vs. Steroids Effect estimate (95% CI) Conclusion	Quality (SoE)
Invasive procedures (arthroplasty)	3 months	1 RCT (N=68) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-2)	**HA vs. steroid** 0% vs. 3.1% Conclusion: No firm conclusions can be drawn; this appears to be a rare event.	⊕◯◯◯ INSUFFICIENT
KQ 1b: Safety								
Serious treatment related adverse events	3 months	1 RCT (N=68) Qvistgaard, 2016	Yes (-1)	Unknown	No	Yes (-1)	**HA vs. steroid** Authors state that no serious adverse events occurred and report pain flare occurred in 3 patients but don't say for which treatment. Conclusion: No conclusions can be drawn;	⊕◯◯◯ INSUFFICIENT

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster University Osteoarthritis index
*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

† Estimated from graph; MD calculated where possible

7.2 Strength of Evidence Summary: Results for PRP

7.2.1 Strength of Evidence Summary: PRP vs. Placebo for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: WOMAC physical function scores (0-68; lower score = better function)	Short term (1-3 mos.)	Randomized by patient 5 RCTs (N=923) Chu, 2022 Dorio, 2021 Elik, 2020 Nunes-Tamashiro, 2022 Patel, 2013 Randomized by knees 2 NRSIs (N=80 knees, 40 patients) Ghai, 2019 Wu, 2018	Yes (-1)	No	No	Yes (-1)	Randomized by patient **Pooled MD:** -5.06, 95% CI -9.44 to -1.78, I^2=55% [4 RCTs, N=775, excluding outlier trial (Patel 2013) that reported knees] Randomized by knees **Pooled MD:** -5.88, 95% CI -10.23 to -1.31, I^2=87.4% Conclusion: Small improvement with PRP versus placebo (saline)	⊕⊕⊕◯ MODERATE
	Intermediate term (6 mos.)	Randomized by patient 4 RCTs (N=856) Chu, 2022 Dorio, 2021 Elik, 2020 Patel, 2013 Randomized by knees	Yes (-1)	Yes (-1)	No	Yes (-1)	Randomized by patient **Pooled MD:** -14.11, 95% CI -19.29 to -8.92, I^2=82% [3 RCTs, N=815, excluding outlier trial (Dorio 2021)] Randomized by knees **Pooled MD:** -3.14, 95% CI -5.01 to -1.55, I^2=0%	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
		2 NRSIs (N=80 knees, 40 patients) Ghai, 2019 Wu, 2018					Conclusion: Moderate improvement with PRP versus placebo (saline)	
	Long term (12 mos.)	2 RCTs (N=677) Chu, 2022† Nunes-Tamashiro, 2022	Yes (-1)	No	No	Yes (-1)	**Pooled MD:** -16.29, 95% CI -18.36 to -11.81, I^2=46% Conclusion: Large improvement with PRP versus placebo (saline)	⊕⊕◯◯ LOW
KOOS ADL and KOOS Sports (0-100, lower = better function)	Short term (2-3 mos.	4 RCTs (N=668) Bennell, 2021 Dorio, 2021 Lewis, 2022 Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	KOOS ADL **Pooled MD:** -3.08, 95% CI -13.62 to 7.28, I^2=88.4% KOOS Sport **Pooled MD:** -0.81, 95% CI -10.61 to 10.21, I^2=79.4% Conclusion: No difference.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	3 RCTs (N=380) Dorio, 2021 Lewis, 2022 Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	KOOS ADL **Pooled MD:** -2.09, 95% CI -15.96 to 12.12, I^2=83.6% KOOS Sport **Pooled MD:** 1.02, 95% CI -12.68 to 16.17, I^2=77.8% Conclusion: No difference.	⊕⊕◯◯ LOW
	Long term (12 mos. and 24 mos.)	12 months 3 RCTs (N=627) Bennell, 2021 Lewis, 2022 Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	12 months **KOOS ADL** **Pooled MD:** -2.39, 95% CI -11.61 to 2.18, I^2=61.8% **KOOS Sport**	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
		24 months 1 RCT (N=237) Yurtbay, 2022					**Pooled MD:** -4.02, 95% CI -13.87 to 6.43, I^2=65.5% 24 months **KOOS ADL** **MD:** -4.50, 95% CI -16.68 to 7.68 **KOOS Sport** **MD:** -6.50, 95% CI -18.68 to 5.68 Conclusion: No difference.	
IKDC (0-100, lower = better function)	Short term (3 mos.)	1 RCT (N=610) Chu, 2022†	Yes (-2)†	Unknown	No	No	**MD**: -5.10, 95% CI -6.92 to -3.29 Conclusion: Small improvement with PRP vs. placebo (saline).	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	2 RCTs (N=733) Chu, 2022† Gormeli, 2017	Yes (-1)	Yes (-1)	No	Yes (-1)	**Pooled MD**: -15.90, 95% CI -23.22 to -8.75, I^2=93.9% Conclusion: Moderate improvement with PRP vs. placebo (saline); estimate is imprecise	INSUFFICENT ⊕◯◯◯
	Long term (12 mos.)	1 RCT (N=610) Chu, 2022†	Yes (-2)†	Unknown	No	No	**MD**: -16.10, 95% CI -17.85 to -14.35 Conclusion: Moderate improvement with PRP vs. placebo (saline).	⊕⊕◯◯ LOW
WOMAC pain scores (0-20) (lower = less pain)	Short term (3 mos.)	Randomized by patient 5 RCTs (N=923) Chu, 2022 Dorio, 2021	Yes (-1)	No	No	No	Randomized by patient **MD**: -2.76, 95% CI -3.40 to -1.63, I^2=52.7% Randomized by knee	⊕⊕⊕◯ MODERATE

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
		Elik, 2020 Nunes-Tamashiro, 2022 Patel, 2013 Randomized by knees 2 NRSIs (N=80 knees, 40 patients) Ghai, 2019 Wu, 2018					**MD:** -4.64, 95% CI -5.48 to -2.98, I^2=54.0% Conclusion: Moderate improvement with PRP vs. placebo (saline).	
	Intermediate term (6 mos.)	Randomized by patient 4 RCTs (N=856) Chu, 2022 Dorio, 2021 Elik, 2020 Patel, 2013 Randomized by knees 2 NRSIs (N=80 knees, 40 patients) Ghai, 2019 Wu, 2018	Yes (-1)	Yes (-1)	No	No	Randomized by patient **MD**: -3.62. 95% CI -6.79 to -0.46, I^2=93.0% Randomized by knee **MD:** -3.27, 95% CI -4.12 to -2.33, I^2=0% Conclusion: Moderate improvement with PRP vs. placebo (saline).	⊕⊕⊕◯ MODERATE
	Long term (12 mos.)	Randomized by patient 2 RCTs (N=677) Chu, 2022† Nunes-Tamashiro, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	Randomized by patient **MD**: -4.38, 95% CI -9.96 to 1.45, I^2=96.5% Chu (N=610), 3 injections: MD -6.60, 95% CI -7.05 to -6.15	INSUFFICENT ⊕◯◯◯

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
							Nunes-Tamashiro (N=67), 1 injection: MD -1.87, 95% CI -3.53 to -0.21 <u>Conclusion</u>: Large improvement with PRP vs. placebo (saline).	
KOOS pain (0-100, lower = better function)	Short term (2-3 mos.	4 RCTs (N=668) Bennell, 2021 Dorio, 2021 Lewis, 2022 Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	**Pooled MD:** -6.61, 95% CI -22.27 to 8.89, I^2=95.3% <u>Conclusion</u>: No difference.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	3 RCTs (N=380) Dorio, 2021 Lewis, 2022 Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	**Pooled MD:** -3.53, 95% CI -19.42 to 12.24, I^2=90.3% <u>Conclusion</u>: No difference.	⊕⊕◯◯ LOW
	Long term (12 mos. and 24 mos.)	<u>12 months</u> 3 RCTs (N=627) Bennell, 2021 Lewis, 2022 Yurtbay, 2022 <u>24 months</u> 1 RCT (N=237) Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	<u>12 months</u> **Pooled MD:** -2.66, 95% CI -11.37 to 2.64, I^2=63.4% <u>24 months</u> **MD:** -4.50, 95% CI -16.68 to 7.68 <u>Conclusion</u>: No difference.	⊕⊕◯◯ LOW
VAS pain scores (0-10 scale)	Short term (3 mos.)	<u>Randomized by patient</u> 7 RCTs (N=1,402) Bennell, 2021 Lewis, 2022 Chu, 2022 Dório, 2021	Yes (-1)	Yes (-1)	No	Yes (-1)	<u>Randomized by patient</u> **MD**: -0.80, 95% CI -1.79 to 0.19, I^2=95.1% <u>Randomized by knee</u> **MD**: -2.15, 95% CI -3.24 to -1.06	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
		Elik, 2020 Nunes-Tamashiro, 2022 Yurtbay, 2022 <u>Randomized by knee</u> 1 NRSI (N=40 knees in 20 patients) Ghai, 2019					<u>Conclusion</u>: No difference (based on RCTs that randomized by patient)	
	Intermediate term (6 mos.)	<u>Randomized by patient</u> 6 RCTs (N=1,195) Lewis, 2022 Chu, 2022 Dório, 2021 Elik, 2020 Patel, 2013 Yurtbay, 2022 <u>Randomized by knee</u> 1 NRSI (N=40 knees in 20 patients) Ghai, 2019	Yes (-1)	Yes (-1)	No	Yes (-1)	<u>Randomized by patient</u> **MD:** -1.71, 95% CI -3.04 to -0.32, I^2=98.7% <u>Randomized by knee</u> **MD**: -0.85, 95% CI -2.52 to 0.82 <u>Conclusion</u>: Moderate improvement in pain with PRP vs. placebo (based on RCTs that randomized by patient)	⊕⊕◯◯ LOW
	Long term (12 mos.)	<u>Randomized by patient</u> 5 RCTs (N=1,310) Bennell, 2021 Lewis, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	**MD:** -1.14, 95% CI -2.58 to 0.38, I^2=98.3% <u>Conclusion</u>: No difference. Removal of one outlier	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
		Chu, 2022 Nunes-Tamashiro, 2022 Yurtbay, 2022					attenuated effect and still nonsignificant.	
OMERACT-OARSI Responder	Short (3 mos.) and intermediate (6 mos.) term	1 RCT (N=41) Dorio, 2021	Yes (-1)	Unknown	No	Yes (-1)	3 months **PRP:** 95% (19/20) vs. **Placebo:** 76% (16/21); **RR** 1.25, 95% CI 0.96 to 1.62 6 months **PRP:** 80% (16/20) vs. **Placebo:** 86% (18/21); **RR** 0.93, 95% CI 0.71 to 1.24 Conclusion: Small increase in the likelihood of achieving response with PRP vs. placebo short term, but no difference between groups intermediate term.	⊕⊕◯◯ LOW
Secondary Invasive interventions (TKA)	12-24 mos.	2 RCTs (N=545) Bennell, 2021 Yurtbay, 2022	Yes (-1)	No	No	Yes (-1)	**PRP:** 2.2% (6/271) vs. **Placebo:** 2.6% (7/274); **RR** 0.87, 95% CI 0.30 to 2.55 Conclusion: No difference.	⊕⊕◯◯ LOW
KQ 2b: Safety								
Serious AEs	6 mos.	3 RCT (N=409) Elik, 2020 Patel, 2013 Bennell, 2021 1 RCT (N=308, PRP arm only)	Yes (-1)	Unknown	No	Yes (-1)	RCTs: No SAEs in either treatment arm across 3 RCTs‡; 1 RCT reported no SAEs in PRP arm only 1 NRSI:	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Placebo Effect estimate (95% CI) Conclusion	Quality (SoE)
		Chu, 2022† 1 NRSI (N=40 knees in 20 patients) Ghai, 2019					Severe inflammation with swelling and stiffness immediately post-injection: **PRP:** 5% (1/20 knees) vs. **Placebo:** 0% (0/20 knees) Conclusion: Serious events appear to be rare; studies likely underpowered to detect rare events.	

ADL = Function in daily living, AE = Adverse event, CI = Confidence interval, IKDC = International knee documentation committee, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, NRSI = Non-randomized study of interventions, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, RR = Risk ratio, SoE = Strength of evidence, TKA = Total knee arthroplasty, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

†Patients who underwent surgery (e.g., total knee arthroplasty or arthroscopy) and injections during the follow-up period were excluded from the study and are not accounted for in any analyses. The authors do not indicate how many patients were excluded for these reasons so there is concern about the impact of these exclusions on the results.

‡SAEs defined as fever, infection, deep vein thrombosis, hematoma, tissue hypertrophy, marked muscle atrophy, adhesion formation (1 RCT); septic infection, long-term pain, bleeding (1 RCT); and undefined (1 RCT).

7.2.2 Strength of Evidence Summary: PRP vs. Steroid for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: KOOS ADL (0-100 scale, lower = better)	Short term (3 mos.) and Intermediate term (6 mos.)	2 RCTs (N=131)† Jubert, 2017 (single injections) Nabi, 2018 (3 injections, 1 mo. intervals)	Yes (-1)	Yes (-1)	No	Yes (-1)	3 months **MD:** -7.63, 95% CI -11.64 to -1.26, I^2=0% 6 months **MD:** -17.87, 95% CI -22.34 to -7.49, I^2=55.6% Conclusion: Small improvement in function short term and a moderate improvement intermediate term with PRP vs. steroid in pooled analysis; individual trial results conflicted. Differences in injection regimens may partially explain the heterogeneity as the pooled results were driven by the 3 injection protocol (Nabi 2018).	⊕◯◯◯ INSUFFICIENT
Function: KOOS Sports and Recreation (0-100 scale, lower = better)	Short term (3 mos.) and Intermediate term (6 mos.)	2 RCTs (N=131)† Jubert, 2017 (single injections) Nabi, 2018 (3 injections, 1 mo. intervals)	Yes (-1)	Yes (-1)	No	Yes (-1)	3 months **MD:** -6.42, 95% CI -9.99 to 1.00, I^2=29.2% 6 months **MD:** -12.94, 95% CI -18.03 to 0.03, I^2=55.6% Conclusion: No difference between groups in pooled analysis; individually the trials reported conflicting results. Differences in injection regimens	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
							may partially explain the heterogeneity.	
Function: KSS scores (0-100 scale, lower = better)	Short term (3 mos.)	2 RCTs (N=86) Elksniņš-Finogejevs, 2020 Freire, 2020	Yes (-1)	Yes (-1)	No	Yes (-1)	**MD:** -9.61, 95% CI -23.60 to 3.89, I^2=79.2% Conclusion: No difference.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	2 RCTs (N=86) Elksniņš-Finogejevs, 2020 Freire, 2020	Yes (-1)	No	No	Yes (-1)	**MD:** -12.08, 95% CI -22.89 to -2.36, I^2=56.5% Conclusion: Moderate improvement in function with PRP vs. steroid	⊕⊕◯◯ LOW
Function: WOMAC physical function scores (0-68 lower score = better)	Short term (3 mos.) and long term (12 mos.)	1 RCT (N=67) Nunes-Tamashiro, 2022	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** 1.4, 95% CI -3.58 to 6.38 12 months **MD:** -2.2, 95% CI -7.70 to 3.30 Conclusion: No difference.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	1 RCT (N=103) Khan, 2018	Yes (-2)	Unknown	No	Yes (-1)	**MD:** 1.6, 95% CI -0.89 to 4.17 Conclusion: No difference between groups in one poor-quality trial.	⊕◯◯◯ INSUFFICIENT
Function: IKDC scores (0-100 lower score = better)	Short term (3 mos.), intermediate term (7 mos.), and Long term (13 mos.)	1 RCT (N=36) Elksnins-Finogejevs, 2020	Yes (-2)	Unknown	No	Yes (-1)	3 months **MD:** -20.5, 95% CI -29.63 to -11.37 7 months **MD:** -21.2, 95% CI -31.65 to -10.75 13 months	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
							MD: -22.2, 95% CI -32.65 to -11.75 Conclusion: Large improvement in function with PRP vs. steroid from one-poor quality trial.	
Pain: KOOS Pain (0-100 scale, lower = better)	Short term (3 mos.)	2 RCTs (N=131)† Jubert, 2017 (single injections) Nabi, 2018 (3 injections, 1 mo. intervals)	Yes (-1)	No	No	Yes (-1)	**MD:** -6.26, 95% CI -11.52 to 2.39, I^2=19.3% Conclusion: No difference between groups; individually the trials provided conflicting results. Differences in injection regimens may partially explain difference.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	2 RCTs (N=131) Jubert, 2017 (single injections) Nabi, 2018 (3 injections, 1 mo. intervals)	Yes (-1)	Yes (-1)	No	Yes (-1)	6 months **MD:** -12.67, 95% CI -26.23 to 5.04, I^2=78.7% Conclusion: No difference between groups; individually the trials provided conflicting results. Differences in injection regimens may partially explain the heterogeneity.	⊕◯◯◯ INSUFFICIENT
Pain: WOMAC pain (0-20, lower score = better)	Short term (3 mos.) and long term (12 mos.)	1 RCT (N=67) Nunes-Tamashiro, 2022	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** -0.51, 95% CI -4.18 to 3.88 12 months **MD:** -0.41, 95% CI -2.19 to 1.37 Conclusion: No difference in function between groups.	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
	Intermediate term (6 mos.)	1 RCT (N=103) Khan, 2018	Yes (-2)	Unknown	No	Yes (-1)	**MD:** -1.08, 95% CI -2.31 to 0.16 Conclusion: One poor-quality trial found no difference in function between groups.	⊕◯◯◯ INSUFFICIENT
Pain: VAS Pain (0-10, lower score = better)	Short term (1-3 mos.)	5 RCTs (N=314)† Elksniņš-Finogejevs, 2020 Jubert, 2017 Nabi, 2018 Nunes-Tamashiro, 2022 Phul, 2018	Yes (-2)	No	No	Yes (-1)	**MD:** -0.68, 95% CI -0.95 to -0.03, I^2=40.5% Conclusion: Small improvement in function with PRP vs. steroid.	⊕⊕◯◯ LOW
	Intermediate term (6-7 mos.)	4 RCTs (N=270) Elksniņš-Finogejevs, 2020 Jubert, 2017 Khan, 2018 Nabi, 2018	Yes (-1)	Yes (-1)	No	Yes (-1)	**MD:** -0.62, 95% CI -2.25 to 1.01, I^2=92.6% Conclusion: No difference in function between groups. Results varied widely across the trials. Difference in injection regimens may explain some of the heterogeneity.	⊕◯◯◯ INSUFFICIENT
	Long term (12-13 mos.)	3 RCTs (N=183) Elksniņš-Finogejevs, 2020 Huang, 2019 Nunes-Tamashiro, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	**MD:** -0.78, 95% CI -2.40 to 0.85, I^2=79.1% Conclusion: No difference in function between groups.	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
Function: WOMAC total scores (0-96 lower score = better)	Short term (1-3 mos.) and Intermediate term (6-9 mos.)	2 RCTs (N=130) Freire, 2020 Huang, 2019	Yes (-1)	Yes (-1)	No	Yes (-1)	1-3 months **MD:** -3.87, 95% CI -14.09 to 6.36, I^2=96.7% 6-9 months **MD:** -11.29, 95% CI -19.17 to -3.43, I^2=94.2% Conclusion: No difference between groups short term; point estimates for the trials went in opposite directions. Moderate improvement with PRP vs. steroid intermediate term; however, magnitudes of effects were very different between the trials.	⊕◯◯◯ INSUFFICIENT
	Long term (12 mos.)	1 RCT (N=80) Huang, 2019	Yes (-1)	Unknown	No	No	**MD:** -16.08, 95% CI -19.17 to -12.99 Conclusion: One poor-quality trial found moderate improvement with PRP vs. steroid.	⊕◯◯◯ INSUFFICIENT
Need for secondary invasive procedure	13 mos.	1 RCT (N=40) Elksniņš-Finogejevs, 2020	Yes (-1)	Unknown	No	Yes (-1)	TKA **PRP:** 0% (0/20) vs. **Steroid:** 15% (3/20) Conclusion: Data from one poor-quality trial are insufficient to draw conclusions regarding need for surgery.	⊕◯◯◯ INSUFFICIENT
KQ 2b: Safety								

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Steroid Effect estimate (95% CI) Conclusion	Quality (SoE)
Serious AEs	13 mos.	1 RCT (N=40) Elksniņš-Finogejevs, 2020	Yes (-1)	Unknown	No	Yes (-2)	No events in either group (SAEs not further defined)	⊕◯◯◯ INSUFFICIENT

ADL = Function in daily living, AE = Adverse event, CI = Confidence interval, IKDC = International knee documentation committee, KOOS = Knee injury and osteoarthritis outcome score, KSS = Knee society score, MD = Mean difference, Mos. = Months, NRSI = Non-randomized study of interventions, OA = Osteoarthritis, OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

†One poor-quality trial (Forogh 2016)[49] was a consistent outlier (favoring PRP). If patients were symptomatic in both knees, both knees were treated; the second knee was injected 3 weeks after the first and results were reported out of knees (not patients). Given both the study quality and the difference in the treatment protocol and reporting compared to the other trials, this RCT was excluded from pooled analyses.

7.2.3 Strength of Evidence Summary: PRP vs. Oral Analgesics for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Oral Analgesics Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: "Success" (Responders): ≥20% decrease in WOMAC Physical Function scores	Intermediate term (6 mos.) and long term (12 mos.)	1 RCT (N=66) Buendia-Lopez, 2018	Yes (-1)	Unknown	No	Yes (-1)	6 months **PRP:** 46% (15/33) vs. **NSAID** (etoricoxib 60 mg.): 12% (4/33) **RR**: 3.75, 95 CI 1.39 to 10.11 12 months **PRP:** 24% (8/33) vs. **NSAID** (etoricoxib 60 mg.): 0% (0/33) Conclusion: Large increase in the likelihood of achieving ≥20% decrease in WOMAC physical function scores with PRP vs. NSAIDs.	⊕⊕◯◯ LOW
Function: WOMAC physical function scores (0-68 scale, lower = better)	Short term (3 mos.)	2 RCTs (N=125) Reyes-Sosa, 2020 Simental-Mendía, 2016	Yes (-1)	No	No	Yes (-1)	**MD:** -10.00, 95% CI -14.81 to -5.19, I^2=0% Conclusion: Moderate improvement in function with PRP vs. oral analgesics.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	3 RCTs (N=191) Buendía-López, 2018 Reyes-Sosa, 2020 Simental-Mendía, 2016	Yes (-1)	No	No	Yes (-1)	**MD:** -7.17, 95% CI -8.01 to -6.60, I^2=0% Conclusion: Moderate improvement in function with PRP vs. oral analgesics.	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Oral Analgesics Effect estimate (95% CI) Conclusion	Quality (SoE)
	Long term (12 mos.)	2 RCTs (N=125) Buendía-López, 2018 Reyes-Sosa, 2020	Yes (-1)	No	No	Yes (-1)	**MD:** -6.58, 95% CI -7.54 to -5.92, I^2=13.2% Conclusion: Small improvement in function with PRP vs. oral analgesics.	⊕⊕◯◯ LOW
Pain: "Success" (Responders): ≥20% decrease in WOMAC pain scores and VAS pain scores	Intermediate term (6 mos.) and long term (12 mos.)	1 RCT (N=66) Buendia-Lopez, 2018	Yes (-1)	Unknown	No	Yes (-1)	**WOMAC pain responders** 6 months **PRP:** 49% (16/33) vs. **NSAID** (etoricoxib 60 mg.): 15% (5/33) **RR**: 3.20, 95 CI 1.33 to 7.72 12 months **PRP:** 30% (10/33) vs. **NSAID** (etoricoxib 60 mg.): 0% (0/33) **VAS pain responders** 6 months **PRP:** 49% (16/33) vs. **NSAID** (etoricoxib 60 mg.): 18% (6/33) **RR**: 2.67, 95 CI 1.19 to 5.96 12 months **PRP:** 15% (5/33) vs. **NSAID** (etoricoxib 60 mg.): 6% (2/33) **RR**: 2.50, 95% CI 0.52 to 11.98 Conclusion: Large increase in the likelihood of achieving ≥20% decrease in WOMAC pain scores with PRP vs. NSAIDs.	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Oral Analgesics Effect estimate (95% CI) Conclusion	Quality (SoE)
Pain: WOMAC pain scores (0-20 scale, lower = better)	Short term (3 mos.)	2 RCTs (N=125) Reyes-Sosa, 2020 Simental-Mendía, 2016	Yes (-1)	No	No	Yes (-1)	**MD:** -2.56, 95% CI -3.91 to -1.26, I^2=0% Conclusion: Moderate improvement in pain with PRP vs. oral analgesics.	⊕⊕◯◯ LOW
	Intermediate term (6 mos.)	3 RCTs (N=191) Buendía-López, 2018 Reyes-Sosa, 2020 Simental-Mendía, 2016	Yes (-1)	No	No	Yes (-1)	**MD:** -1.92, 95% CI -3.64 to -0.62, I^2=79.5% Conclusion: Small improvement in pain with PRP vs. oral analgesics.	⊕⊕◯◯ LOW
	Long term (12 mos.)	2 RCTs (N=125) Buendía-López, 2018 Reyes-Sosa, 2020	Yes (-1)	Yes (-1)	No	Yes (-1)	**MD:** -1.89, 95% CI -4.96 to 0.84, I^2=91.1% Conclusion: Insufficient evidence to draw conclusions; both RCTs favored PRP individually but the magnitudes of effect were very different (small vs. large) and the pooled estimate was not statistically significant.	⊕◯◯◯ INSUFFICIENT
Pain: VAS pain scores (0-10 scale, lower = better)	Short term (3 mos.)	2 RCTs (N=125) Reyes-Sosa, 2020 Simental-Mendía, 2016	Yes (-1)	No	No	No	**MD:** -1.99, 95% CI -2.86 to -1.13, I^2=0% Conclusion: Moderate improvement in pain with PRP vs. oral analgesics.	⊕⊕⊕◯ LOW
	Intermediate term (6 mos.)	3 RCTs (N=191) Buendía-López, 2018 Reyes-Sosa, 2020	Yes (-1)	No	No	No	**MD:** -0.96, 95% CI -1.66 to -0.72, I^2=23.4%	⊕⊕⊕◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Oral Analgesics Effect estimate (95% CI) Conclusion	Quality (SoE)
		Simental-Mendía, 2016					Conclusion: Small improvement in pain with PRP vs. oral analgesics.	
	Long term (12 mos.)	2 RCTs (N=125) Buendía-López, 2018 Reyes-Sosa, 2020	Yes (-1)	Yes (-1)	No	Yes (-1)	**MD:** -1.32, 95% CI -3.21 to 0.33, I^2=82.2% Conclusion: Insufficient evidence to draw conclusions; both RCTs favored PRP individually but the magnitudes of effect were very different (small vs. large) and the pooled estimate was not statistically significant.	⊕◯◯◯ INSUFFICIENT
Need for secondary invasive procedure	-----	No evidence	-----	-----	-----	-----	-----	-----
KQ 2b: Safety								
Serious AEs	-----	No evidence	-----	-----	-----	-----	-----	-----

ADL = Function in daily living, AE = Adverse event, CI = Confidence interval, MD = Mean difference, Mos. = Months, OA = Osteoarthritis, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, RR = Risk ratio, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index
*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.2.4 Strength of Evidence Summary: PRP (plus exercise) vs. Exercise alone for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (w/ exercise) vs. Exercise Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: WOMAC physical function scores (0-68; lower score = better function)	Short term (3 mos.)	Randomized by patient 1 RCTs (N=60) Akan, 2018	Yes (-1)	Unknown	No	Yes (-1)	Randomized by patient **MD:** -1.19, 95% CI -7.91 to 5.54 Conclusion: No difference.	⊕◯◯◯ INSUFFICIENT
	Intermediate term (6-8 mos.)	Randomized by patient 2 RCTs (N=122) Akan, 2018 Rayegani, 2014 Randomized by knees 1 NRSI (N=42 knees, 21 patients) Raeissadat, 2020	Yes (-1)	No	No	Yes (-1)	Randomized by patient (6 months) **Pooled MD:** -1.48, 95% CI -7.25 to 3.94, I^2=0% Randomized by knees (8 months) **MD:** -1.9, 95% CI -6.46 to 2.66, I^2=0% Conclusion: No difference.	⊕◯◯◯ INSUFFICIENT
Function: KOOS ADL and Sports and Recreation scores (0-100; lower score = better function)	Short term (2 mos.)	Randomized by patient 1 RCT (N=50) Angoorani, 2015	Yes (-1) [all fair]	Unknown	No	Yes (-1)	*PRP vs. Exercise + TENS* KOOS ADL **MD:** -10.2, -12.37 to -8.03 KOOS Sports and Recreation **MD:** 4.1, 1.40 to 6.80 Conclusion: Moderate improvement in function with PRP vs. Exercise and TENS on the KOOS ADL; exercise and TENS was favored based on the KOOS	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (w/ exercise) vs. Exercise Effect estimate (95% CI) Conclusion	Quality (SoE)
							Sports and Recreation scores, but the difference was below the threshold for a small effect.	
Pain: WOMAC pain scores (0-20; lower score = better function)	Short term (3 mos.)	Randomized by patient 1 RCTs (N=60) Akan, 2018	Yes (-1)	Unknown	No	Yes (-1)	Randomized by patient **MD:** -1.82, 95% CI -3.04 to -0.59 Conclusion: Small improvement in pain with PRP (plus exercise) vs. exercise alone	⨁◯◯◯ INSUFFICIENT
	Intermediate term (6-8 mos.)	Randomized by patient 2 RCTs (N=122) Akan, 2018 Rayegani, 2014 Randomized by knees 1 NRSI (N=42 knees, 21 patients) Raeissadat, 2020	Yes (-1)	No	No	Yes (-1)	Randomized by patient (6 months) **Pooled MD:** -2.14, 95% CI -3.89 to 0.14, I^2=53.4% Randomized by knees (8 months) **MD:** -0.19, 95% CI -1.98 to 1.60 Conclusion: No difference.	⨁⨁◯◯ LOW
Pain: KOOS Pain (0-100); lower score = less pain)	Short term (2 mos.)	Randomized by patient 1 RCT (N=50) Angoorani, 2015	Yes (-1) [all fair]	Unknown	No	Yes (-1)	**MD**: -6.5, 95% CI -8.49 to -4.51 Conclusion: Small improvement with PRP vs. Exercise + TENS.	⨁◯◯◯ INSUFFICIENT
Pain: VAS pain (0-10); lower score = less pain)	Short term (2 mos.) and Intermediate term (8 mos.)	Randomized by patient 1 RCT (N=50) Angoorani 2015 2 months	Yes (-1) [all fair, knees poor]	Unknown	No	Yes (-1)	2 months (patients) **MD:** -0.3, 95% CI -1.38 to 0.78 8 months (knees) **MD:** -0.66, 95% CI -1.84 to 0.52	⨁◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (w/ exercise) vs. Exercise Effect estimate (95% CI) Conclusion	Quality (SoE)
		Randomized by knees 1 NRSI (N=42 knees, 21 patients) Raeissadat 2020 8 months					Conclusion: No difference at short or intermediate term.	
Need for secondary invasive procedures	12 months	Randomized by patient 1 RCTs (N=60) Akan, 2018	Yes (-1)	Unknown	No	Yes (-1)	TKA PRP: 3.3% (1/30) vs. 0% (0/30) Conclusion: No difference in frequency of TKA with PRP plus exercise vs. exercise alone.	⨁◯◯◯ INSUFFICIENT
KQ 2b: Safety								
Serious AEs	2 months	Randomized by patient 1 RCT (N=50) Angoorani, 2015	Yes (-1)	Unknown	No	Yes (-2)	No SAEs occurred in either group (not further defined)	⨁◯◯◯ INSUFFICIENT

ADL = Function in daily living, AE = Adverse event, CI = Confidence interval, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, NRSI = Non-randomized study of interventions, OA = Osteoarthritis, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, SAE = Serious adverse events, SoE = Strength of evidence, TKA = Total knee arthroplasty, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.2.5 Strength of Evidence Summary: PRP vs. PT for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. PT Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: WOMAC physical function scores (0-68; lower score = better function) **Pain: VAS pain** (0-10); lower score = less pain)	Short term (3 mos.)	1 RCT (N=40) Gabella, 2019	Yes (-1)	Unknown	No	Yes (-1)	Function **MD:** -30.2, 95% CI -35.14 to -25.26 Pain **MD:** -3.5, 95% CI -4.09 to -2.91 Conclusion: One poor-quality trial reported substantial improvement in function and pain with PRP vs. PT	⨁◯◯◯ INSUFFICIENT
Need for secondary invasive procedures	-----	No evidence	-----	-----	-----	-----	-----	-----
KQ 2b: Safety								
Serious AEs	-----	No evidence	-----	-----	-----	-----	-----	-----

AE = Adverse event, CI = Confidence interval, MD = Mean difference, Mos. = Months, OA = Osteoarthritis, PRP = Platelet-rich plasma, PT = Physical therapy, RCT = Randomized controlled trial, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.2.6 Strength of Evidence Summary: PRP vs. Prolotherapy for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Prolotherapy Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: WOMAC physical function scores (0-68; lower score = better function)	Short term (2 mos.) and intermediate term (6 mos.)	1 RCT (N=42) Rahimzadeh, 2018	Yes (-1)	Unknown	No	Yes (-1)	2 months **MD:** -5.40, 95% CI -9.28 to -1.52 6 months **MD:** -5.00, 95% CI -9.05 to -0.95 Conclusion: One poor-quality trial found a small improvement in function with PRP vs. prolotherapy short and intermediate term.	⊕◯◯◯ INSUFFICIENT
Pain: WOMAC pain scores (0-68; lower score = less pain) **VAS pain scores** (0-10); lower score = less pain)	Short term (1-2 mos.) and intermediate term (6 mos.)	WOMAC pain 1 RCT (N=42) Rahimzadeh, 2018 VAS pain 1 RCT (N=60) Pishgahi, 2020	Yes (-1)	Unknown?	No	Yes (-1)	**WOMAC** 2 months **MD:** -1.70, 95% CI -2.76 to -0.64 6 months **MD:** -1.80, 95% CI -2.93 to -0.67 **VAS** 1 month **MD:** -0.70, 95% CI -0.77 to -0.63 6 months **MD:** -0.83, 95% CI -0.92 to -0.74 Conclusion: Two poor-quality trials reported small improvements in WOMAC and VAS pain with PRP vs. prolotherapy short and intermediate term.	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP vs. Prolotherapy Effect estimate (95% CI) Conclusion	Quality (SoE)
Need for secondary invasive procedures	-----	No evidence	-----	-----	-----	-----	-----	-----
KQ 2b: Safety								
Serious AEs	6 months	1 RCT (N=60) Pishgahi, 2020	Yes (-1)	Unknown	No	Yes (-2)	No SAEs in either treatment arm (no further details provided).	⨁◯◯◯ INSUFFICIENT

AE = Adverse event, CI = Confidence interval, MD = Mean difference, Mos. = Months, OA = Osteoarthritis, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, SAE = Serious Adverse Event, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index
*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.2.7 Strength of Evidence Summary: Fewer vs. Greater Number of PRP injections for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function "Success" (Responders): WOMAC physical function scale	Short term (3 mos.)	**1 vs. 2 (3-week interval) PRP injections** 1 RCT (N=56) Tavassoli, 2019	Yes (-1)	Unknown	No	Yes (-1)	**≥30% decrease:** **PRP x 1**: 42.9% (12/28) vs. **PRP x 2**: 82.1% (23/28) **RR**: 0.52, 95% CI 0.33 to 0.83 **≥50% decrease:** **PRP x 1**: 3.6% (1/28) vs. **PRP x 2**: 17.9% (5/28) **RR:** 0.20, 95% CI 0.22 to 1.60 Conclusion: Moderate decrease in likelihood of response with 1 vs. 2 injections of PRP with 30% threshold but not 50%.	⊕◯◯◯ INSUFFICIENT
Function: WOMAC physical function scores (0-68 scale, lower = better)	Short term (3 mos.) and intermediate term (6 mos.)	**1 vs. 2 (2–3-week intervals) PRP injections** 3 RCTs (N=279) Kavadar, 2015 Patel, 2013 Tavassoli, 2019	Yes (-1)	Yes (-1)	No	Yes (-1)	3 months 3 RCTs (N=279) **Pooled MD:** 4.76, 95% CI -3.94 to 13.96, I^2=96.9% 6 months 2 RCTs (N=167) **Pooled MD:** 3.93, 95% CI -11.70 to 20.18, I^2=97.2% Conclusion: No difference. Substantial imprecision and heterogeneity are noted.	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
	Short term (3 mos.) and intermediate term (6 mos.)	**1 vs. 3 (2-week intervals) PRP injections** 1 RCT (N=66) Kavadar, 2015	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** 9.60, 95% CI 6.11 to 13.09 6 months **MD:** 8.60, 95% CI 5.11 to 12.09 Conclusion: Moderate improvement in function with 3 PRP injections versus 1 injection. Substantial imprecision and heterogeneity are noted.	⊕◯◯◯ INSUFFICIENT
	Short term (3 mos.) and intermediate term (6 mos.)	**2 vs. 3 (both 2-week intervals) PRP injections** 1 RCT (N=66) Kavadar, 2015	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** -2.20, 95% CI -6.51 to 2.11 6 months **MD:** -2.30, 95% CI -6.61 to 2.01 Conclusion: No difference. Substantial imprecision and heterogeneity are noted.	⊕◯◯◯ INSUFFICIENT
Function: KOOS ADL (0-100 scale, lower = better)	Short term (3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	**1 (+ 2 placebo) vs. 3 injections (all 1-week intervals)** 1 good-quality RCT (N=74) Lewis, 2022 **1 vs. 3 injections (all 1-month intervals)** 1 fair-quality RCT (N=125)	Yes (-1)	Yes (-1)	No	Yes (-1)	Good-quality RCT: **3 months: MD** -5.60, 95% CI -12.14 to 0.94 **6 months: MD** -5.40, 95% CI -12.26 to 1.46 **12 months: MD** -3.60, 95% CI -10.42 to 3.22 Fair-quality RCT: **3 months: MD** 3.00, 95% CI -2.14 to 8.14 **6 months: MD** 9.00, 95% CI 3.86 to 14.14	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
		Yurtbay, 2022					**12 months: MD** 17.50, 95% CI 12.36 to 22.64 Conclusion: No difference in pooled estimates; individual point estimates when in opposite directions and heterogeneity was substantial. Difference in intervals between injections may explain some of the variation.	
Function: KOOS Sports and Recreation (0-100 scale, lower = better)	Short term (3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	**1 (+ 2 placebo) vs. 3 injections (all 1-week intervals)** 1 good-quality RCT (N=74) Lewis, 2022 **1 vs. 3 injections (all 1-month intervals)** 1 fair-quality RCT (N=125) Yurtbay, 2022	Yes (-1)	No (short term) Yes (-1) (intermediate and long term)	No	Yes (-1)	**3 months** Pooled MD: -3.98, 95% CI -13.89 to 4.71, I^2=25.8% Good-quality RCT: **6 months: MD** -13.80, 95% CI -24.01 to -3.59 **12 months: MD** -9.40, 95% CI -20.78 to 1.98 Fair-quality RCT: **6 months: MD** 8.00, 95% CI 0.02 to 15.98 **12 months: MD** 12.00, 95% CI 4.02 to 19.98 Conclusion: No difference short term. At intermediate and long term, there was also no difference in pooled estimates but individual point estimates when in opposite directions and heterogeneity was substantial. Difference in	⊕⊕◯◯ LOW Short term (3 mos.) ⊕◯◯◯ INSUFFICIENT Intermediate and long term (6, 12 mos.)

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
							intervals between injections may explain some of the variation.	
IKDC, 0-100	Intermediate term (6 mos.)	**1 (+ 2 placebo) vs 3 injections (all 1-week intervals)** 1 RCT (N=83) Gormeli, 2017	Yes (-1)	Unknown	No	Yes (-1)	MD 10.6, 95% CI 6.94 to 14.26 Conclusion: Moderate improvement in function with 3 injections versus 1 injection of PRP.	⨁◯◯◯ INSUFFICIENT
Pain "Success" (Responders): WOMAC and VAS pain scales	Short term (3 mos.)	**1 vs. 2 (3-week interval) PRP injections** 1 RCT (N=56) Tavassoli, 2019	Yes (-1)	Unknown	No	Yes (-1)	**WOMAC Pain** **≥30% decrease:** **PRP x 1**: 85.7% (24/28) vs. **PRP x 2**: 100% (28/28) **RR**: 0.86, 95% CI 0.74 to 1.00 **≥50% decrease:** **PRP x 1**: 21.4% (6/28) vs. **PRP x 2**: 57.1% (16/28) **RR**: 0.38, 95% CI 0.17 to 0.82 **VAS Pain** **≥50% decrease:** **PRP x 1**: 7.1% (2/28) vs. **PRP x 2**: 60.7% (17/28) **RR:** 0.12, 95% CI 0.03 to 0.46 Conclusion: Two injections of PRP is associated with greater likelihood of achieving	⨁◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
							response of the WOMAC and VAS pain scales.	
Pain: VAS pain (0-10 scale, lower = better)	Short term (3 mos.) and intermediate term (6 mos.)	**1 vs. 2 (2–3-week intervals) PRP injections** 3 RCTs (N=279) Kavadar, 2015 Patel, 2013 Tavassoli, 2019	Yes (-1)	Yes (-1)	No	Yes (-1)	3 months 2 RCT (N=177) **Pooled MD:** 0.95, 95% CI 0.43 to 1.73, I^2=0% 6 months 2 RCTs (N=167) **Pooled MD:** 0.23, 95% CI -1.21 to 1.64, I^2=89.3% Conclusion: No difference. Substantial imprecision and heterogeneity (at 6 months) are noted.	⨁◯◯◯ INSUFFICIENT
	Short term (3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	**1 vs. 3 injections** 3 RCTs (N=265) Kavadar, 2015 (2-week interval) Lewis, 2022 (1-week interval) Yurtbay, 2022 (1-month interval)	Yes (-1)	Yes (-1)	No	Yes (-1)	3 months **Pooled MD:** 0.74, 95% CI -1.23 to 3.38, I^2=81.8% 6 months **Pooled MD:** 0.48, 95% CI -0.94 to 2.57, I^2=85.8% 12 months 2 RCTs (N=199) **Pooled MD**: 0.94, 95% CI -1.14 to 2.89, I^2=93.0%	⨁◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
							Conclusion: No difference. Differences in interval timing for multiple PRP injections may explain some of the heterogeneity.	
	Short term (3 mos.) and intermediate term (6 mos.)	**2 vs. 3 (both 2-week intervals) PRP injections** 1 RCT (N=66) Kavadar, 2015	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** 1.80, 95% CI -1.19 to 4.79 6 months **MD:** 1.90, 95% CI -0.25 to 4.05 Conclusion: No difference.	⨁◯◯◯ INSUFFICIENT
Pain: WOMAC pain scores (0-20 scale, lower = better)	Short term (3 mos.) and intermediate term (6 mos.)	**1 vs. 2 (2–3-week intervals) PRP injections** 3 RCTs (N=280) Kavadar, 2015 Patel, 2013 Tavassoli, 2019	Yes (-1)	Yes (-1)	No	Yes (-1)	3 months **Pooled MD:** 0.21, 95% CI -1.95 to 4.72, I^2=94.7% 6 months 2 RCTs (N=167) **Pooled MD:** 0.17, 95% CI -3.23 to 3.72, I^2=95.2% Conclusion: No difference. Substantial imprecision and heterogeneity are noted.	⨁◯◯◯ INSUFFICIENT
	Short term (3 mos.) and intermediate term (6 mos.)	**1 vs. 3 (2-week intervals) PRP injections** 1 RCT (N=66) Kavadar, 2015	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** 7.00 95% CI -1.85 to 15.85 6 months **MD:** 2.80, 95% CI 2.01 to 3.59 Conclusion: No difference at short term; moderate	⨁◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
							improvement in function with 3 PRP injections versus 1 injection at intermediate term.	
	Short term (3 mos.) and intermediate term (6 mos.)	**2 vs. 3 (both 2-week intervals) PRP injections** 1 RCT (N=66) Kavadar, 2015	Yes (-1)	Unknown	No	Yes (-1)	3 months **MD:** 1.20, 95% CI 0.32 to 2.08 6 months **MD:** 1.10, 95% CI 0.15 to 2.05 Conclusion: Small improvement with 3 injections vs. 2 injections.	⨁◯◯◯ INSUFFICIENT
KOOS Pain	Short term (3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	**1 (+ 2 placebo) vs. 3 injections (all 1-week intervals)** 1 good-quality RCT (N=74) Lewis, 2022 **1 vs. 3 injections (all 1-month intervals)** 1 fair-quality RCT (N=125) Yurtbay, 2022	Yes (-1)	Yes (-1)	No	Yes (-1)	Good-quality RCT: **3 months: MD** -8.10, 95% CI -14.69 to -1.51 **6 months: MD** -8.30, 95% CI -15.35 to -1.25 **12 months: MD** -3.10, 95% CI -9.75 to 3.55 Fair-quality RCT: **3 months: MD** 0.00, 95% CI -5.24 to 5.24 **6 months: MD** 10.00, 95% CI 4.76 to 15.24 **12 months: MD** 15.50, 95% CI 10.26 to 20.74 Conclusion: No difference in pooled estimates; individual point estimates when in	⨁◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	PRP (↓ injs.) vs. PRP (↑ injs.) Effect estimate (95% CI) Conclusion	Quality (SoE)
							opposite directions and heterogeneity was substantial. Difference in intervals between injections may explain some of the variation.	
Need for secondary invasive procedure	-----	No evidence	-----	-----	-----	-----	-----	-----
KQ 2b: Safety								
Serious AEs	6 mos.	1 RCT (N=102) Kavadar, 2015	Yes (-1)	Unknown	No	Yes (-2)	No SAE in either treatment arm (not further defined).	⨁◯◯◯ INSUFFICIENT

ADL = Function in daily living, AE = Adverse event, CI = Confidence interval, IKDC = International knee documentation committee, Inj. = Injection, KOOS = Knee injury and osteoarthritis outcome score, MD = Mean difference, Mos. = Months, OA = Osteoarthritis, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, RR = Risk ratio, SAE = Serious Adverse Event, SoE = Strength of evidence, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index
*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

7.2.8 Strength of Evidence Summary: Leukocyte-poor (LP)-PRP vs. leukocyte-rich (LR)-PRP for Knee OA

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	LP-PRP vs. LR-PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
KQ 2a: Efficacy								
Function: WOMAC physical function scores (0-68 scale, lower = better)	Short term (2-3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	2 RCTs (N=113) Yaradilmis, 2020 Zhou, 2023	Yes (-1)	No	No	Yes (-1)	2-3 months **Pooled MD:** 0.69, 95% CI -4.88 to 7.04, I^2=0% 6 months **Pooled MD:** 1.45, 95% CI -4.39 to 9.01, I^2=17.0% 12 months **Pooled MD:** 0.90, 95% CI -4.87 to 8.67, I^2=0% Conclusion: No difference.	⊕⊕◯◯ LOW
Pain: WOMAC pain scores (0-20 scale, lower = better)	Short term (2-3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	2 RCTs (N=113) Yaradilmis, 2020 Zhou, 2023	Yes (-1)	Yes (-1)	No	Yes (-1)	2-3 months **Pooled MD:** 2.44, 95% CI -5.02 to 10.11, I^2=94.3% **Good-quality RCT**: MD -0.57, 95% CI -2.26 to 1.12 **Fair-quality RCT**: MD 5.70, 3.30 to 8.10 6 months **Pooled MD:** 2.94, 95% CI -4.64 to 10.71, I^2=96.6% **Good-quality RCT**: MD -0.13, 95% CI -1.26 to 1.00 **Fair-quality RCT**: MD 6.23, 4.22 to 8.24 12 months **Pooled MD:** 2.71, 95% CI -4.16 to 9.76, I^2=94.0%	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	LP-PRP vs. LR-PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
							Good-quality RCT: MD -0.07, 95% CI -1.69 to 1.55 **Fair-quality RCT**: MD 5.70, 3.45 to 7.95 Conclusion: No difference in pooled analyses; individual trial results conflicted. The good-quality trial showed no difference and the fair-quality trial favored LR-PRP at all timepoints.	
Pain: VAS pain scores (0-10 scale, lower = better)	Short term (2-3 mos.) and intermediate term (6 mos.) and long term (12 mos.)	2 RCTs (N=113) Yaradilmis, 2020 Zhou, 2023	Yes (-1)	No (short term) Yes (-1) (intermediate and long term)	No	Yes (-1)	2-3 months **Pooled MD:** 0.00, 95% CI -0.54 to 0.66, I^2=0% 6 months **Pooled MD:** 0.45, 95% CI -0.86 to 1.94, I^2=78.8% **Good-quality RCT**: MD -0.03, 95% CI -0.60 to 0.54 **Fair-quality RCT**: MD 1.14, 0.25 to 2.03 12 months **Pooled MD:** 0.75, 95% CI -1.62 to 3.37, I^2=90.3% **Good-quality RCT**: MD -0.14, 95% CI -0.61 to 0.33 **Fair-quality RCT**: MD 1.94, 0.76 to 73.12 Conclusion: No difference in pooled analyses; individual trial results conflicted. The good-	⊕⊕◯◯ LOW (Short term) ⊕◯◯◯ INSUFFICIENT (Intermediate and long term)

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	LP-PRP vs. LR-PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
							quality trial showed no difference and the fair-quality trial favored LR-PRP at all timepoints.	
Need for secondary invasive procedure	6 months	1 RCT (N=53) Zhou, 2023	No	Unknown	No	Yes (-2)	TKA **LP-PRP:** 0% (0/27) vs. **LR-PRP:** 3.8% (1/26) Conclusion: No difference in risk of TKA	⊕◯◯◯ INSUFFICIENT
KQ 2b: Safety								
Serious AEs	12 mos.	1 RCT (N=53) Zhou, 2023	No	Unknown	No	Yes (-2)	Serious swelling and low-grade fever (not beyond 37.5 C): **LP-PRP:** 0% (0/27) vs. **LR-PRP:** 11.5% (3/26) [1 patient required arthroscopic debridement to relieve symptoms] Conclusion: Serious events appear to be rare; tend to be more common with LR-PRP. Studies likely underpowered to detect rare events.	⊕◯◯◯ INSUFFICIENT

AE = Adverse event, CI = Confidence interval, LP = Leukocyte poor, LR = Leukocyte rich, MD = Mean difference, Mos. = Months, OA = Osteoarthritis, PRP = Platelet-rich plasma, RCT = Randomized controlled trial, RR = Risk ratio, SoE = Strength of evidence, TKA = Total knee arthroplasty, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster osteoarthritis index

*All outcomes are scaled such that a lower score means a better outcome, i.e., a negative mean difference favors the intervention (HA or PRP).

8 References

1. A collection of R functions supporting the text book Modern Epidemiology, Second Edition, by Kenneth J. Rothman and Sander Greenland. GitHub, Inc., 2017. (Accessed October 13, 2017, at https://github.com/epijim/episheet.).
2. Medical Device Material Performance Study. Hyaluronic Acid (HA) Safety Profile. Prepared by ECRI for the U.S. FDA Center for Devices and Radiological Health. https://www.fda.gov/media/158489/download.
3. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
4. [No authors listed]. Summary of Safety and Effectiveness Data (SSED). Gel-One® (Gel-200). PMA No: P080020/S020. Approval Date: September 27, 2016. Accessed at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P080020S020.
5. Akan Ö, Sarıkaya NÖ, Koçyiğit H. Efficacy of platelet-rich plasma administration in patients with severe knee osteoarthritis: Can platelet-rich plasma administration delay arthroplasty in this patient population? International Journal of Clinical and Experimental Medicine 2018;11:9473-83.
6. Altman RD, Rosen JE, Bloch DA, Hatoum HT. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial. Osteoarthritis Cartilage 2011;19:1169-75.
7. Anandacoomarasamy A, March L. Current evidence for osteoarthritis treatments. Ther Adv Musculoskelet Dis 2010;2:17-28.
8. Angoorani H, Mazaherinezhad A, Marjomaki O, Younespour S. Treatment of knee osteoarthritis with platelet-rich plasma in comparison with transcutaneous electrical nerve stimulation plus exercise: a randomized clinical trial. Med J Islam Repub Iran 2015;29:223.
9. Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. Curr Med Res Opin 2014;30:279-86.
10. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. BMJ 2004;328:869.
11. Askari A, Gholami T, NaghiZadeh MM, Farjam M, Kouhpayeh SA, Shahabfard Z. Hyaluronic acid compared with corticosteroid injections for the treatment of osteoarthritis of the knee: a randomized control trail. Springerplus 2016;5:442.
12. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. Bmj 2004;328:1490.
13. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011;19:611-9.
14. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009;61:1704-11.
15. Bao X, Tan JW, Flyzik M, Ma XC, Liu H, Liu HY. Effect of therapeutic exercise on knee osteoarthritis after intra-articular injection of botulinum toxin type A, hyaluronate or saline: A randomized controlled trial. J Rehabil Med 2018;50:534-41.
16. Battaglia M, Guaraldi F, Vannini F, et al. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics 2013;36:e1501-8.
17. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to

antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
18. Bennell KL, Hunter DJ, Paterson KL. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. Curr Rheumatol Rep 2017;19:24.
19. Bennell KL, Paterson KL, Metcalf BR, et al. Effect of Intra-Articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients with Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. JAMA - Journal of the American Medical Association 2021;326:2021-30.
20. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD)2013.
21. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. Clin Exp Rheumatol 2016;34:857-63.
22. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. Obes Rev 2014;15:578-86.
23. Brander V, Skrepnik N, Petrella RJ, Jiang GL, Accomando B, Vardanyan A. Evaluating the use of intra-articular injections as a treatment for painful hip osteoarthritis: a randomized, double-blind, multicenter, parallel-group study comparing a single 6-mL injection of hylan G-F 20 with saline. Osteoarthritis Cartilage 2019;27:59-70.
24. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín M. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. J Orthop Traumatol 2018;19:3.
25. Campos ALS, RSP EA, da Silva EB, et al. Viscosupplementation in patients with severe osteoarthritis of the knee: six month follow-up of a randomized, double-blind clinical trial. Int Orthop 2017;41:2273-80.
26. Carbone LD, Satterfield S, Liu C, et al. Assistive walking device use and knee osteoarthritis: results from the Health, Aging and Body Composition Study (Health ABC Study). Arch Phys Med Rehabil 2013;94:332-9.
27. Castro JC, Daza AM, Misas JD. Cost-effectiveness Analysis of Viscosupplementation versus Conventional Supportive Therapy for Knee Osteoarthritis in Colombia. Value Health Reg Issues 2015;8:56-61.
28. Osteoarthritis. 2015. (Accessed September 21, 2022,
29. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 2012;40:2822-7.
30. Chou CW, Lue KH, Lee HS, Lin RC, Lu KH. Hylan G-F 20 has better pain relief and cost-effectiveness than sodium hyaluronate in treating early osteoarthritic knees in Taiwan. J Formos Med Assoc 2009;108:663-72.
31. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD2016 February.
32. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review No. 229. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC011. Rockville, MD2020.

33. Chou R, Wagner J, Ahmed AY, et al. Treatments for Acute Pain: A Systematic Review. Comparative Effectiveness Review No. 240. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20(21)-EHC006. Rockville, MD2020 December.
34. Choueiri M, Chevalier X, Eymard F. Intraarticular Corticosteroids for Hip Osteoarthritis: A Review. Cartilage 2021;13:122S-31S.
35. Chu J, Duan W, Yu Z, et al. Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2022;30:4063-71.
36. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. Am J Sports Med 2017;45:339-46.
37. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. BioDrugs 2012;26:257-68.
38. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S208-28.
39. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323-30.
40. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ 2021;375:n2321.
41. Dório M, Pereira RMR, Luz AGB, Deveza LA, de Oliveira RM, Fuller R. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. BMC Musculoskelet Disord 2021;22:822.
42. Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. Osteoarthritis Cartilage 2000;8:395-403.
43. Elik H, Dogu B, Yilmaz F, Begoglu FA, Kuran B. The efficiency of platelet-rich plasma treatment in patients with knee osteoarthritis. J Back Musculoskelet Rehabil 2020;33:127-38.
44. Elksniņš-Finogejevs A, Vidal L, Peredistijs A. Intra-articular platelet-rich plasma vs corticosteroids in the treatment of moderate knee osteoarthritis: a single-center prospective randomized controlled study with a 1-year follow up. J Orthop Surg Res 2020;15:257.
45. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
46. Farr J, Gomoll AH, Yanke AB, Strauss EJ, Mowry KC. A Randomized Controlled Single-Blind Study Demonstrating Superiority of Amniotic Suspension Allograft Injection Over Hyaluronic Acid and Saline Control for Modification of Knee Osteoarthritis Symptoms. J Knee Surg 2019;32:1143-54.
47. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med 2015;43:1575-82.

48. Food and Drug Administration (FDA). Intent To Consider the Appropriate Classification of Hyaluronic Acid Intra-articular Products Intended for the Treatment of Pain in Osteoarthritis of the Knee Based on Scientific Evidence. 2018.
49. Forogh B, Mianehsaz E, Shoaee S, Ahadi T, Raissi GR, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness 2016;56:901-8.
50. Freire MRM, da Silva PMC, Azevedo AR, Silva DS, da Silva RBB, Cardoso JC. Comparative Effect between Infiltration of Platelet-rich Plasma and the Use of Corticosteroids in the Treatment of Knee Osteoarthritis: A Prospective and Randomized Clinical Trial. Rev Bras Ortop (Sao Paulo) 2020;55:551-6.
51. Gaballa NM, Mohammed YA, Kamel LM, Mahgoub HM. Therapeutic efficacy of intra-articular injection of platelet–rich plasma and ozone therapy in patients with primary knee osteoarthritis. Egyptian Rheumatologist 2019;41:183-7.
52. Gato-Calvo L, Magalhaes J, Ruiz-Romero C, Blanco FJ, Burguera EF. Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Ther Adv Chronic Dis 2019;10:2040622319825567.
53. Ghai B, Gupta V, Jain A, Goel N, Chouhan D, Batra YK. Effectiveness of platelet rich plasma in pain management of osteoarthritis knee: double blind, randomized comparative study. Brazilian Journal of Anesthesiology 2019;69:439-47.
54. Gomoll AH, Farr J, Cole BJ, et al. Safety and Efficacy of an Amniotic Suspension Allograft Injection Over 12 Months in a Single-Blinded, Randomized Controlled Trial for Symptomatic Osteoarthritis of the Knee. Arthroscopy 2021;37:2246-57.
55. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2017;25:958-65.
56. Guner S, Gokalp MA, Gozen A, Unsal SS, Guner SI. Effectiveness of etofenamate for treatment of knee osteoarthritis: a randomized controlled trial. Ther Clin Risk Manag 2016;12:1693-9.
57. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
58. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380-2.
59. Hangody L, Szody R, Lukasik P, et al. Intraarticular Injection of a Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal) to Provide Symptomatic Relief of Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Trial. Cartilage 2018;9:276-83.
60. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. Stat Med 1996;15:619-29.
61. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am 1969;51:737-55.
62. Hatoum HT, Fierlinger AL, Lin SJ, Altman RD. Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. J Med Econ 2014;17:326-37.
63. Hermans J, Bierma-Zeinstra SMA, Bos PK, Niesten DD, Verhaar JAN, Reijman M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: a randomised controlled trial. BMC Musculoskelet Disord 2019;20:196.
64. Hermans J, Reijman M, Goossens LMA, Verburg H, Bierma-Zeinstra SMA, Koopmanschap MA. Cost-Utility Analysis of High Molecular Weight Hyaluronic Acid for Knee Osteoarthritis in Everyday

Clinical Care in Patients at a Working Age: An Economic Evaluation of a Randomized Clinical Trial. Arthritis Care Res (Hoboken) 2018;70:89-97.
65. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
66. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org2011.
67. Huang Y, Liu X, Xu X, Liu J. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis : A prospective randomized controlled study. Orthopade 2019;48:239-47.
68. Hummer CD, Angst F, Ngai W, et al. High molecular weight Intraarticular hyaluronic acid for the treatment of knee osteoarthritis: a network meta-analysis. BMC Musculoskelet Disord 2020;21:702.
69. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 2001;29:600-13.
70. Jones IA, Togashi RC, Thomas Vangsness C, Jr. The Economics and Regulation of PRP in the Evolving Field of Orthopedic Biologics. Curr Rev Musculoskelet Med 2018;11:558-65.
71. Jubert NJ, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis: A prospective, randomized, double-blinded clinical trial. Orthopaedic Journal of Sports Medicine 2017;5.
72. Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine 2003;70:276-81.
73. Kavadar G, Demircioglu DT, Celik MY, Emre TY. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: a randomized prospective study. J Phys Ther Sci 2015;27:3863-7.
74. Ke Y, Jiang W, Xu Y, et al. Efficacy and safety of a single intra-articular injection of 6 ml Hylan G-F 20 compared to placebo in Chinese patients with symptomatic knee osteoarthritis : C-SOUND study, a 26-week multicenter double-blind randomized placebo-controlled trial in China. BMC Musculoskelet Disord 2021;22:428.
75. Khan AF, Gillani SFUHS, Khan AF. Role of intra-articular corticosteroid with xylocaine vs plate rich plasma for the treatment of early grade II knee osteoarthritis at Akhtar Saeed Teaching Hospital Lahore: A randomized controlled trail. Pakistan Journal of Medical and Health Sciences 2018;12:1432-5.
76. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res 2016;474:1886-93.
77. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. J Stem Cells Regen Med 2016;12:69-78.
78. Leighton R, Akermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. Osteoarthritis Cartilage 2014;22:17-25.
79. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation--value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987;65:85-9.
80. Lespasio MJ, Sultan AA, Piuzzi NS, et al. Hip Osteoarthritis: A Primer. Perm J 2018;22:17-084.
81. Lewis E, Merghani K, Robertson I, et al. The effectiveness of leucocyte-poor platelet-rich plasma injections on symptomatic early osteoarthritis of the knee: the PEAK randomized controlled trial. The bone & joint journal 2022;104-B:663-71.

82. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. Arthroscopy 2019;35:106-17.
83. Lisi C, Perotti C, Scudeller L, et al. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clin Rehabil 2018;32:330-9.
84. Can arthritis pain medications be harmful? (Accessed September 21, 2022, at https://www.mayoclinic.org/diseases-conditions/arthritis/expert-answers/arthritis-pain-medications/faq-20058391.)
85. listed] Na. EQ-5D-3L User Guide: Version 6.0. EuroQol, 2018. (Accessed January 10, 2023). Access at: https://euroqol.org/publications/user-guides/.
86. Losina E, Daigle ME, Suter LG, et al. Disease-modifying drugs for knee osteoarthritis: can they be cost-effective? Osteoarthritis Cartilage 2013;21:655-67.
87. Louis ML, Magalon J, Jouve E, et al. Growth Factors Levels Determine Efficacy of Platelets Rich Plasma Injection in Knee Osteoarthritis: A Randomized Double Blind Noninferiority Trial Compared With Viscosupplementation. Arthroscopy 2018;34:1530-40 e2.
88. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med 1982;10:150-4.
89. Marshall KW. Intra-articular hyaluronan therapy. Curr Opin Rheumatol 2000;12:468-74.
90. Migliore A, Integlia D, Pompilio G, Di Giuseppe F, Aru C, Brown T. Cost-effectiveness and budget impact analysis of viscosupplementation with hylan G-F 20 for knee and hip osteoarthritis. Clinicoecon Outcomes Res 2019;11:453-64.
91. Nabi BN, Sedighinejad A, Mardani-Kivi M, et al. Comparing the Effectiveness of Intra-articular Platelet-Rich Plasma and Corticosteroid Injection under Ultrasound Guidance on Pain Control of Knee Osteoarthritis. Iran Red Crescent Med J 2018;20:e62157.
92. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011;70:1957-62.
93. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014;43:701-12.
94. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2013;39:1-19.
95. Nunes-Tamashiro JC, Natour J, Ramuth FM, et al. Intra-articular injection with platelet-rich plasma compared to triamcinolone hexacetonide or saline solution in knee osteoarthritis: A double blinded randomized controlled trial with one year follow-up. Clinical rehabilitation 2022;36:900-15.
96. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
97. Ornetti P, Dougados M, Paternotte S, Logeart I, Gossec L. Validation of a numerical rating scale to assess functional impairment in hip and knee osteoarthritis: comparison with the WOMAC function scale. Ann Rheum Dis 2011;70:740-6.
98. Osteoarthritis Action Alliance TARCatUoNC. OA Prevalence and Burden2021.
99. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Ann Intern Med 1992;116:78-84.
100. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. The American journal of sports medicine 2013;41:356-64.
101. Petrella RJ, Decaria J, Petrella MJ. Long term efficacy and safetyof a combined low and highmolecular weight hyaluronicacid in the treatment of osteoarthritis of the knee. Rheumatology Reports 2011;3:16-21.

102. Petterson SC, Plancher KD. Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: a multicenter, double-blind, randomized, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2019;27:1992-2002.
103. Phul SH, Mobushir M, Jilani RUA, Khan IS, Malik H, Jan G. Comparison of intra-articular steroids injection versus platelets rich plasma injection in patients with osteoarthritic knee joints. Pakistan Journal of Medical and Health Sciences 2018;12:931-4.
104. Pishgahi A, Abolhasan R, Shakouri SK, et al. Effect of dextrose prolotherapy, platelet rich plasma and autologous conditioned serum on knee osteoarthritis: A randomized clinical trial. Iranian Journal of Allergy, Asthma and Immunology 2020;19:243-52.
105. Primorac D, Molnar V, Rod E, et al. Knee Osteoarthritis: A Review of Pathogenesis and State-Of-The-Art Non-Operative Therapeutic Considerations. Genes (Basel) 2020;11.
106. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006;14:163-70.
107. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, et al. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. BMC Musculoskelet Disord 2021;22:134.
108. Raeissadat SA, Ghorbani E, Taheri MS, et al. MRI changes after platelet rich plasma injection in knee osteoarthritis (Randomized clinical trial). Journal of Pain Research 2020;13:65-73.
109. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: Platelet-rich plasma (PRP) versus hyaluronic acid (A one-year randomized clinical trial). Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2015;8.
110. Rahimzadeh P, Imani F, Faiz SHR, Entezary SR, Zamanabadi MN, Alebouyeh MR. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clinical Interventions in Aging 2018;13:73-9.
111. Rayegani SM, Raeissadat SA, Taheri MS, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthopedic Reviews 2014;6:112-7.
112. Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage 2002;10:506-17.
113. Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum 2007;57:1410-8.
114. Reyes-Sosa R, Lugo-Radillo A, Cruz-Santiago L, Garcia-Cruz CR, Mendoza-Cano O. Clinical comparison of platelet-rich plasma injection and daily celecoxib administration in the treatment of early knee osteoarthritis: A randomized clinical trial. J Appl Biomed 2020;18:41-5.
115. Rezasoltani Z, Azizi S, Najafi S, Sanati E, Dadarkhah A, Abdorrazaghi F. Physical therapy, intra-articular dextrose prolotherapy, botulinum neurotoxin, and hyaluronic acid for knee osteoarthritis: randomized clinical trial. Int J Rehabil Res 2020;43:219-27.
116. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998;28:88-96.
117. Rosen J, Niazi F, Dysart S. Cost-Effectiveness of Treating Early to Moderate Stage Knee Osteoarthritis with Intra-articular Hyaluronic Acid Compared to Conservative Interventions. Adv Ther 2020;37:344-52.

118. Rosen J, Sancheti P, Fierlinger A, Niazi F, Johal H, Bedi A. Cost-Effectiveness of Different Forms of Intra-Articular Injections for the Treatment of Osteoarthritis of the Knee. Adv Ther 2016;33:998-1011.
119. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012;157:180-91.
120. Saccomanno MF, Donati F, Careri S, Bartoli M, Severini G, Milano G. Efficacy of intra-articular hyaluronic acid injections and exercise-based rehabilitation programme, administered as isolated or integrated therapeutic regimens for the treatment of knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2016;24:1686-94.
121. Salmon JH, Rat AC, Charlot-Lambrecht I, Eschard JP, Jolly D, Fautrel B. Cost Effectiveness of Intra-Articular Hyaluronic Acid and Disease-Modifying Drugs in Knee Osteoarthritis. Pharmacoeconomics 2018;36:1321-31.
122. Samson DJ, Grant MD, Ratko TA, Bonnell CJ, Ziegler KM, Aronson N. Treatment of primary and secondary osteoarthritis of the knee. Evid Rep Technol Assess (Full Rep) 2007:1-157.
123. Samuelson EM, Ebel JA, Reynolds SB, Arnold RM, Brown DE. The Cost-Effectiveness of Platelet-Rich Plasma Compared With Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis. Arthroscopy - Journal of Arthroscopic and Related Surgery 2020;36:3072-8.
124. Sanchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy 2012;28:1070-8.
125. Schunemann HJ, Tugwell P, Reeves BC, et al. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. Res Synth Methods 2013;4:49-62.
126. Sdeek M, Sabry D, El-Sdeek H, Darweash A. Intra-articular injection of Platelet rich plasma versus Hyaluronic acid for moderate knee osteoarthritis. A prospective, double-blind randomized controlled trial on 189 patients with follow-up for three years. Acta Orthop Belg 2021;87:729-34.
127. Simental-Mendía M, Vílchez-Cavazos JF, Peña-Martínez VM, Said-Fernández S, Lara-Arias J, Martínez-Rodríguez HG. Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Archives of Orthopaedic and Trauma Surgery 2016;136:1723-32.
128. Singh JA, Luo R, Landon GC, Suarez-Almazor M. Reliability and clinically important improvement thresholds for osteoarthritis pain and function scales: a multicenter study. J Rheumatol 2014;41:509-15.
129. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review No. 227. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC009. Rockville, MD2020 April.
130. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. Rockville, MD2018 June.
131. Skou ST, Roos EM. Physical therapy for patients with knee and hip osteoarthritis: supervised, active treatment is current best practice study. Clin Exp Rheumatol 2020;38:1036.
132. StataCorp. Stata Statistical Software: Release 14. College Station, TX. 2015.
133. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

134. Strand V, Baraf HS, Lavin PT, Lim S, Hosokawa H. Effectiveness and Safety of a Multicenter Extension and Retreatment Trial of Gel-200 in Patients with Knee Osteoarthritis. Cartilage 2012;3:297-304.
135. Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis Cartilage 2012;20:350-6.
136. Strand V, Kelman A. Outcome measures in osteoarthritis: randomized controlled trials. Curr Rheumatol Rep 2004;6:20-30.
137. Strand V, Lim S, Takamura J. Evidence for safety of retreatment with a single intra-articular injection of Gel-200 for treatment of osteoarthritis of the knee from the double-blind pivotal and open-label retreatment clinical trials. BMC Musculoskelet Disord 2016;17:240.
138. Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. JAMA 2014;311:405-11.
139. Szwedowski D, Szczepanek J, Paczesny L, et al. The Effect of Platelet-Rich Plasma on the Intra-Articular Microenvironment in Knee Osteoarthritis. Int J Mol Sci 2021;22.
140. Takamura J, Seo T, Strand V. A Pooled Analysis of Two Multicenter, Randomized Controlled Trials of a Single Intra-articular Injection of Gel-200 for Treatment of Osteoarthritis of the Knee. Clin Med Insights Arthritis Musculoskelet Disord 2018;11:1179544118773068.
141. Takamura J, Seo T, Strand V. A Single Intra-Articular Injection of Gel-200 for Treatment of Symptomatic Osteoarthritis of the Knee Is More Effective than Phosphate Buffered Saline at 6 Months: A Subgroup Analysis of a Multicenter, Randomized Controlled Trial. Cartilage 2019;10:417-22.
142. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-Articular, Single-Shot Hylan G-F 20 Hyaluronic Acid Injection Compared with Corticosteroid in Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial. J Bone Joint Surg Am 2016;98:885-92.
143. Tavassoli M, Janmohammadi N, Hosseini A, Khafri S, Esmaeilnejad-Ganji SM. Single- and double-dose of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: A randomized controlled trial. World J Orthop 2019;10:310-26.
144. Thomas T, Amouroux F, Vincent P. Intra articular hyaluronic acid in the management of knee osteoarthritis: Pharmaco-economic study from the perspective of the national health insurance system. PLoS One 2017;12:e0173683.
145. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthritis Cartilage 2002;10:518-27.
146. Tuong B, White J, Louis L, Cairns R, Andrews G, Forster BB. Get a kick out of this: the spectrum of knee extensor mechanism injuries. Br J Sports Med 2011;45:140-6.
147. Turkiewicz A, Petersson IF, Bjork J, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. Osteoarthritis Cartilage 2014;22:1826-32.
148. Vaishya R, Pandit R, Agarwal AK, Vijay V. Intra-articular hyaluronic acid is superior to steroids in knee osteoarthritis: A comparative, randomized study. J Clin Orthop Trauma 2017;8:85-8.
149. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. Arthroscopy 2013;29:1635-43.
150. Villanova-Lopez MM, Nunez-Nunez M, Fernandez-Prieto D, et al. Randomized, double-blind, controlled trial, phase III, to evaluate the use of platelet-rich plasma versus hyaluronic acid in hip coxarthrosis. Rev Esp Cir Ortop Traumatol (Engl Ed) 2020;64:134-42.

151. Viswanathan M, Ansari MT, Berkman ND, et al. Chapter 9: Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
152. Walker K, Basehore BM, Goyal A, Zito PM. Hyaluronic Acid. StatPearls. Treasure Island (FL)2023.
153. Wallach JD, Sullivan PG, Trepanowski JF, Sainani KL, Steyerberg EW, Ioannidis JP. Evaluation of Evidence of Statistical Support and Corroboration of Subgroup Claims in Randomized Clinical Trials. JAMA Intern Med 2017;177:554-60.
154. Wang Z, Wang R, Xiang S, et al. Assessment of the effectiveness and satisfaction of platelet-rich plasma compared with hyaluronic acid in knee osteoarthritis at minimum 7-year follow-up: A post hoc analysis of a randomized controlled trial. Front Bioeng Biotechnol 2022;10:1062371.
155. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
156. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
157. Ware JEKM, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, New England Medical Center; 1994.
158. Wu YT, Hsu KC, Li TY, Chang CK, Chen LC. Effects of Platelet-Rich Plasma on Pain and Muscle Strength in Patients With Knee Osteoarthritis. Am J Phys Med Rehabil 2018;97:248-54.
159. Yaradilmis YU, Demirkale I, Safa Tagral A, Caner Okkaoglu M, Ates A, Altay M. Comparison of two platelet rich plasma formulations with viscosupplementation in treatment of moderate grade gonarthrosis: A prospective randomized controlled study. J Orthop 2020;20:240-6.
160. Yen ZS, Lai MS, Wang CT, et al. Cost-effectiveness of treatment strategies for osteoarthritis of the knee in Taiwan. J Rheumatol 2004;31:1797-803.
161. Yurtbay A, Say F, Çinka H, Ersoy A. Multiple platelet-rich plasma injections are superior to single PRP injections or saline in osteoarthritis of the knee: the 2-year results of a randomized, double-blind, placebo-controlled clinical trial. Arch Orthop Trauma Surg 2022;142:2755-68.
162. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. Arthritis Res Ther 2015;17:51.
163. Zhao X, Shah D, Gandhi K, et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. Osteoarthritis Cartilage 2019;27:1618-26.
164. Zhou Y, Li H, Cao S, et al. Clinical Efficacy of Intra-Articular Injection with P-PRP Versus that of L-PRP in Treating Knee Cartilage Lesion: A Randomized Controlled Trial. Orthop Surg 2023;15:740-9.