Washington State Health Care Authority

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

Final Appendices

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

Aggregate Analytics, Inc.

Final Appendices

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Table of Contents

APPENDIX A. ALGORITHM FOR ARTICLE SELECTION....1
APPENDIX B. SEARCH STRATEGIES....2
APPENDIX C. EXCLUDED ARTICLES....4
APPENDIX D. RISK OF BIAS, STRENGTH OF EVIDENCE, AND QHES DETERMINATION....21
APPENDIX E. STUDY QUALITY: RISK OF BIAS EVALUATION OF RCTS AND QHES OF ECONOMIC STUDIES 27
APPENDIX F. DATA ABSTRACTION OF INCLUDED STUDIES....46
APPENDIX G. DETAILED CHARACTERISTICS AND DEMOGRAPHIC TABLES....47
APPENDIX H. ADDITIONAL FOREST PLOTS....169
APPENDIX I. ECONOMIC TABLES....180
APPENDIX J. DEFINITIONS FOR MAGNITUDE OF EFFECTS....196
APPENDIX K. FDA APPROVED HA BRANDS/FORMULATIONS....198
APPENDIX L. CLINICAL EXPERT PEER REVIEW....199
APPENDIX M. PUBLIC COMMENT....200
APPENDIX N. APPENDIX REFERENCES....201

Appendix Tables

APPENDIX TABLE B1: PUBMED SEARCH STRATEGY FOR HA* 2
APPENDIX TABLE B2: PUBMED SEARCH STRATEGY FOR PRP* 2
APPENDIX TABLE C1. LIST OF EXCLUDED ARTICLES 4
APPENDIX TABLE C2. LIST OF EXCLUDED ARTICLES PRIOR TO 2012 15
APPENDIX TABLE D1. DEFINITION OF THE RISK OF BIAS CATEGORIES FOR INDIVIDUAL STUDIES OF TESTING....21
APPENDIX TABLE D2: ASSESSMENT OF ROB FOR INDIVIDUAL STUDIES OF THERAPY....21
APPENDIX TABLE D3. RATING OVERALL CONFIDENCE IN THE RESULTS OF THE REVIEW (DETTORI 2020). 22
APPENDIX TABLE D4. ASSESSMENT OF QUALITY OF HEALTH ECONOMIC STUDIES CRITERIA 24
APPENDIX TABLE D5. EXAMPLE METHODOLOGY OUTLINE FOR DETERMINING OVERALL STRENGTH OF EVIDENCE (SOE): 26
APPENDIX TABLE E1. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS PLACEBO 27
APPENDIX TABLE E2. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS STEROID28
APPENDIX TABLE E3. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS NSAID...29

APPENDIX TABLE E4. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS USUAL CARE....29

APPENDIX TABLE E5. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS PHYSICAL THERAPY AND PROLOTHERAPY (SAME STUDY) 30

APPENDIX TABLE E6. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS EXERCISE 30

APPENDIX TABLE E7. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING PRP VERSUS PLACEBO THAT RANDOMIZED BY PARTICIPANT 32

APPENDIX TABLE E8. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS* EVALUATING PRP VERSUS PLACEBO THAT RANDOMIZED BY KNEES....33

APPENDIX TABLE E9. RISK OF BIAS ASSESSMENT: KNEE OA RCTS EVALUATING PRP VERSUS STEROID.34

APPENDIX TABLE E10. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING PRP VERSUS ORAL ANALGESICS....35

APPENDIX TABLE E11. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING PRP VERSUS EXERCISE WITH OR WITHOUT TENS 36

APPENDIX TABLE E12. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS* EVALUATING PRP (PLUS EXERCISE) VERSUS EXERCISE ALONE THAT RANDOMIZED BY KNEES....37

APPENDIX TABLE E13. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING PRP VERSUS PT/REHABILITATION....38

APPENDIX TABLE E14. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING PRP VERSUS PROLOTHERAPY....38

APPENDIX TABLE E15. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING PRP VERSUS PRP ...39

APPENDIX TABLE E16. RISK OF BIAS ASSESSMENT: HIP OA TRIALS EVALUATING HA VERSUS PRP 40

APPENDIX TABLE E17. RISK OF BIAS ASSESSMENT: HIP OA TRIALS EVALUATING HA VERSUS PLACEBO41

APPENDIX TABLE E18. RISK OF BIAS ASSESSMENT: HIP OA TRIALS EVALUATING HA VERSUS STEROID 42

APPENDIX TABLE E19. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS PRP.....42

APPENDIX TABLE E20. RISK OF BIAS ASSESSMENT: KNEE OA TRIALS EVALUATING HA VERSUS PRP, CONTINUED. 43

APPENDIX TABLE E21. QHES ASSESSMENT OF U.S. COST-EFFECTIVENESS STUDIES 44

APPENDIX TABLE E22. QHES ASSESSMENT OF NON-U.S. COST-EFFECTIVENESS STUDIES....45

APPENDIX TABLE G1. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO PRP 47

APPENDIX TABLE G2. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO PLACEBO 57

APPENDIX TABLE G3. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO STEROIDS 81

APPENDIX TABLE G4. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO ORAL ANALGESICS 86

APPENDIX TABLE G5. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO USUAL CARE....86

APPENDIX TABLE G6. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO PHYSICAL THERAPY AND PROLOTHERAPY 88

APPENDIX TABLE G7. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO EXERCISE 88

APPENDIX TABLE G8. PATIENT CHARACTERISTICS OF STUDIES COMPARING HA TO OTHER TREATMENTS FOR HIP OSTEOARTHRITIS 90

APPENDIX TABLE G9. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO PLACEBO 96

APPENDIX TABLE G10. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO STEROIDS 107

APPENDIX TABLE G11. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO OTHER TREATMENTS FOR ORAL ANALGESICS 118

APPENDIX TABLE G12. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO EXERCISE 121

APPENDIX TABLE G13. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO PHYSIOTHERAPY 127

APPENDIX TABLE G14. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO PROLOTHERAPY 128

APPENDIX TABLE G15. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO OTHER QUANTITIES OF PRP 129

APPENDIX TABLE G16. PATIENT CHARACTERISTICS OF STUDIES COMPARING PRP TO OTHER TREATMENTS FOR KNEE OSTEOARTHRITIS (KNEES RANDOMIZED) 139

APPENDIX TABLE G17A. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PRP FOR KNEE OSTEOARTHRITIS (1-3 OF 11) 142

APPENDIX TABLE G17B. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PRP FOR KNEE OSTEOARTHRITIS (4-6 OF 11) 144

APPENDIX TABLE G17C. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PRP FOR KNEE OSTEOARTHRITIS (7-9 OF 11) 145

APPENDIX TABLE G17D. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PRP FOR KNEE OSTEOARTHRITIS (10-11 OF 11) 146

APPENDIX TABLE G18A. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PLACEBO FOR KNEE OSTEOARTHRITIS (1-3 OF 9) 147

APPENDIX TABLE G18B. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PLACEBO FOR KNEE OSTEOARTHRITIS (4-6 OF 9) 148

APPENDIX TABLE G18C. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO PLACEBO FOR KNEE OSTEOARTHRITIS (7-9 OF 9) 149

APPENDIX TABLE G19A. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO STEROID FOR KNEE OSTEOARTHRITIS (1-3 OF 6) 150

APPENDIX TABLE G19B. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO STEROID FOR KNEE OSTEOARTHRITIS (4-6 OF 6) 151

APPENDIX TABLE G20. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING HA TO NSAIDS FOR KNEE OSTEOARTHRITIS (1-2 OF 2) 152

APPENDIX TABLE G21A. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PLACEBO FOR KNEE OSTEOARTHRITIS (1-3 OF 9)....153

APPENDIX TABLE G21B. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PLACEBO FOR KNEE OSTEOARTHRITIS (4-5 OF 9)....154

APPENDIX TABLE G21C. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PLACEBO FOR KNEE OSTEOARTHRITIS (6-7 OF 9)....155

APPENDIX TABLE G21D. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PLACEBO FOR KNEE OSTEOARTHRITIS (8 OF 9)....156

APPENDIX TABLE G21E. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PLACEBO FOR KNEE OSTEOARTHRITIS (9 OF 9)....157

APPENDIX TABLE G22. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PLACEBO FOR KNEE OSTEOARTHRITIS (1-3 OF 3) (KNEES RANDOMIZED)....158

APPENDIX TABLE G23A. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO STEROID FOR KNEE OSTEOARTHRITIS (1-3 OF 9)....159

APPENDIX TABLE G23B. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO STEROID FOR KNEE OSTEOARTHRITIS (4-6 OF 9)....161

APPENDIX TABLE G23C. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO STEROID FOR KNEE OSTEOARTHRITIS (7-9 OF 9)....162

APPENDIX TABLE G24. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO ORAL ANALGESICS FOR KNEE OSTEOARTHRITIS (1-3 OF 3)....163

APPENDIX TABLE G25. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO EXERCISE FOR KNEE OSTEOARTHRITIS (1-3 OF 3)....164

APPENDIX TABLE G26. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO EXERCISE FOR KNEE OSTEOARTHRITIS (1 OF 1) (KNEES RANDOMIZED)....165

APPENDIX TABLE G27A. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PRP BY NUMBER OF INJECTIONS FOR KNEE OSTEOARTHRITIS (1-3 OF 6) 166

APPENDIX TABLE G27B. PATIENT SUMMARY DEMOGRAPHICS IN STUDIES COMPARING PRP TO PRP BY NUMBER OF INJECTIONS FOR KNEE OSTEOARTHRITIS (4-6 OF 6) 168

FIGURE H1. WOMAC PHYSICAL FUNCTION SCORES (0-68 SCALE): COMPARISON OF HA AND PRP EXCLUDING OUTLIERS AT SHORT TERM (TAVASSOLI) AND LONG TERM (LANA)....169

FIGURE H2. WOMAC PAIN SUBSCALE (0-20) SCORES: HA VERSUS PRP FOLLOWING EXCLUSION OF EXTREME OUTLIER (LANA)....170

FIGURE H3. VAS PAIN SCORES (0-10) SCORES: HA VERSUS PRP FOLLOWING EXCLUSION OF EXTREME OUTLIER (LANA)....171

FIGURE H4. PRP VS. PLACEBO: WOMAC PHYSICAL FUNCTION – SENSITIVITY ANALYSIS REMOVING OF PATEL SHORT TERM AND DÓRIO INTERMEDIATE TERM (OUTLIERS)....172

FIGURE H5. PRP VS. PLACEBO: KOOS ADL – SENSITIVITY ANALYSIS REMOVING OF YURTBAY (OUTLIER) INTERMEDIATE AND LONG TERM 173

FIGURE H6. PRP VS. PLACEBO: KOOS SPORTS AND RECREATION – SENSITIVITY ANALYSIS REMOVING OF YURTBAY (OUTLIER) INTERMEDIATE AND LONG TERM 174

FIGURE H7. PRP VS. PLACEBO: WOMAC PAIN – SENSITIVITY ANALYSIS REMOVING OF PATEL SHORT TERM AND DÓRIO INTERMEDIATE TERM (OUTLIERS) 175

FIGURE H8. PRP VS. PLACEBO: KOOS PAIN – SENSITIVITY ANALYSIS REMOVING OF YURTBAY (OUTLIER) INTERMEDIATE AND LONG TERM 176

FIGURE H9. PRP VS. PLACEBO: WOMAC TOTAL – SENSITIVITY ANALYSIS REMOVING OF PATEL SHORT TERM AND DÓRIO INTERMEDIATE TERM (OUTLIERS) 177

FIGURE H10. PRP VS. PLACEBO: KOOS QOL – SENSITIVITY ANALYSIS REMOVING OF YURTBAY (OUTLIER) INTERMEDIATE AND LONG TERM 178

FIGURE H11. PRP VS. PLACEBO: SF-36 PCS AND MCS SCORES 179

APPENDIX TABLE I1. U.S. COST-EFFECTIVENESS STUDY TABLES 180

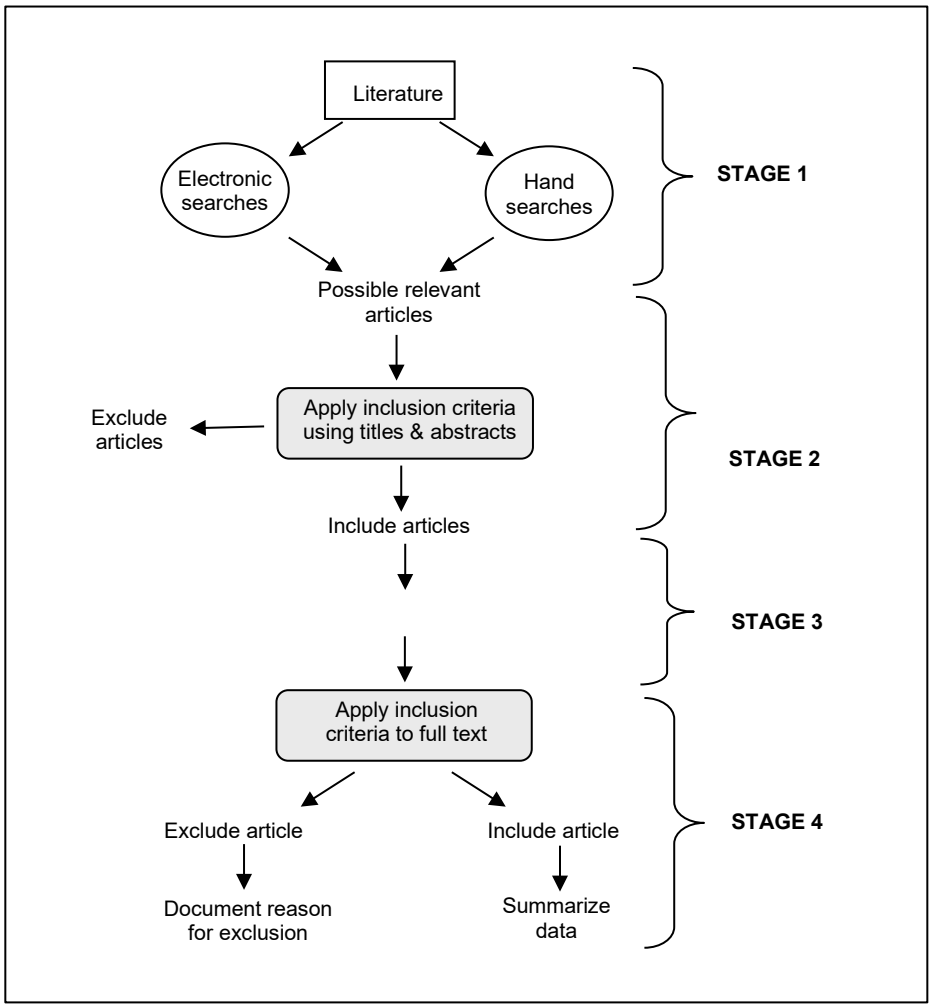
APPENDIX TABLE I2. NON-U.S. COST-EFFECTIVENESS STUDY TABLES 188

TABLE J1. DEFINITIONS FOR MAGNITUDE OF EFFECTS, BASED ON MEAN BETWEEN-GROUP DIFFERENCES 196

TABLE J2. DEFINITIONS OF EFFECT SIZES 197

TABLE K1. FDA APPROVED HA BRANDS/FORMULATIONS 198

APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources. In addition, hand-searching of included studies was performed. 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.

Electronic Database Searches
The following databases have been searched for relevant information:

Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Database of Reviews of Effectiveness (Cochrane Library)
PubMed
ClinicalTrials.gov

Additional Economics, Clinical Guideline and Gray Literature Databases
AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google

Appendix Table B1: PubMed Search Strategy for HA*
Search period: through 1/1/2013 – 12/31/2022

1.	(viscosupplementation OR hyaluronic acid OR HA OR hyaluron* OR hylan OR Hyalgan OR Synvisc OR Supartz OR Monovisc OR Orthovisc OR Euflexxa OR Gel-One)
2.	("Osteoarthritis"[Mesh] OR "degenerative joint" OR "degenerative arthritis")
3.	#1 and #2
4.	(randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))
5.	#3 and #4
6.	#3 and #4 Filters: English, Abstract
7.	#3 Filters: English Abstract
8.	#7 NOT (Cadaver*[tw] OR Case Reports[Publication Type] OR Infant[mh] OR rat[tw] OR rats[tw] OR mouse[tw] OR mice[tw] OR dog[tw] or dogs[tw])

*Adapted from prior report

Appendix Table B2: PubMed Search Strategy for PRP*
Search period: through 1/1/2015 – 12/31/2022

1.	("Blood Platelets"[Mesh]) OR ("Platelet-Rich Plasma"[Mesh] OR "Platelet Transfusion"[Mesh] OR "Platelet Count"[Mesh])
2.	"Platelet concentrate" OR "Platelet-rich" OR "Platelet rich" OR "Platelet-leukocyte" OR "Platelet leukocyte" OR (platelet AND (gel* OR concentrate*) OR "buffy layer"
3.	#1 OR #2

4.	"Blood Component Transfusion"[Mesh] OR "Blood Transfusion, Autologous"[Mesh] OR "whole blood"[TIAB] OR "blood injection*"[TIAB] OR "autologous blood injection*"[TIAB] OR "blood injections"[TIAB]
5.	#3 OR 4
6.	("Osteoarthritis"[Mesh])
7.	(osteoarthritis[TIAB] OR “osteoarthritis" OR "degenerative joint" OR "degenerative arthritis")
8.	#6 OR #7
9.	#5 AND #8
10.	#5 AND #8 Filters: Humans; Abstract; English
11.	#10 NOT (Cadaver*[tw] OR Case Reports[Publication Type] OR Infant[mh] OR rat[tw] OR rats[tw] OR mouse[tw] OR mice[tw] OR dog[tw] or dogs[tw])

*Adapted from prior report

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

Appendix Table C1. List of Excluded Articles

	Citation	Reason for exclusion after full-text review
1.	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 random- ized, double-blind, triple-parallel, placebo-controlled clinical trial. Arthroscopy. 2019;35(1):106-117.	HA arm excluded only: Non-FDA approved HA product/brand
2.	Huang Y, Liu X, Xu X, Liu J (2019) Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis: a prospective randomized controlled study. Ortho-pade 48:239–247. https://doi. org/ 10. 1007/ s00132- 018- 03659-5	HA arm excluded only: HA product/brand NR (unclear if FDA approved)
3.	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;20:240-246.	HA arm excluded only: Non-FDA approved HA product/brand
4.	Yu, W.; Xu, P.; Huang, G.; Liu, L. Clinical therapy of hyaluronic acid combined with platelet-rich plasma for the treatment of knee osteoarthritis. Exp. Ther. Med.2018,16, 2119–2125. [CrossRef]	Ineligible intervention/comparator: HA product/brand NR (unclear if FDA approved); no results provided for Placebo group so cannot compare with PRP vs. placebo
5.	Bansal H, Leon J, Pont JL, Wilson DA, Bansal A, Agarwal D, et al. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: correct dose critical for long term clinical efficacy. Sci Rep 2021;11:3971. https://doi.org/10.1038/s41598-021- 83025-2. Erratum in: Sci Rep. 2021;11.	Ineligible intervention/comparator: HA product/brand NR (unclear if FDA approved)
6.	Park YB, Kim JH, Ha CW, Lee DH. Clinical Efficacy of Platelet-Rich Plasma Injection and Its Association With Growth Factors in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized Double-Blind Controlled Clinical Trial As Compared With Hyaluronic Acid. Am J Sports Med. 2021 Feb;49(2):487-496. doi: 10.1177/0363546520986867. PMID: 33523756.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
7.	Di Martino A, Di Matteo B, Papio T, Tentoni F, Selleri F, Cenac-chi A, Kon E, Filardo G (2019) Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. Am J Sports Med. 2019 Feb;47(2):347–354. PMID: 30545242 DOI: 10.1177/0363546518814532	Ineligible intervention/comparator: Non-FDA approved HA product/brand
8.	Ahmad HS, Farrag SE, Okasha AE, Kadry AO, Ata TB, Monir AA, Shady I (2018) Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma	Ineligible intervention/comparator: HA product/brand NR (unclear if FDA approved)

	Citation	Reason for exclusion after full-text review
	treatment for knee osteoarthritis. Int J Rheum Dis 21:960–966. https:// doi. org/ 10. 1111/ 1756- 185X. 13315	
9.	Duymus TM, Mutlu S, Dernek B et al (2017) Choice of intra-articular injection in treatment of knee osteoarthritis: plate-let-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc 25:485–492. https:// doi. org/ 10. 1007/s00167- 016- 4110-5	Ineligible intervention/comparator: Non-FDA approved HA product/brand
10.	Su K, Bai Y, Wang J, Zhang H, Liu H, Ma S. Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis. Clin Rheumatol 2018;37:1341e50. https://doi.org/10.1007/s10067-018-3985-6.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
11.	Montanez-Heredia E, Irizar S, Huertas PJ, Otero E, Del Valle M, Prat I, Diaz-Gallardo MS, Peran M, Marchal JA, Hernandez-Lamas Mdel C (2016) Intra-articular injections of platelet-rich plasma versus hyaluronic acid in the treatment of osteoarthritic knee pain: a randomized clinical trial in the context of the Spanish national health care system. Int J Mol Sci. https:// doi. org/ 10.3390/ ijms1 70710 64	Ineligible intervention/comparator: Non-FDA approved HA product/brand
12.	Papalia R, Zampogna B, Russo F, Vasta S, Tirindelli M, Nobile C, et al. Comparing hybrid hyaluronic acid with PRP in end career athletes with degenerative cartilage lesions of the knee. J Biol Regul Homeost Agents. 2016;30(4 Suppl. 1):17-23.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
13.	Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E (2015) Platelet-rich plasma intra-articular knee injections show no superiority versus visco-supplementation: a randomized controlled trial. Am J Sports Med 43:1575–1582. https:// doi. org/ 10. 1177/ 03635 46515 582027	Ineligible intervention/comparator: Non-FDA approved HA product/brand
14.	Say F, Gürler D, Yener K, Bülbül M, Malkoc M. Plateletrich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chir Orthop Traumatol Cech 2013;80:278-283.	Ineligible study design: Not a RCT (Pro NRSI)
15.	Cerza F, Carni S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M (2012) Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 40:2822–2827. https:// doi. org/ 10. 1177/ 03635 46512 461902	Ineligible intervention/comparator: autologous conditioned plasma
16.	Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A (2012) Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil 91(5):411–417. https://doi.org/10.1097/PHM.0b013e3182aab72	Ineligible intervention/comparator: Non-FDA approved HA product/brand
17.	Kon, E.; Mandelbaum, B.; Buda, R.; Filardo, G.; Delcogliano, M.; Timoncini, A.; Fornasari, P.M.; Giannini, S.; Marcacci, M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From	Ineligible study design: Not a RCT (Pro NRSI)

	Citation	Reason for exclusion after full-text review
	early degeneration to osteoarthritis.Arthroscopy2011,27, 1490–1501. [CrossRef] [PubMed]	
18.	Henrotin Y, Berenbaum F, Chevalier X, Marty M, Richette P, Rannou F: Reduction of the serum levels of a specific biomarker of cartilage degradation (Coll2-1) by hyaluronic acid (KARTILAGE® CROSS) compared to placebo in painful knee osteoarthritis patients: the EPIKART study, a pilot prospective comparative randomized. BMC Musculoskelet Disord. 2017, 18:222.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
19.	van der Weegen W, Wullems JA, Bos E, Noten H, Drumpt RAM van. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. J Arthroplasty 2015;30:754–757.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
20.	Kosuwon W. Determination of Cartilage Volume Using MRI in Patients with Knee Osteoarthritis: Efficacy Study of 25 Milligrams of Sodium Hyaluronate (2.5 Ml) Versus Placebo. Clin Exp Pharmacol 2012;02.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
21.	Siddharth R, Harleen U. A prospective, randomized trial on comparative study of intrarticular hyaluronic acid with corticosteroid injections for the treatment of osteoarthritis of the knee joint. Indian J Public Heal Res Dev 2017;8:14–18.	Ineligible intervention/comparator: HA product/brand NR (unclear if FDA approved)
22.	Trueba Davalillo CÁ, Trueba Vasavilbaso C, Navarrete Álvarez JM, Coronel Granado P, García Jiménez OA, Gimeno Del Sol M, Gil Orbezo F. Clinical efficacy of intra-articular injections in knee osteoarthritis: a prospective randomized study comparing hyaluronic acid and betamethasone. Open Access Rheumatol. 2015 Jan 9;7:9-18. doi: 10.2147/OARRR.S74553. PMID: 27790040; PMCID: PMC5045121.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
23.	Housman L, Arden N, Schnitzer TJ, et al. Intra-articular hylastan versus steroid for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2014;22:1684-1692.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
24.	Wang SZ, Wu DY, Chang Q, Guo YD, Wang C, Fan WM: Intra-articular, single-shot co-injection of hyaluronic acid and corticosteroids in knee osteoarthritis: a randomized controlled trial. Exp Ther Med. 2018, 16:1928-34.	Ineligible intervention/comparator: HA combined with steroid
25.	Campos GC de, Rezende MU, Pailo AF, Frucchi R, Camargo OP. Adding triamcinolone improves viscosupplementation: a randomized clinical trial. Clin Orthop Relat Res 2013;471:613–620.	Ineligible intervention/comparator: HA combined with steroid
26.	Ishijima M, Nakamura T, Shimizu K, et al. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther. 2014;16(1):R18.	Ineligible intervention/comparator: HA product/brand NR (unclear if FDA approved)
27.	Hosseini B, Taheri M, Pourroustaei Ardekani R, et al: Periarticular hypertonic dextrose vs intraarticular hyaluronic acid injections: A comparison of two minimally invasive techniques in the treatment	Ineligible intervention/comparator: Non-FDA approved HA product/brand

	Citation	Reason for exclusion after full-text review
	of symptomatic knee osteoarthritis. Open Access Rheumatol2019;11:269–74	
28.	Hashemi SM, Madadi F, Razavi S, et al: Intra-articular hyaluronic acid injections vs .dextrose prolotherapy in the treatment of osteoarthritic knee pain. Tehran Univ Med J2012;70:119–25	Ineligible study design: Not in English
29.	Ip D, Fu NY: Can combined use of low-level lasers and hyaluronic acid injections prolong the longevity of degenerative knee joints?. Clin Interv Aging. 2015, 10:1255-8.	Ineligible intervention: multiple treatments: HA + physical therapy + low level laser
30.	Maheu E, Avouac B, Dreiser RL, Bardin T: A single intra-articular injection of 2.0% non-chemically modified sodium hyaluronate vs 0.8% hylan G-F 20 in the treatment of symptomatic knee osteoarthritis: a 6-month, multicenter, randomized, controlled non-inferiority trial. PLoS One. 2019, 14:e0226007.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
31.	Guo Y, Yang P, Liu L: Origin and efficacy of hyaluronan injections in knee osteoarthritis: randomized, double-blind trial. Med Sci Monit. 2018, 24:4728-37.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
32.	Sun SF, Hsu CW, Lin HS, Liou IH, Chen YH, Hung CL. Comparison of Single Intra-Articular Injection of Novel Hyaluronan (HYA-JOINT Plus) with Synvisc-One for Knee Osteoarthritis: A Randomized, Controlled, Double-Blind Trial of Efficacy and Safety. J Bone Joint Surg Am. 2017 Mar 15;99(6):462-471. doi: 10.2106/JBJS.16.00469. PMID: 28291178.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
33.	Petrella RJ, Emans PJ, Alleyne J, Dellaert F, Gill DP, Maroney M: Safety and performance of Hydros and Hydros-TA for knee osteoarthritis: a prospective, multicenter, randomized, double-blind feasibility trial. BMC Musculoskelet Disord. 2015, 16:57.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
34.	Ozcamdalli M, Misir A, Kizkapan TB, Uzun E, Duygulu F, Yazici C, Kafadar IH: Comparison of intra-articular injection of hyaluronic acid and N -acetyl cysteine in the treatment of knee osteoarthritis: a pilot study. Cartilage. 2019, 32:1143-54.	Ineligible intervention/comparator: N-acetyl cysteine
35.	Mochizuki T, Ikari K, Yano K, Okazaki K: Comparison of patient-reported outcomes of treatment with low- and intermediate molecular weight hyaluronic acid in Japanese patients with symptomatic knee osteoarthritis: a prospective, randomized, single-blind trial. Asia Pac J Sports Med Arthrosc Rehabil Technol. 2020, 21:22-6.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
36.	Bahrami MH, Raeissadat SA, Cheraghi M, Rahimi-Dehgolan S, Ebrahimpour A: Efficacy of single high- molecular-weight versus triple low-molecular-weight hyaluronic acid intra-articular injection among knee osteoarthritis patients. BMC Musculoskelet Disord. 2020, 21:550.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
37.	Gigis I, Fotiadis E, Nenopoulos A, Tsitas K, Hatzokos I: Comparison of two different molecular weight intra- articular injections of hyaluronic acid for the treatment of knee osteoarthritis. Hippokratia. 2016, 20:26-31.	Ineligible intervention/comparator: HA product/brand NR (unclear if FDA approved)

	Citation	Reason for exclusion after full-text review
38.	Berenbaum F, Grifka J, Cazzaniga S, D'Amato M, Giacovelli G, Chevalier X, Rannou F, Rovati LC, Maheu E. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis. 2012 Sep;71(9):1454-60. doi: 10.1136/annrheumdis-2011-200972. Epub 2012 Jan 31. PMID: 22294639; PMCID: PMC3414228.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
39.	Ha CW, Park YB, Choi CH, et al.: Efficacy and safety of single injection of cross-linked sodium hyaluronate vs. three injections of high molecular weight sodium hyaluronate for osteoarthritis of the knee: a double- blind, randomized, multi-center, non-inferiority study. BMC Musculoskelet Disord. 2017, 18:223.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
40.	Suppan VK, Wei CY, Siong TC, et al.: Randomized controlled trial comparing efficacy of conventional and new single larger dose of intra-articular viscosupplementation in management of knee osteoarthritis. J Orthop Surg (Hong Kong). 2017, 25:2309499017731627.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
41.	Camurcu Y, Sofu H, Ucpunar H et al (2018) Single-dose intra-articular corticosteroid injection prior to platelet-rich plasma injection resulted in better clinical outcomes in patients with knee osteoarthritis: A pilot study. J Back Musculoskelet Rehabil 31:603–610. https:// doi. org/ 10. 3233/ BMR- 171066	Ineligible study design: Not a RCT (Pro NRSI)
42.	Kesiktas, FN, Dernek B, Sen EI, et al. Comparison of the short-term results of single-dose intra-articular peptide with hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized study. Clin Rheumatol. 2020 Oct;29(10):3057-3064. PMID: 32358661.	Ineligible study design: <20 patients per arm
43.	Paterson KL, Nicholls M, Bennell KL, Bates D (2016) Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: a double-blind, randomized controlled pilot study. BMC Musculoskelet Disord 17:67. https:// doi. org/ 10. 1186/ s12891- 016- 0920-3	Ineligible study design: <20 patients per arm
44.	DeCaria JE, Montero-Odasso M, Wolfe D, Chesworth BM, Petrella RJ. The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: a randomized, controlled study. Arch Gerontol Geriatr 2012;55:310-315.	Ineligible study design: <20 patients per arm
45.	Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: An FDA-sanctioned, randomized, double- blind, placebo-controlled clinical trial. Am J Sports Med 2016;44:884-891.	Ineligible study design: <20 patients per arm
46.	Güvendi EU, Aşkin A, Güvendi G, Koçyiğit H. Comparison of efficiency between corticosteroid and platelet rich plasma injection therapies in patients with knee osteoarthritis. Arch Rheumatol. 2018;33(3):273-81.	Ineligible study design: <20 patients per arm
47.	Elgendy MH, Elsamahy SA, Mostafa MSEM, Hamza MSK. Efficacy of shockwave therapy versus intra-articular platelet-rich plasma	Ineligible study design: <20 patients per arm

	Citation	Reason for exclusion after full-text review
	injection in management of knee osteoarthritis: a randomized controlled trial. Int J Pharm Res 2020;12. https://doi.org/10.31838/ijpr/2020.12.04.589.	
48.	Simental-Mendía M, C. A. Acosta-Olivo, A. N. Hernández-Rodríguez et al., "Intraarticular injection of platelet-rich plasma in knee osteoarthritis: single versus triple application approach. Pilot study," Acta Reumatológica Portuguesa, vol. 44, no. 2, pp. 138–144, 2019.	Ineligible study design: <20 patients per arm
49.	Martin Martin LS, Massafra U, Bizzi E, Migliore A: A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint"). BMC Musculoskelet Disord. 2016, 17:94.	Ineligible intervention/comparator: "MD-Knee"
50.	Yoon S, Kang JJ, Kim J, Park S, Kim JM: Efficacy and safety of intra-articular injections of hyaluronic acid combined with polydeoxyribonucleotide in the treatment of knee osteoarthritis. Ann Rehabil Med. 2019, 43:204-14.	Ineligible intervention/comparator: HA combined with protein?
51.	Hong Z, Chen J, Zhang S, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: A double-blind randomized self- controlled trial. Int Orthop 2019;43:1123-1134.	Ineligible intervention/comparator: stromal vascular fraction
52.	Lu L, Dai C, Zhang Z, et al. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose- derived mesenchymal progenitor cells: A prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. Stem Cell Res Ther 2019;10:143.	Ineligible intervention/comparator: stem cells
53.	Matas J, Orrego M, Amenabar D, et al.: Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. Stem Cells Transl Med. 2019, 8:215-24.	Ineligible intervention/comparator: stem cells
54.	Raeissadat SA, Rayegani SM, Forogh B, Abadi PH, Moridnia M, Dehgolan SR: Intra-articular ozone or hyaluronic acid injection: which one is superior in patients with knee osteoarthritis? A 6-month randomized clinical trial. J Pain Res. 2018, 11:111-7.	Ineligible intervention/comparator: ozone
55.	Goncars V, Jakobsons E, Blums K, et al.: The comparison of knee osteoarthritis treatment with single-dose bone marrow-derived mononuclear cells vs. hyaluronic acid injections. Medicina (Kaunas). 2017, 53:101-8.	Ineligible intervention/comparator: stem cells
56.	Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, Orozco L, Soler R, Fuertes JJ, Huguet M, Sánchez A, García-Sancho J. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. Transplantation. 2015 Aug;99(8):1681-90. doi: 10.1097/TP.0000000000000678. PMID: 25822648.	Ineligible intervention/comparator: stem cells
57.	Lamo-Espinosa JM, Mora G, Blanco JF, et al.: Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of	Ineligible intervention/comparator: stem cells

	Citation	Reason for exclusion after full-text review
	knee osteoarthritis: long- term follow up of a multicenter randomized controlled clinical trial (phase I/II). J Transl Med. 2018, 16:213.	
58.	Giombini A, Menotti F, Di Cesare A, Giovannangeli F, Rizzo M, Moffa S, Martinelli F. Comparison between intrarticular injection of hyaluronic acid, oxygen ozone, and the combination of both in the treatment of knee osteoarthrosis. J Biol Regul Homeost Agents. 2016 Apr-Jun;30(2):621-5. PMID: 27358159.	Ineligible intervention/comparator: ozone
59.	Raeissadat SA, Gharooee Ahangar A, Rayegani SM, Minator Sajjadi M, Ebrahimpour A, Yavari P: Platelet-rich plasma-derived growth factor vs hyaluronic acid injection in the individuals with knee osteoarthritis: a one year randomized clinical trial. J Pain Res. 2020, 13:1699-711.	Ineligible intervention/comparator: plasma rich in growth factors
60.	Raeissadat SA, Rayegani SM, Ahangar AG, Abadi PH, Mojgani P, Ahangar OG: Efficacy of intra-articular injection of a newly developed plasma rich in growth factor (PRGF) versus hyaluronic acid on pain and function of patients with knee osteoarthritis: a single-blinded randomized clinical trial. Clin Med Insights Arthritis Musculoskelet Disord. 2017, 10:1179544117733452.	Ineligible intervention/comparator: plasma rich in growth factors
61.	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(10):1635-1643.	Ineligible intervention/comparator: plasma rich in growth factors
62.	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(8):1070-1078.	Ineligible intervention/comparator: plasma rich in growth factors
63.	Sun SF, Lin GC, Hsu CW, Lin HS, Liou IS, Wu SY. Comparing efficacy of intraarticular single crosslinked Hyaluronan (HYAJOINT Plus) and platelet-rich plasma (PRP) versus PRP alone for treating knee osteoarthritis. Sci Rep. 2021 Jan 8;11(1):140. doi: 10.1038/s41598-020-80333-x. PMID: 33420185; PMCID: PMC7794411.	Ineligible intervention/comparator: HA combined with PRP
64.	"Anz AW, Hubbard R, Rendos NK et al (2020) Bone marrow aspirate concentrate is equivalent to platelet-rich plasma for the treatment of knee osteoarthritis at 1 year: a prospective randomized trial. Orthop J Sport Med 8:232596711990095. https://doi.org/10.1177/2325967119900958	Ineligible intervention/comparator: bone marrow concentrate
65.	Lamo-Espinosa, J. M., Blanco, J. F., Sánchez, M., Moreno, V., Granero-Moltó, F., Sánchez-Guijo, F., ... & Prósper, F. (2020). Phase II multicenter randomized controlled clinical trial on the efficacy of intra-articular injection of autologous bone marrow mesenchymal stem cells with platelet rich plasma for the treatment of knee osteoarthritis. Journal of translational medicine, 18(1), 1-9.	Ineligible intervention/comparator: stem cells

	Citation	Reason for exclusion after full-text review
66.	Jacob G, Shetty V, Shetty S (2017) A study assessing intra-articular PRP vs PRP with HMW HA vs PRP with LMW HA in early knee osteoarthritis. J Arthrosc Jt Surg 4:65–71. https:// doi. org/ 10.1016/j. jajs. 2017. 08. 008	Ineligible intervention/comparator: HA combined with PRP
67.	Mendes, J. G., Natour, J., Nunes-Tamashiro, J. C., Toffolo, S. R., Rosenfeld, A., & Furtado, R. N. V. (2019). Comparison between intra-articular Botulinum toxin type A, corticosteroid, and saline in knee osteoarthritis: a randomized controlled trial. Clinical rehabilitation, 33(6), 1015-1026.	Ineligible intervention: botox (no HA or PRP arm)
68.	Ravaud, P., Moulinier, L., Giraudeau, B., Ayral, X., Guerin, C., Noel, E., ... & Dougados, M. (1999). Effects of joint lavage and steroid injection in patients with osteoarthritis of the knee: results of a multicenter, randomized, controlled trial. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 42(3), 475-482.	Ineligible intervention: lavage (no HA or PRP arm)
69.	Chao, J., Wu, C., Sun, B., Hose, M. K., Quan, A., Hughes, T. H., ... & Kalunian, K. C. (2010). Inflammatory characteristics on ultrasound predict poorer long term response to intraarticular corticosteroid injections in knee osteoarthritis. The Journal of rheumatology, 37(3), 650-655.	Ineligible intervention: steroid vs. placebo (no HA or PRP arm)
70.	McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, Ward RJ. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA. 2017 May 16;317(19):1967-1975. doi: 10.1001/jama.2017.5283. PMID: 28510679; PMCID: PMC5815012.	Ineligible intervention: steroid vs. placebo (no HA or PRP arm)
71.	Yavuz, U., Sökücü, S., Albayrak, A., & Öztürk, K. (2012). Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. Rheumatology international, 32, 3391-3396.	Ineligible intervention: steroid vs. placebo (no HA or PRP arm)
72.	Kon E, Engebretsen L, Verdonk P, Nehrer S, Filardo G. Clinical outcomes of knee osteoarthritis treated with an autologous protein solution injection: a 1-year pilot double-blinded randomized controlled trial. Am J Sports Med. 2018;46(1):171-80.	Ineligible intervention: autologous protein solution (no HA or PRP arm)
73.	Kuah D, Sivell S, Longworth T, James K, Guermazi A, Cicuttini F, Wang Y, Craig S, Comin G, Robinson D, Wilson J. Safety, tolerability and efficacy of intra-articular Progenza in knee osteoarthritis: a randomized double-blind placebo-controlled single ascending dose study. J Transl Med. 2018 Mar 6;16(1):49. doi: 10.1186/s12967-018-1420-z. PMID: 29510712; PMCID: PMC5840781.	Ineligible intervention: stem cells (no HA or PRP arm)
74.	Lopes de Jesus, C. C., Dos Santos, F. C., de Jesus, L. M. O. B., Monteiro, I., Sant'Ana, M. S. S. C., & Trevisani, V. F. M. (2017). Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study. PloS one, 12(7), e0179185.	Ineligible intervention: ozone (no HA or PRP arm)

	Citation	Reason for exclusion after full-text review
75.	Garza, J. R., Campbell, R. E., Tjoumakaris, F. P., Freedman, K. B., Miller, L. S., Santa Maria, D., & Tucker, B. S. (2020). Clinical efficacy of intra-articular mesenchymal stromal cells for the treatment of knee osteoarthritis: a double-blinded prospective randomized controlled clinical trial. The American Journal of Sports Medicine, 48(3), 588-598.	Ineligible intervention: stromal vacular fraction (no HA or PRP arm)
76.	Babaei-Ghazani, A., Najarzadeh, S., Mansoori, K., Forogh, B., Madani, S. P., Ebadi, S., ... & Eftekharsadat, B. (2018). The effects of ultrasound-guided corticosteroid injection compared to oxygen–ozone (O 2–O 3) injection in patients with knee osteoarthritis: a randomized controlled trial. Clinical rheumatology, 37, 2517-2527.	Ineligible intervention: ozone (no HA or PRP arm)
77.	de Menezes Freire MR, da Silva PMC, Azevedo AR, Silva DS, da Silva RBB, Cardoso JC. Efeito comparativo entre a infiltração de plasma rico em plaquetas e o uso de corticosteroides no tratamento de osteoartrite do joelho: estudo clínico prospectivo e randomizado. Rev Bras Ortop. 2018. doi:10.1016/j.rbo.2018.01.001	Ineligible study design: Not in English
78.	Saravanan V, Morgan T, Stobbs D, Daymond TJ. Inflammatory effusion after viscosupplementation with Hylan G-F 20. Rheumatology (Oxford). 2002;41:121.	Ineligible study design: Abstract only
79.	Shichikawa K, Igarashi M, Sugawara SIwasaka Y. Clinical evaluation of high molecular weight sodium hyaluronate (SPH) on osteoarthritis of the knee—multi-center well con- trolled comparative study [in Japanese]. Jpn J Clin Pharmacol Ther. 1983;4:545-58.	Ineligible study design: Not in English
80.	Hermans J Niesten D, Verhaar JA, Reijman M B-ZSM. The visk study: A pragmatic randomized clinical trial for the effectiveness of intra articular hyaluronic acid for knee osteoarthritis. 2013;21:S148.	Ineligible study design: Abstract only
81.	Wang, Y.; Hall, S.; Hanna, F.; Wluka, E.A.; Grant, G.; Marks, P.; Feletar, M.; Cicuttini, F.M. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: A two-year single-blind clinical trial. BMC Musculoskelet. Disord.2011,12, 195. [CrossRef]	Ineligible study design: Not a RCT (Pro NRSI); ineligible outcomes: cartilage volume only, etc.
82.	Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord 2012;13:229	Ineligible study design: preliminary results for an included trial - used final/full results
83.	"Patel S, Dhillon MS, Bansal T: 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 - letter to the	Ineligible study design: letter to the editor and response (Lana 2016)
84.	Guler O, Mutlu S, Isyar M, et al. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid	Ineligible study design: Not a RCT (Pro NRSI)

	Citation	Reason for exclusion after full-text review
	treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol 2015; 25(3): 509–513.	
85.	Kilincoglu V, Yeter A, Servet E, et al. Short term results comparison of intraarticular platelet-rich plasma (prp) and hyaluronic acid (ha) applications in early stage of knee osteoarthritis. Int J Clin Exp Med 2015; 8(10): 18807–18812	Ineligible study design: Not a RCT (Pro NRSI)
86.	Li M, Zhang C, Ai Z, et al. Therapeutic effectiveness of intra-knee-articular injection of platelet-rich plasma on knee articular cartilage degeneration. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2011;25:1192–6.	Ineligible study design: Not in English
87.	Lee JK, Lee BY, Shin WY, An MJ, Jung KI, Yoon SR. Effect of Extracorporeal Shockwave Therapy Versus Intra-articular Injections of Hyaluronic Acid for the Treatment of Knee Osteoarthritis. Ann Rehabil Med. 2017, 41(5):828-35. DOI: https://doi.org/10.5535/arm.2017.41.5.828	Ineligible intervention/comparator: ESWT
88.	Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis. 2011 Jan;70(1):110-6. doi: 10.1136/ard.2009.127183. Epub 2010 Nov 10. PMID: 21068096.	Ineligible study design: <20 patients per arm
89.	Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. doi: 10.3928/01477447-20131120-13. PMID: 24579221.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
90.	Dallari D, Stagni C, Rani N, Sabbioni G, Pelotti P, Torricelli P, Tschon M, Giavaresi G. Ultrasound-Guided Injection of Platelet-Rich Plasma and Hyaluronic Acid, Separately and in Combination, for Hip Osteoarthritis: A Randomized Controlled Study. Am J Sports Med. 2016 Mar;44(3):664-71. doi: 10.1177/0363546515620383. Epub 2016 Jan 21. PMID: 26797697.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
91.	Doria C, Mosele GR, Caggiari G, Puddu L, Ciurlia E. Treatment of Early Hip Osteoarthritis: Ultrasound-Guided Platelet Rich Plasma versus Hyaluronic Acid Injections in a Randomized Clinical Trial. Joints. 2017 Aug 11;5(3):152-155. doi: 10.1055/s-0037-1605584. PMID: 29270545; PMCID: PMC5738493.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
92.	Nouri F, Babaee M, Peydayesh P, Esmaily H, Raeissadat SA. Comparison between the effects of ultrasound guided intra-articular injections of platelet-rich plasma (PRP), high molecular weight hyaluronic acid, and their combination in hip osteoarthritis: a randomized clinical trial. BMC Musculoskelet Disord. 2022 Sep 12;23(1):856. doi: 10.1186/s12891-022-05787-8. PMID: 36096771; PMCID: PMC9464606.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
93.	Baltzer AW, Ostapczuk MS, Stosch D, Seidel F, Granrath M. A new treatment for hip osteoarthritis: clinical evidence for the efficacy of autologous conditioned serum. Orthop Rev (Pavia). 2013 Jun 14;5(2):59-64. doi: 10.4081/or.2013.e13. PMID: 23888203; PMCID: PMC3718237.	Ineligible intervention: autologous conditions serum (ACS)

	Citation	Reason for exclusion after full-text review
94.	Di Sante L, Villani C, Santilli V, Valeo M, Bologna E, Imparato L, Paoloni M, Iagnocco A. Intra-articular hyaluronic acid vs platelet-rich plasma in the treatment of hip osteoarthritis. Med Ultrason. 2016 Dec 5;18(4):463-468. doi: 10.11152/mu-874. PMID: 27981279.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
95.	Bennell KL, Hunter DJ, Paterson KL. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. Curr Rheumatol Rep. 2017 May;19(5):24. doi: 10.1007/s11926-017-0652-x. PMID: 28386761.	Ineligible study design: not a RCT
96.	Clementi D, D'Ambrosi R, Bertocco P, Bucci MS, Cardile C, Ragni P, Giaffreda G, Ragone V. Efficacy of a single intra-articular injection of ultra-high molecular weight hyaluronic acid for hip osteoarthritis: a randomized controlled study. Eur J Orthop Surg Traumatol. 2018 Jul;28(5):915-922. doi: 10.1007/s00590-017-2083-9. Epub 2017 Nov 21. PMID: 29164399.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
97.	Singh JR, Haffey P, Valimahomed A, Gellhorn AC. The Effectiveness of Autologous Platelet-Rich Plasma for Osteoarthritis of the Hip: A Retrospective Analysis. Pain Med. 2019 Aug 1;20(8):1611-1618. doi: 10.1093/pm/pnz041. PMID: 30958873.	Ineligible study design: not a RCT
98.	Kraeutler MJ, Houck DA, Garabekyan T, Miller SL, Dragoo JL, Mei-Dan O. Comparing Intra-articular Injections of Leukocyte-Poor Platelet-Rich Plasma Versus Low-Molecular Weight Hyaluronic Acid for the Treatment of Symptomatic Osteoarthritis of the Hip: A Double-Blind, Randomized Pilot Study. Orthop J Sports Med. 2021 Jan 20;9(1):2325967120969210. doi: 10.1177/2325967120969210. PMID: 33786329; PMCID: PMC7934058.	Ineligible study design: <20 patients per arm
99.	Scaturro D, Vitagliani F, Terrana P, Tomasello S, Falco V, Cuntrera D, Spoto I, Midiri M, Letizia Mauro G. Hybrid Hyaluronic Acid versus High Molecular Weight Hyaluronic Acid for the Treatment of Hip Osteoarthritis in Overweight/Obese Patients. J Funct Morphol Kinesiol. 2022 Feb 9;7(1):20. doi: 10.3390/jfmk7010020. PMID: 35225906; PMCID: PMC8883906.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
100	Micu MC, Micu A, Bolboacă SD. Ultrasound-guided injection with hyaluronic acid in hip osteoarthritis: efficacy and safety in a real-life setting. Clin Rheumatol. 2022 Aug;41(8):2491-2498. doi: 10.1007/s10067-022-06154-7. Epub 2022 Apr 7. PMID: 35389116.	Ineligible study design: not a RCT
101	Koyano G, Jinno T, Koga D, Hoshino C, Okawa A. Intra-articular Injections of Cross-linked Hyaluronic Acid in Japanese Patients with Symptomatic Osteoarthritis of the Hip. Prog Rehabil Med. 2021 Sep 29;6:20210038. doi: 10.2490/prm.20210038. PMID: 34632157; PMCID: PMC8476323.	Ineligible study design: not a RCT
102	Setaro N, Luciani P, Farinelli L, Gigante A. Conservative treatment of hip osteoarthritis; comparison between three medium/high molecular weight hyaluronic acid injections and two injections of HYADD®4: a randomized controlled double-blind study. J Biol Regul Homeost Agents. 2020 Nov-Dec;34(6):2401-2405. doi: 10.23812/20-575-L. PMID: 33307600.	Ineligible intervention/comparator: Non-FDA approved HA product/brand

	Citation	Reason for exclusion after full-text review
103	Kraeutler, Matthew J.Miller, Shannon. A Double-Blind, Randomized Controlled Trial Comparing Platelet-Rich Plasma versus Hyaluronic Acid for Early Osteoarthritis of the Hip Joint Arthroscopy, Volume 35, Issue 12, e16	Ineligible study design: <20 patients per arm
104	Tikiz C, Unlü Z, Sener A, Efe M, Tüzün C. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. Clin Rheumatol 2005;24(3):244–50.	Ineligible study design: <20 patients per arm
105	Richette P, Ravaud P, Conrozier T, Euller-Ziegler L, Mazières B, Maugars Y, Mulleman D, Clerson P, Chevalier X. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. Arthritis Rheum. 2009 Mar;60(3):824-30. doi: 10.1002/art.24301. PMID: 19248105.	Ineligible intervention/comparator: Non-FDA approved HA product/brand
106	van den Bekerom MP, Rys B, Mulier M. Viscosupplementation in the hip: evaluation of hyaluronic acid formulations. Arch Orthop Trauma Surg. 2008;128:275-80.	Ineligible study design: not a RCT
107	Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, et al. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix®) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther. 2009;11:R183.	Ineligible intervention/comparator: Non-FDA approved HA product/brand

Appendix Table C2. List of Excluded Articles Prior to 2012

	Citation	Reason for exclusion after full-text review
1.	Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, la Serna AR de, Naranjo A, 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;70:1957–1962.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
2.	Petrella RJ, Decaria J, Petrella MJ. Long term efficacy and safety of a combined low and high molecular weight hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatol Reports 2011;3:16–21	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
3.	Baltzer AWA, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthr Cartil 2009;17:152–160.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
4.	"Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum2009;39:1-9."	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
5.	Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre,	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.

	Citation	Reason for exclusion after full-text review
	double-blind, placebo controlled trial. Ann Rheum Dis2010;69:113-119	
6.	Jørgensen A, Stengaard-Pedersen K, Simonsen O, Pfeiffer- Jensen M, Eriksen C, Bliddal H, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. Ann Rheum Dis. 2010;69:1097-102.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
7.	Diracoglu D, Vural M, Baskent A, Dikici F, Aksoy C. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. J Back Musculoskelet Rehabil. 20 09;22:1-9.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
8.	Blanco FJ, Fernandez-Sueiro J.L., Pinto-Tasende JA, Fernandez-Lopez JC, Ramallal M, Freire A, et al. Intra-Articular Hyaluronan Treatment of Patients with Knee Osteoarthritis Waiting for Replacement Surgery. Open Arthritis J 2008;1:1–7.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
9.	Lundsgaard C, Dufour N, Fallentin E, Winkel P, Gluud C. Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. Scand J Rheumatol. 2008 Mar-Apr;37(2):142-50. doi: 10.1080/03009740701813103. PMID: 18415773.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
10.	Petrella RJ, Cogliano A, Decaria J. Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Clin Rheumatol. 2008;27:975-81.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
11.	Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int 2006;26:325–330.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report; also ineligible study design: <20 patients per arm
12.	Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol 2006;33:951-956.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
13.	Cubukçu D, Ardiç F, Karabulut N, Topuz O. Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: clinical and MRI assessment. Clin Rheumatol. 2005 Aug;24(4):336-41. doi: 10.1007/s10067-004-1043-z. Epub 2004 Dec 14. PMID: 15599642.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report; also ineligible study design: <20 patients per arm
14.	Rolf CG, Engstrom B, Ohrvik J, Valentin A, Lilja B, Levine DW. A comparative study of the efficacy and safety of hyaluronan viscosupplements and placebo in patients with symptomatic and arthroscopy-verified cartilage pathology. J Drug Assess. 2005;8:183-200.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
15.	Sezgin, M., Demirel, A. C., Karaca, C., Ortancıl, Ö., Ülkar, G. B., Kanık, A., & Çakçı, A. (2005). Does hyaluronan affect inflammatory cytokines in knee osteoarthritis?. Rheumatology international, 25, 264-269.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report; also

	Citation	Reason for exclusion after full-text review
		ineligible study design: <20 patients per arm
16.	Altman RD, Akermark C, Beaulieu AD, Schnitzer T, Group DIS. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthr Cartil 2004;12:642–649.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
17.	Day R, Brooks P, Conaghan PG, Petersen M, Multicenter Trial G. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intra- articular hyaluronan in osteoarthritis of the knee. J Rheumatol 2004;31:775-782.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
18.	Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. Int J Clin Pract. 2003 Jul-Aug;57(6):467-74. PMID: 12918884.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
19.	Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford) 2002;41:1240–1248.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
20.	Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res 2001:130–143.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
21.	Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford) 1999;38:602–607.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
22.	Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998;20:410–423.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
23.	Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. Zhonghua Yi Xue Za Zhi (Taipei). 1997;59:99-106.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
24.	Lohmander LS, Dalen N, Englund G, Hämäläinen M, Jensen EM, Karlsson K, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis. 1996;55:424-31.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
25.	Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis. 1994 Aug;53(8):529-34. doi: 10.1136/ard.53.8.529. PMID: 7944639; PMCID: PMC1005394.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
26.	Dougados, M.; Nguyen, M.; Listrat, V.; Amor, B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: A 1 year placebo-controlled trial. Osteoarthr. Cartil.1993,1, 97–103. [CrossRef]	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.

	Citation	Reason for exclusion after full-text review
27.	Dixon AS, Jacoby RK, Berry H, Hamilton EB. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. Curr Med Res Opin 1988;11:205–213.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
28.	Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med. 2002;162(3):292-298.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
29.	Dickson DJ, Hosie G, English JR. A double-blind, placebo-controlled comparison of hylan G-F 20 against diclofenac in knee osteoarthritis. J Clin Res. 2001;4:41-52.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
30.	Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group.JRheumatol.1998;25(11):2203-2212.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
31.	Pham, T.; Le Henanff, A.; Ravaud, P.; Dieppe, P.; Paolozzi, L.; Dougados, M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann. Rheum. Dis.2004,63, 1611–1617. [CrossRef]	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
32.	Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee--hyaluronan versus triamcinolone: a prospective, randomized, double-blind, monocentric study. Eur J Med Res. 2009 Apr 16;14(4):157-64. doi: 10.1186/2047-783x-14-4-157. PMID: 19380288; PMCID: PMC3401005.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
33.	Caborn D, Rush J, Lanzer W, Parenti D, Murray C. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol. 2004;31:333-343.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
34.	Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee: a prospective, randomized trial. J Bone Joint Surg Am. 2003;85(7):1197-1203.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
35.	Tasciotaoglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Clin Rheumatol 2003;22:112–117.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
36.	Frizziero L, Pasquali Ronchetti I. Intra-articular treatment of osteoarthritis of the knee: An arthroscopic and clinical comparison between sodium hyaluronate (500-730 kDa) and methylprednisolone acetate. J Orthop Traumatol 2002;3:89–96.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
37.	Tekeoglu I, Adak B, Goksoy T, Tosun N. Effects of intra-articular injections of sodium hyaluronate (orthovisc) and betamethasone on osteoarthritis of the knee. J Rheum Med Rehab. 1998;9:220-224.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.

	Citation	Reason for exclusion after full-text review
38.	Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage. 1995;3:269-273.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
39.	Leardini G, Mattara L, Franceschini M, Perbellini A. Intra-articular treatment of knee osteoarthritis. A comparative study between hyaluronic acid and 6-methyl prednisolone acetate. Clin Exp Rheumatol. 1991;9:375-381.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
40.	Pietrogrande V, Melanotte PL, D'Agnolo B, et al. Hyaluronic acid versus methylprednisolone intraarticularly injected for treatment of osteoarthritis of the knee. Curr Ther Res Clin Exp. 1991;50:691-701.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
41.	Maia PA, Cossich VR, Salles-Neto JI, Aguiar DP, de Sousa EB: Viscosupplementation improves pain, function and muscle strength, but not proprioception, in patients with knee osteoarthritis: a prospective randomized trial. Clinics (Sao Paulo). 2019, 74:e1207.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report; also ineligible study design: <20 patients per arm
42.	Shimizu M, Higuchi H, Takagishi K, Shinozaki T, Kobayashi T. Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid. J Orthop Sci. 2010;15:51-56.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
43.	Skwara, A., Peterlein, C. D., Tibesku, C. O., Rosenbaum, D., & Fuchs-Winkelmann, S. (2009). Changes of gait patterns and muscle activity after intraarticular treatment of patients with osteoarthritis of the knee: a prospective, randomised, double-blind study. The Knee, 16(6), 466-472.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
44.	Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int 2006;26:314–319.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
45.	Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) antacids alone. Osteoarthritis Cartilage. 1995;3(4):213-225.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
46.	Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medico economic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine. 2003;70(4):276–81.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
47.	Raynauld J-P, 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(7):506-517.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.

	Citation	Reason for exclusion after full-text review
48.	Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006;26:873-878.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
49.	Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, et al. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower- molecular-weight hyaluronan. Clin Ther. 1999;21(9):1549–62.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
50.	Puhl W, Bernau A, Greiling H, Köpcke W, Pförringer W, Steck KJ, Zacher J, Scharf HP. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. Osteoarthritis Cartilage. 1993 Oct;1(4):233-41. doi: 10.1016/s1063-4584(05)80329-2. PMID: 15449510.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
51.	Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV. Efficacy of Hylan G-F 20 and sodium hyaluronate in the treatment of osteoarthritis of the knee -- a prospective randomized clinical trial. Knee. 2008;15(4):318–24.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
52.	Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005;32:1928-36.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
53.	Chou CW, Lue KH, Lee HS, et al. Hylan G-F 20 has better pain relief and cost-effectiveness than sodium hyaluronate in treating early osteoarthritic knees in Taiwan. Journal of the Formosan Medical Association;108(8):663-672.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.
54.	Kawasaki T, Kurosawa H, Ikeda H, et. al. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. Journal of Orthopaedic Science;14(2):182-191.	PRIOR TO 2012; assumed to be subsumed by SRs/MAs from 2012 report.

APPENDIX D. Risk of Bias, Strength of Evidence, and QHES Determination

Each included comparative study is rated against pre-set criteria that resulted in a Risk of Bias (ROB) assessment and presented in a table. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[1,2] 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 in Table D1. Discrepancies in ratings between reviewers were resolved through discussion and consensus. The final quality assessments are provided in Appendix E.

Table D2 provides an example of the format used to assess ROB for comparative studies of testing/therapy. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author. Risk of bias assessments were not conducted for case series; all were considered High risk of bias.

Appendix Table D1. Definition of the risk of bias categories for individual studies of testing

Rating	Description and Criteria
Good	• Least risk of bias; study results generally considered valid • Employ valid methods for selection, inclusion, and allocation of patients to testing; report similar baseline characteristics in different test groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
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 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

Appendix Table D2: Assessment of ROB for individual studies of therapy

Methodological Principle	Author 1, 2014	Author 2, 2012	Author 3, 2010
Study design			
Randomized controlled trial	■	■	■
Prospective cohort study			
Retrospective cohort study			
Case-control			
Case-series			
Random sequence generation*			
Statement of concealed allocation*			

Analysis according to random assignment (i.e., intention to treat)*			
Independent or blinded outcome assessment			
Outcome assessors independent or blinded			
Care providers blinded			
Patients blinded			
Complete follow-up of >80%			
<10% difference in follow-up between groups			
Patient characteristics comparable at baseline†			
Overall quality rating			

*Applies to randomized controlled trials only.

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)

Appendix Table D3. Rating overall Confidence in the Results of the Review (Dettori 2020).

High: No or 1 noncritical weakness	The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate: More than 1 noncritical weakness*	The systematic review has more than 1 weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
Low: One critical flaw with or without noncritical weaknesses	The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
Critically low: More than 1 critical flaw with or without noncritical weaknesses	The review has more than 1 critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

* Multiple noncritical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al. embodies the primary components relevant for critical appraisal of economic studies[3]. It also incorporates a weighted scoring process which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique. Table D4 below provides a template of the instrument.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?

Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?

Appendix Table D4. Assessment of Quality of Health Economic Studies Criteria

Question	Possible Points*	Criteria For Credit*
1. Was the study **objective** presented in a clear, specific, and measurable manner?	7	Authors must fully describe the objective; is it measurable?
2. Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	Authors must state perspective, provide rationale AND have done the correct analysis corresponding to the perspective
3. Were **variable estimates** used in the analysis from the best available source (i.e., randomized controlled trial - best, expert opinion - worst)?	8	No credit if most of estimates are not from the best sources available
4. If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study?	1	
5. Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	NO credit if they do not give details regarding type of sensitivity analysis, methods (e.g., what assumptions or factors were varied/why), AND the results (what factors are influential, what is the range of ICERs, etc.)
6. Was **incremental analysis** performed between alternatives for resources and costs?	6	
7. Was the methodology for **data abstraction** (including the value of health states and other benefits) stated?	5	No credit if sources of model inputs and process of choosing model inputs not specified
8. Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	No credit if time horizon is too short to allow for important outcomes
9. Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	No credit if sources of cost data or methods of estimating costs not clearly described
10. Were the primary **outcome measure(s**) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	NO credit if major important outcomes are not included or if time horizon did not allow for important outcomes to be measured
11. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	No credit if sources of outcome data or not clearly described or if outcome data is not appropriate for the study population/outcome of interest (i.e., using utility weights from QOL measures that aren't validated or apply to a different population)
12. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	Must provide explicit detail for methods and should be able to trace/identify specific components, how they were derived, etc.
13. Were the choice of economic model, main **assumptions, and limitations** of the study stated and justified?	7	NO credit if insufficient detail of model, assumptions AND limitations are provided (No credit if they do not provide justifications/rationale)
14. Did the author(s) explicitly discuss direction and magnitude of potential **biases?**	6	NO credit if no discussion of direction and magnitude of biases
15. Were the **conclusions/recommendations** of the study justified and based on the study results?	8	NO credit if conclusions/recommendations are stronger than warranted based on findings
16. Was there a statement disclosing the **source of funding** for the study?	3	
Total	100	

ICER = Incremental Cost-Effectiveness Ratio; QOL = quality of life.

* Study must fit criteria in order to receive full points. Partial credit is not given. If criteria is not met, then the question receives no points.

Determination of Overall Strength (Quality) of Evidence

The strength of evidence for the overall body of evidence for all *critical health outcomes* was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ)[1]. The strength of evidence was based on the highest quality evidence available for a given *primary* outcome. In determining the strength of body of evidence regarding a given *primary* 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 are similar in terms of range and variability.
- **Directness:** describes whether the evidence is directly related to patient health outcomes.
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication bias:** is considered when there is concern of selective publishing.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, and if possible, publication bias) were assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those that comprised nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the *nonrandomized* studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, presence of a dose-response relationship, and large magnitude of effect (strength of association) *if no downgrades for domains above*. Publication and reporting bias are difficult to assess. Publication bias is particularly difficult to assess with fewer than 10 RCTs (AHRQ methods guide). When publication bias was unknown in all studies and this domain is often eliminated from the strength of evidence tables for our reports. The final strength of evidence for each **primary** outcome 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 probably stable, but some doubt remains.

Low— Limited confidence that effect size estimates lie close to the true effect for this outcome; important 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 deficiencies precluding judgment.

Similar 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.

Appendix Table D5. Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table below.
Baseline strength: HIGH = RCTs. LOW = observational, cohort studies, administrative data studies.
DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)
UPGRADE (non-randomized studies): Large magnitude of effect (1 or 2); Dose response gradient (1) done for observational studies ***if no downgrade for domains above***

Outcome	Strength of Evidence	Conclusions & Comments	Baseline SOE	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates; high quality (moderately low ROB)	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.
**Single study = "consistency unknown", may or may not be downgraded

APPENDIX E. Study Quality: Risk of Bias Evaluation of RCTs and QHES of Economic Studies

Appendix Table E1. Risk of Bias Assessment: Knee OA trials evaluating HA versus Placebo

Methodological Principle	Hangody, 2018	Petterson, 2019	Takamura SSED, 2019	Arden, 2014	Görmeli, 2017	Strand, 2012	Ke, 2021	Bao, 2018	Farr, 2019	Gomoll, 2021
Study design										
Randomized controlled trial	■	■	■	■	■	■	■	■	■	■
Random sequence generation	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Intention to treat	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Outcome assessors independent or blinded	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Care providers blinded	Yes	Yes	No	Unclear	No	No	No	Unclear	Unclear	No
Patients blinded	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
<10% difference in follow-up between groups	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Groups comparable at baseline*	Yes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Risk of Bias	**Good**	**Good**	**Fair**	**Good**	**Fair**	**Good**	**Good**	**Poor**	**Poor**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

*Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E2. Risk of Bias Assessment: Knee OA trials evaluating HA versus Steroid

Methodological Principle	Vaishya, 2017	Askari, 2016	Bisicchia, 2016	Tammachote, 2016	Leighton, 2014	Campos, 2017
Study design						
Randomized controlled trial	■	■	■	■	■	■
Random sequence generation*	Yes	Yes	Yes	Yes	Yes	Unclear
Concealed allocation*	No Unclear	Yes	Yes	Yes	Yes	Unclear
Intention to treat*	Unclear	Yes	3 mos = yes 12-26 mos - NO	No/Unclear	Yes	No
Outcome assessors independent or blinded	Unclear	Yes	Yes	Yes	Yes	Yes/Unclear
Care providers blinded	Unclear	Yes	No	No	No	Unclear
Patients blinded	Unclear?	Yes	No	Yes	Yes	Yes
Complete follow-up of ≥80%	Unclear	Yes	Yes	Yes	No	No
<10% difference in follow-up between groups	Unclear	Yes	Unclear	Yes	Yes	Yes
Groups comparable at baseline†	Yes	Yes	Unclear	Yes	Yes	No
Risk of Bias	**Poor**	**Good**	**Fair (3 mos.) Poor (6, 12 mos.)**	**Fair**	**Fair**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

*Applies only to randomized controlled trials.

†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E3. Risk of Bias Assessment: Knee OA trials evaluating HA versus NSAID

Methodological Principle	Guner, 2016	Buendía-López, 2019
Study design		
Randomized controlled trial	■	■
Random sequence generation*	Yes	Yes
Concealed allocation*	Unclear	Unclear
Intention to treat*	Yes	Unclear
Outcome assessors independent or blinded	Yes	Yes
Care providers blinded	No	No
Patients blinded	No	No
Complete follow-up of ≥80%	Yes	Yes
<10% difference in follow-up between groups	Yes	Yes
Groups comparable at baseline†	Yes	Yes
Risk of Bias	**Fair**	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E4. Risk of Bias Assessment: Knee OA trials evaluating HA versus Usual Care

Methodological Principle	Hermans, 2019
Study design	
Randomized controlled trial	■
Random sequence generation*	Yes
Concealed allocation*	Unclear
Intention to treat*	Yes
Outcome assessors independent or blinded	No (PROs)
Care providers blinded	No
Patients blinded	No
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Groups comparable at baselines†	No

Risk of Bias	Poor

PRO = patient reported outcomes
Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E5. Risk of Bias Assessment: Knee OA trials evaluating HA versus Physical Therapy and Prolotherapy (Same Study)

Methodological Principle	Rezasoltani, 2020
Study design	
Randomized controlled trial	■
Random sequence generation*	Yes
Concealed allocation*	Yes
Intention to treat*	Unclear
Outcome assessors independent or blinded	unclear
Care providers blinded	No
Patients blinded	No
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Groups comparable at baseline†	Yes
Risk of Bias	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E6. Risk of Bias Assessment: Knee OA trials evaluating HA versus Exercise

Methodological Principle	Saccomano, 2016
Study design	
Randomized controlled trial	■
Random sequence generation*	Yes
Concealed allocation*	Yes
Intention to treat*	Yes
Outcome assessors independent or blinded	Yes
Care providers blinded	No

Patients blinded	No
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Groups comparable at baseline†	No
Risk of Bias	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E7. Risk of Bias Assessment: Knee OA trials evaluating PRP versus placebo that randomized by participant

Methodological Principle	Bennell, 2021	Chu, 2022	Dório, 2021[§]	Elik, 2020[**]	Görmeli, 2017	Lewis, 2022[††]	Nunes-Tamashiro, 2022[‡‡§§]	Patel, 2013[††]	Yurtbay, 2022[§***]
Study design									
Randomized controlled trial	■	■	■	■	■	■	■	■	■
Random sequence generation[*]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation[*]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Intention to treat[*]	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	No
Outcome assessors independent or blinded	Yes	Yes[‡]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Care providers blinded	Yes	Yes[‡]	Yes	No	No	Unclear	No	Unclear	Yes
Patients blinded	Yes	Yes[‡]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Complete follow-up of ≥80%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<10% difference in follow-up between groups	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes – 1 inj. PRP vs. placebo No – 2 inj. PRP vs. placebo	Yes – 1 and 2 PPR vs. 1 placebo; No – 2 PRP vs. 2 NS; 1 PRP vs. 2 NS
Patient characteristics comparable at baseline[†]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Quality	**Good**	**Fair**	**Fair**	**Fair**	**Fair**	**Good**	**Fair**	**Fair**	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

* Applies only to randomized controlled trials.

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

‡ Chu 2022 removed blinding at 60-month follow-up.

§ In bilateral cases, the knee selected for treatment was the one reported with higher pain score as reported by the participant.

** All patients were prescribed exercise.

†† Included multiple arms for different injection schedules for PRP and placebo.

‡‡ Included arms for PRP, placebo, and steroid.

§§ Bilateral Knee OA. Injection performed on the most symptomatic knee according to the patient perception

*** Unilateral; bilateral injection was not applied to any patient

Appendix Table E8. Risk of Bias Assessment: Knee OA trials* evaluating PRP versus placebo that randomized by knees

Methodological Principle	Ghai, 2019‡	Wu, 2018‡	Lin, 2019§
Study design			
Prospective cohort study	■	■	■
Random sequence generation*	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A
Intention to treat*	N/A	N/A	N/A
Accounting for repeated measures	Yes	Yes	Yes
Outcome assessors independent or blinded	Yes	Yes	Yes
Care providers blinded	Unclear	Unclear	Yes
Patients blinded	Yes	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes	Yes
<10% difference in follow-up between groups	N/A	N/A	N/A
Patient characteristics comparable at baseline†	N/A	N/A	N/A
Quality	**Fair**	**Fair**	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

*Described as randomized controlled trials, however, for purposes of this report they are considered prospective nonrandomized studies of interventions (NRSIs) since the randomization was done to both knees within the same patient (i.e., one knee received PRP the other knee received placebo). These three criteria apply only to randomized controlled trials.

†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

‡ Bilateral OA. Each patient had one knee randomized to intervention and the other to control.

§ Some bilateral with KNEES randomized, received injections of different products in different knees. 53 patients, 87 knees; 19 single = 19 knees; 34 bilateral = 68 knees.

Appendix Table E9. Risk of Bias Assessment: Knee OA RCTs evaluating PRP versus steroid

Methodological Principle	Elksniņš-Finogejevs, 2020	Forogh, 2015‡	Freire, 2020	Huang, 2019	Jubert, 2017	Khan, 2018	Nabi, 2018	Nunes-Tamashiro, 2022§**	Phul, 2018
Study design									
Prospective cohort study	■	■	■	■	■	■	■	■	■
Random sequence generation*	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Concealed allocation*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Intention to treat*	No	No	Yes	Yes	Yes	Unclear	No	Yes	Unclear
Outcome assessors independent or blinded	Yes – CRO No – PRO	Yes	Yes	Unclear	Yes	Unclear	Yes – CRO No -PRO	Yes	Unclear
Care providers blinded	No	No	Yes	Unclear	Yes	Unclear	No	No	Unclear
Patients blinded	No	Yes	Yes	Unclear	Yes	Unclear	No	Yes	Unclear
Complete follow-up of ≥80%	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear
<10% difference in follow-up between groups	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear
Patient characteristics comparable at baseline†	No	No	No	No	No	No	No	No	No
Quality	**Poor**	**Poor**	**Fair**	**Poor**	**Fair**	**Poor**	**Poor**	**Fair**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

* Applies only to randomized controlled trials.

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

‡ Bilateral - each knee (in same patient) received same injection (either PRP or steroid).

§ Bilateral - Only a single intra-articular injection was performed on the most symptomatic knee according to the patient perception.

** Included arms for PRP, placebo, and steroid.

Appendix Table E10. Risk of Bias Assessment: Knee OA trials evaluating PRP versus Oral Analgesics

Methodological Principle	Buendía-López, 2019	Reyes-Sosa, 2020‡	Simental-Mendia, 2016
Study design			
Randomized controlled trial	■	■	■
Random sequence generation*	Yes	Yes	Unclear
Concealed allocation*	Unclear	Unclear	Unclear
Intention to treat*	Unclear	Yes	No
Outcome assessors independent or blinded	Yes	No	No
Care providers blinded	No	No	No
Patients blinded	No	No	No
Complete follow-up of ≥80%	Yes	Yes	Yes
<10% difference in follow-up between groups	Yes	Yes	Unclear
Patient characteristics comparable at baseline†	Yes	Yes	No
Quality	**Fair**	**Fair**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

* Applies only to randomized controlled trials.

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

‡ Both knees treated in patients with bilateral knee OA: 19 vs. 18 (63% vs. 60%)

Appendix Table E11. Risk of Bias Assessment: Knee OA trials evaluating PRP versus exercise with or without TENS

Methodological Principle	Akan, 2018	Angoorani, 2015‡	Rayegani, 2014
Study design			
Randomized controlled trial	■	■	■
Random sequence generation*	Yes	Yes	Yes
Concealed allocation*	Unclear	Unclear	Unclear
Intention to treat*	Yes	No	Yes
Outcome assessors independent or blinded	No	No	No
Care providers blinded	No	No	No
Patients blinded	No	No	No
Complete follow-up of ≥80%	Yes	Yes	Yes
<10% difference in follow-up between groups	Yes	Yes	Yes
Patient characteristics comparable at baseline†	No	Yes	No
Quality	**Fair**	**Fair**	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

* Applies only to randomized controlled trials.

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

‡ Patients randomized to exercise also received transcutaneous electric nerve stimulation (TENS).

Appendix Table E12. Risk of Bias Assessment: Knee OA trials* evaluating PRP (plus exercise) versus exercise alone that randomized by knees

Methodological Principle	Raeissadat, 2020‡
Study design	
Prospective cohort study	■
Random sequence generation*	N/A
Concealed allocation*	N/A
Intention to treat*	N/A
Accounting for repeated measures	Yes
Outcome assessors independent or blinded	CRO – unclear PRO - No§
Care providers blinded	No§
Patients blinded	No§
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	N/A
Patient characteristics comparable at baseline†	N/A
Quality	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

* Described as randomized controlled trials, however, for purposes of this report they are considered prospective nonrandomized studies of interventions (NRSIs) since the randomization was done to both knees within the same patient (i.e., one knee received PRP the other knee received placebo). These three criteria apply only to randomized controlled trials.

†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

‡ Bilateral knees; randomized by knee. All patients were female. In the control group, exercise therapy started immediately and the patients in this group were also asked to use 500 mg of paracetamol without codeine in case of pain; and if the pain was not controlled, paracetamol with codeine was to be used

§ Described as double blind but unclear how this was done as there is no mention of a "sham" injection in the knee that was randomized to exercise.

Appendix Table E13. Risk of Bias Assessment: Knee OA trials evaluating PRP versus PT/rehabilitation

Methodological Principle	Gaballa, 2019
Study design	
Randomized controlled trial	■
Random sequence generation*	Unclear
Concealed allocation*	Unclear
Intention to treat*	Unclear
Outcome assessors independent or blinded	No
Care providers blinded	No
Patients blinded	No
Complete follow-up of ≥80%	Unclear
<10% difference in follow-up between groups	Unclear
Patient characteristics comparable at baseline†	Unclear
Quality	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

* Applies only to randomized controlled trials.

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E14. Risk of Bias Assessment: Knee OA trials evaluating PRP versus prolotherapy

Methodological Principle	Pishgani, 2020	Rahimzadeh, 2018
Study design		
Randomized controlled trial	■	■
Random sequence generation*	No‡	Unclear
Concealed allocation*	Unclear	Unclear
Intention to treat*	Yes	Unclear
Outcome assessors independent or blinded	No	Yes
Care providers blinded	No	Yes
Patients blinded	No	Yes
Complete follow-up of ≥80%	Yes	Unclear
<10% difference in follow-up between groups	Yes	Unclear
Patient characteristics comparable at baseline†	No	No
Quality	**Poor**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
* Applies only to randomized controlled trials.
† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.
‡ RAS (Random) line. The ruler is typically attached by "no pain" (score of 0) and "greater pain intensity" (Score of 100). In this regard, patients were asked to place a mark on the VAS line at the point according to pain severity from the lowest to the highest

Appendix Table E15. Risk of Bias Assessment: Knee OA trials evaluating PRP versus PRP

Methodological Principle	Görmeli, 2017	Kavadar, 2015	Zhou, 2023	Yurtbay, 2022‡	Lewis 2022‡	Patel, 2013‡	Yaradilmis, 2020	Tavassoli, 2019
Study design								
Randomized controlled trial	■	■	■	■	■	■	■	■
Random sequence generation*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation*	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear
Intention to treat*	Unclear	Yes	No	No	Yes	Yes	No	Unclear
Outcome assessors independent or blinded	Yes	CRO- Yes PRO- No	Yes	Yes	Yes	Yes	Yes	Unclear
Care providers blinded	No	No	Yes	Yes	Unclear	Unclear	Unclear	Yes
Patients blinded	Yes	No	Yes	Yes	Yes	Unclear	Yes	No
Complete follow-up of ≥80%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<10% difference in follow-up between groups	No	Yes	Yes	No – 2 PRP vs. 2 NS; 1 PRP vs. 2 NS	No	Yes – 1 inj. PRP vs. placebo No – 2 inj. PRP vs. placebo	Yes	Yes
Patient characteristics comparable at baseline†	Yes	No	Yes	No	Yes	Yes	Unclear	Yes
Quality	**Fair**	**Fair**	**Good**	**Fair**	**Good**	**Fair**	**Fair**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
* Applies only to randomized controlled trials.
† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.
‡ Included multiple arms for different injection schedules for PRP and placebo.

Appendix Table E16. Risk of Bias Assessment: Hip OA trials evaluating HA versus PRP

Methodological Principle	Villanova-Lopez, 2020
Study design	
Randomized controlled trial	■
Random sequence generation*	Unclear
Concealed allocation*	Unclear
Intention to treat*	No
Outcome assessors independent or blinded	Yes
Care providers blinded	Unclear
Patients blinded	Yes
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Patient characteristics comparable at baseline†	Yes
Quality	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

*Applies only to randomized controlled trials.

†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E17. Risk of Bias Assessment: Hip OA trials evaluating HA versus placebo

Methodological Principle	Qvistgaard, 2016	Brander, 2019
Study design		
Randomized controlled trial	■	■
Random sequence generation*	Yes	Yes
Concealed allocation*	Unclear	Unclear
Intention to treat*	Yes	Yes
Outcome assessors independent or blinded	Yes	Yes
Care providers blinded	Yes	No
Patients blinded	Yes	Yes
Complete follow-up of ≥80%	Yes	No
<10% difference in follow-up between groups	No	Yes
Patient characteristics comparable at baseline†	Yes	Yes
Quality	**Fair**	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met

*Applies only to randomized controlled trials.

†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E18. Risk of Bias Assessment: Hip OA trials evaluating HA versus steroid

Methodological Principle	Qvistgaard, 2016
Study design	
Randomized controlled trial	■
Random sequence generation*	Yes
Concealed allocation*	Unclear
Intention to treat*	Yes
Outcome assessors independent or blinded	Yes
Care providers blinded	Yes
Patients blinded	Yes
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	No
Patient characteristics comparable at baseline†	Yes
Quality	**Fair**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E19. Risk of Bias Assessment: Knee OA trials evaluating HA versus PRP

Methodological Principle	Buendía-López, 2019	Cole, 2017	Görmeli, 2017	Lana, 2016	Lisi, 2018	Louis, 2018
Study design						
Randomized controlled trial	■	■	■	■	■	■
Random sequence generation*	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation*	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Intention to treat*	Unclear	Unclear	Unclear	Yes	Yes	Yes
Outcome assessors independent or blinded	Yes	Yes	Yes	Yes	Yes	Yes
Care providers blinded	No	No	No	Unclear	No	Yes
Patients blinded	No	Yes	Yes	Yes	Yes	Yes
Cointerventions applied equally	Yes	Yes	Yes	Yes	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes	Yes	Yes	Yes	Yes – 3 mos. No – 6 mos.
<10% difference in follow-up between groups	Yes	Yes	Yes/No	Yes	No – 6 mos. Yes – 12 mos.	Yes

Controlling for possible confounding†	Yes	Yes	Yes	No	No	No
Risk of Bias	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Good**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E20. Risk of Bias Assessment: Knee OA trials evaluating HA versus PRP, continued.

Methodological Principle	Raeissadat, 2015	Raeissadat, 2021	Sdeek, 2021	Tavassoli, 2019	Wang, 2022
Study design					
Randomized controlled trial	■	■	■	■	■
Random sequence generation*	Yes	Yes	Unclear	Yes	Unclear
Concealed allocation*	Unclear	Unclear	Unclear	Unclear	Unclear
Intention to treat*	Unclear	Unclear	Unclear	Unclear	Yes
Outcome assessors independent or blinded	Unclear	No	Yes	Unclear	Unclear
Care providers blinded	Unclear	Yes	Unclear	Yes	Unclear
Patients blinded	No	No	Yes	No	Unclear
Cointerventions applied equally	Yes	Yes	Yes	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes	Unclear	Yes	Yes
<10% difference in follow-up between groups	Yes	Yes	Unclear	Yes	Yes
Controlling for possible confounding†	No	Yes	Yes	Yes	Yes
Risk of Bias	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table E21. QHES Assessment of U.S. Cost-effectiveness studies

Question	Possible Points*	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
1. Was the study **objective** presented in a clear, specific, and measurable manner?	7	7	7	7	7
2. Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4	4	4	0
3. Were **variable estimates** used in the analysis from the best available source (i.e., randomized controlled trial - best, expert opinion - worst)?	8	8	8	0	8
4. If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study?	1	1	1	1	1
5. Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9	9	9	0
6. Was **incremental analysis** performed between alternatives for resources and costs?	6	6	6	6	6
7. Was the methodology for **data abstraction** (including the value of health states and other benefits) stated?	5	0	5	0	0
8. Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7	7	7	7
9. Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	0	0	8	8
10. Were the primary **outcome measure(s**) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	0	0	6	6
11. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7	0	7
12. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	0	8	8	0
13. Were the choice of economic model, main **assumptions, and limitations** of the study stated and justified?	7	7	0	0	0
14. Did the author(s) explicitly discuss direction and magnitude of potential **biases?**	6	0	6	0	0
15. Were the **conclusions/recommendations** of the study justified and based on the study results?	8	8	8	8	8
16. Was there a statement disclosing the **source of funding** for the study?	3	3	3	3	0
Total	**100**	**67**	**79**	**67**	**58**

* Study must fit criteria in order to receive full points. Partial credit is not given. If criteria is not met, then the question receives no points.

Appendix Table E22. QHES Assessment of Non-U.S. Cost-effectiveness studies

Question	Possible Points*	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
1. Was the study **objective** presented in a clear, specific, and measurable manner?	7	7	7	7	7
2. Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4	4	4	4
3. Were **variable estimates** used in the analysis from the best available source (i.e., randomized controlled trial - best, expert opinion - worst)?	8	8	8	8	0
4. If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study?	1	1	1	1	1
5. Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	0	9	0	0
6. Was **incremental analysis** performed between alternatives for resources and costs?	6	6	6	6	6
7. Was the methodology for **data abstraction** (including the value of health states and other benefits) stated?	5	5	0	0	5
8. Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7	7	7	7
9. Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	8	8	8	8
10. Were the primary **outcome measure(s**) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	0	0	0	6
11. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7	0	7
12. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8	8	0	8
13. Were the choice of economic model, main **assumptions, and limitations** of the study stated and justified?	7	0	0	7	7
14. Did the author(s) explicitly discuss direction and magnitude of potential **biases?**	6	6	0	0	0
15. Were the **conclusions/recommendations** of the study justified and based on the study results?	8	8	8	8	8
16. Was there a statement disclosing the **source of funding** for the study?	3	3	3	3	3
Total	**100**	**78**	**76**	**59**	**77**

* Study must fit criteria in order to receive full points. Partial credit is not given. If criteria is not met, then the question receives no points.

APPENDIX F. Data Abstraction of Included Studies

See associated Excel file.

APPENDIX G. Detailed Characteristics and Demographic Tables

Appendix Table G1. Patient Characteristics of Studies comparing HA to PRP

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. PRP									
Buendía-López, 2019 Spain	N=106	Inclusion: Symptomatic knee osteoarthritis (Spanish Society of Rheumatology and KL grade of 1-2) Exclusion: Varus deformity of >4.2°, valgus deformity, recent trauma, inflammatory arthritis, history of gastrointestinal or cardiovascular disease, concomitant potent analgesics, corticosteroid, NSAID, anticoagulant or anti-platelet therapy within 12 months of enrollment; previous surgery to limb/spine; previous injection to study joint, active local or systemic infection; systemic disorders with NSAID restrictions (diabetes) or potential effect on knee (rheumatic, metabolic, musculoskeletal, neuropathic disorders)	HA (n=36): HMW (100,000 kDA, Durolane); 60mg/2mL; single injection PRP (n=35): Leukocyte poor; 60 ml of peripheral blood extracted, Platelet concentration 1,095,000 ± 23,200/mm^3, <4 x whole blood*; 5mL; single injection NSAID (n=35): 60 mg oral etoricoxib daily, proton pump inhibitor when necessary	None	None	None	HA vs. PRP vs. NSAID Mean age: 56.63 vs. 56.15 vs. 57.42 years Mean BMI: 24.9 vs. 24.9 vs. 25.2 % Female: 53.1% vs. 51.5% vs. 51.5% KL Grade 1: 56.3% vs. 54.5% vs. 51.5% KL Grade 2: 43.7% vs. 45.5% vs. 48.5% Mean symptom duration: NR	6 months: 92.5% (98/106) 12 months: 92.5% (98/106)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Görmeli, 2017 Turkey	N=182	Inclusion: >4 months pain/swelling radiographically documented KL grade 1-4 gonarthrosis Exclusion: Previous lower extremity surgery, systemic disorders (diabetes, rheumatic diseases, severe cardiovascular diseases, hematological diseases, infections), generalized OA, anti-coagulant or antiaggregant therapy, use of NSAIDs in the 5 days before injection, hemoglobin values less than 11 g/dL and platelet values less than 150,000/mm^3	HA group (n=39): HMW (1,000 to 2,900, Orthovisc); 30mg/2mL; 3 injections PRP3 Group (n=46): Leukocyte rich; 150 mL of venous blood, two centrifugations; platelet concentration 5.2× (1118,000 µL), >4 x whole blood[†] +1 mL of $CaCl_2$ to activate platelets, 5mL; 3 injections PRP1 Group (n=45): Leukocyte rich; 150 mL of venous blood, two centrifugations; platelet concentration 5.2× (1118,000 µL), 5mL; single injection PRP followed by 2 injections of placebo	None	PRP3: 3 injections, 3 weeks (every 7 days) PRP1: 3 injections (1 PRP, 2 placebo), 3 weeks (every 7 days) HA: 3 injections, 3 weeks Placebo: 3 injections, 3 weeks (every 7 days)	Paracetamol for discomfort	HA vs. PRP3 vs. PRP1 vs. Placebo Mean age: 53.5 vs. 53.7 vs. 53.8 vs. 52.8 years Mean BMI: 29.7 vs. 28.7 vs. 28.4 vs. 29.5 % Female: 56.4% vs. 58.9% vs. 56.8% vs. 50% Early OA[‡]: 64.1% vs. 66.7% vs. 68.1% vs. 67.5% Advanced OA[‡]: 35.8% vs. 33.3% vs. 31.8% vs. 32.5% Mean symptom duration: >4 months[§]	6 weeks: NR 3 months: NR 6 months: 89.0%	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
			Placebo (saline) (n=45): Dose NR; 3 injections						
Raeissadat, 2021 Iran	N=238**	Inclusion: Age 50-75, knee pain longer than 3 months, knee OA based the criteria of the American College of Rheumatology according to knee X-ray (KL grade 2 or 3) Exclusion: systemic disease such as diabetes mellitus, immunodeficiency, collagen vascular disease, history of malignancy, infection or active wound in the knee, auto-immune diseases, disorders affecting platelets, use of NSAIDs 2 days prior to injection, anticoagulant or anti-platelet meds 10 days before injection, steroid knee injection 3 weeks before the procedure, systemic steroid injection in previous 2 weeks, hemoglobin< 12 mg/dl or platelet< 150,000/µl, history of severe knee trauma, history of vasovagal shock, pregnancy, lactation, genu-valgum or genu-varum more than 20 degrees, allergy to egg protein, chicken proteins or chicken feather or	HA (n=59): LMW (500 to 730 kD, Hyalgan); 20mg/2mL; 3 injections over 3 weeks PRP (n=59): Leukocyte rich; 35mL of blood, double centrifuged: 15 min at 1600 rpm, 7 min at 3500 rpm; 2 injections	None	HA: 3 injections over 3 weeks (once weekly) PRP: 2 injections with a 3-week interval	Cold compression, paracetamol, exercise therapy	HA vs. PRP Mean age: 57.91 vs. 56.01 years Mean BMI: 27.46 vs. 27.41 % Female: 75.5% vs. 75.0% Duration of Pain (yrs): 3.86 vs. 4.44 KL grade 2: 55.1% vs. 50.0% KL grade 3: 44.9% vs. 50.0%	2 months: 85.6% (101/118) 6 months: 85.6% (101/118) 12 months: 85.6% (101/118)	Shahid Beheshti University of Medical Sciences

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		hypersensitivity to hyaluronate, treatment with ACE inhibitors or G6PD deficiency							
Lisi, 2018 Italy	N=58	Inclusion: Grade II/III osteoarthritis of the knee via MRI, according to Shahriaree Classification System – Modified, >18 years old, no previous OA treatment with local hyaluronic acid or steroid injections, life expectancy >1 year (i.e. no cancer, no end-stage liver disease, no end-stage kidney disease, no heart failure New York Heart Association (NYHA) class III or IV), no pregnancy, ability to understand and complete clinical and functional scales, no known allergy to HA, no acute bacterial skin and soft structure infection of the knee Exclusion: NR	HA (n=28): LMW (500 to 730 kD, Hyalgan); 20mg/2mL; 3 injections PRP (n=30): 20 mL blood, centrifuged 900 r/min for 7 minutes; 3 injections	Ultrasound	HA: 3 injections over 3 months (once monthly) PRP: 3 injections over 3 months (once monthly)	None	HA vs. PRP Mean age: 57.1 vs. 53.5 years % Female: 43% vs. 33% Mean BMI: NR KL grade: NR Mean symptom duration: NR	6 months: 86.2% (50/58) 12 months: 81.0% (47/58)	IRCCS Policlinico San Matteo Foundation
Cole, 2017 USA	N=111	Inclusion: Age 18 to 80, mean VAS pain score of >=40 of 100 (worst possible pain) 7 days during previous month, Grade 1-4 radiographic OA as defined by the KL	HA (n=59): HMW (mean 6000 kDa, Synvisc); 16mg/2mL; 3 injections	Ultrasound	HA: 3 injections over 3 weeks (once weekly)	Cold therapy/icing	HA vs. PRP Mean age: 56.8 vs. 55.9 years	3 months: NR 6 months: NR	Industry (Author-specific)

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		classification, unilateral symptoms Exclusion: Knee instability, Pretreatment VAS pain <40 of 100, major axial deviation (.5°valgus or varus deviation), bilateral symptomatic lesions, systemic disorders such as diabetes, rheumatoid arthritis, hematological diseases (coagulopathies), severe cardiovascular diseases, infections, or immunodeficiencies, current use of anticoagulants or NSAIDs used in 5 days before blood donation, history of anemia, recent intra-articular injection of corticosteroids (within 30 days) and prior treatment with HA in past 6 months, pregnancy or possible pregnancy	PRP (n=52): Leukocyte poor; 4 ml (platelets, PRP-to-peripheral blood ratio of platelets 1.73 (SD 0.05),; 3 injections		PRP: 3 injections over 3 weeks (once weekly)		Mean BMI: 29.0 vs. 27.4 % Female: 60% vs. 42.9% KL Grade 1: 0% vs. 6.1%) KL Grade 2 : 54.0% vs. 53.1% KL Grade 3: 44% vs. 40.8% KL Grade 4: 2.0% vs. 0% Mean symptom duration: NR	12 months: 89.2% (99/111)	
Lana, 2016 Brazil	N=105[††]	Inclusion: age 40-70, >=4 months chronic pain and/or joint edema, radiographic evidence of KL grade 2 or 3 OA Exclusion: coagulopathies, axial deviation of lower limb larger than 5° for valgus and	HA (n=36): HMW (2.4-3.6 million Daltons, Eufflexa); 20mg/2mL; 3 injections PRP (n=36): Leukocyte poor; 5 ml (platelets	Ultrasound	HA: 3 total injections at 2 week intervals PRP: 3 total injections	Local icepack, three times a day for 30 minutes each in the first 2 days after injection and switch to hot packs in the third and fourth days after injection. Patients took	HA vs. PRP Mean age: 60.0 vs. 60.9 years Mean BMI: 28.24 vs. 27.42	3 months: 100% 6 months: 100% 12 months: 100%	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		varus knee, severe cardiovascular diseases, diabetes mellitus and, immunosuppressive status, patients on anticoagulants, antithrombotic and anti-platelet drugs and non-steroid anti-inflammatory medication, patients with <11mg/dL of hemoglobin and <150.000mm³ platelets, auto-immune diseases, history of previous surgery in the affected joint and KL grade 4 OA	ranged from 800,000 to 1,600,000 per mm^3, 3 injections		at 2 week intervals	Dipirone 1.0 g twice a day for the first two days after procedure	% Female: 91.7% vs. 80.6% KL grade 1: 25% vs. 25% KL grade 2: 44% vs. 39% KL grade 3: 31% vs. 36% Mean symptom duration: NR		
Louis, 2018 France	N=56	Inclusion: Age 20 to 75, symptomatic knee OA grade 2 in KL scale, failure of well-conducted medical treatment, axial deformity of the lower limb equal to or lower than 5 degrees measured in full-length lower limb radiograph (hip-knee-ankle angle between 175 and 185), BMI between 20 and 30, hemoglobin >10 g/dL, negative pregnancy test Exclusion: knee instability, thrombocytopenia <150G/L, thrombopathy, infectious disease or positive serology	HA (n=28): HMW (100,000 kDA, Durolane); 60mg/3mL; single injection PRP (n=28): Leukocyte poor; 4 ml (platelets >2 but < 4 compared with blood); single injection	Echographic	None	Ice, paracetamol	HA vs. PRP Mean age: 48.5 vs. 53.2 years Mean BMI: 27.0 vs. 25.6 % Female: 54.2% vs. 41.7% KL grade: NR Mean symptom duration: 100.2 vs. 99.5 months	3 months: 91.1% (51/56) 6 months: 78.6% (44/56)	Manufacturer

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		to HIV, hepatitis C virus, hepatitis B virus, or syphilis, current chronic treatment by oral corticosteroid (or last dose <2 weeks before inclusion), intra-articular knee injection of corticosteroid <8 weeks before inclusion, intra-articular knee injection of HA <weeks before inclusion, NSAID treatment completed <2 weeks before injection, fever or recent disease, autoimmune disease, inflammatory arthritis, immune deficit, pregnancy, patient under guardianship or involved in another clinical trial							
Raeissadat, 2015 Iran	N=160	Inclusion: age 40–70, symptom duration >3 months, confirmatory X-ray diagnosis (KL grade 1–4) within the past 3 months Exclusion: history of diabetes mellitus, immunodeficiency and collagen vascular disorders, history/presence of malignant disorders, infection/active wound in the knee area, recent history of severe trauma to the knee,	HA (n=73): LMW (500 to 730 kD, Hyalgan); 20mg/2 mL; 3 injections PRP (n=87): Leukocyte rich; 4-6 ml (platelet concentration 5 x normal values); 35–40 mL blood; 2 injections	None	HA: 3 injections over 3 weeks (once weekly) PRP: 2 injections with a four-week interval	Ice, acetaminophen, acetaminophen with codeine (prescribed on individual basis), exercise therapy	HA vs. PRP Mean age: 61.13 vs. 56.85 years Mean BMI: 27.03 vs. 28.20 % Female: 75.8% vs. 89.6%	12 months: 86.9% (139/160)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		autoimmune/platelet disorders, treatment with anticoagulant and antiplatelet meds 10 days before injection, use of NSAIDs 2 days before injection, history of knee intraarticular injections of corticosteroids during the past 3 weeks or use of systemic corticosteroids 2 weeks before PRP injections, hemoglobin measures of <12g/dL and platelet counts of <150,000/ml, history of vasovagal shock, pregnancy, or breastfeeding, and genu valgum/varum >20 degrees, allergy to avian proteins, feathers and egg products or hypersensitivity to hyaluronate					KL Grade 1: 0% vs. 6% KL Grade 2: 47% vs. 44% KL Grade 3: 37% vs. 38% KL Grade 4: 16% vs. 12%		
Tavassoli, 2019 Iran	N=95	Inclusion: Diagnosis of knee OA defined by the criteria of the American College of Rheumatology, staged using the Ahlback radiological grading, bilateral knee OA with the same Ahlback grade, and all knees with full range of motion. Exclusion: History of diabetes, other joint diseases	HA (n=31): LMW (500 to 730 kD, Hyalgan); 30mg/2mL; 3 injections PRP-1 (n=31): Leukocyte rich; 4-6 ml (platelet conc. NR); 40 mL blood; single injection	None	HA: 3 injections over 3 weeks (once weekly) PRP-1: single injection	Acetaminophen	HA vs. PRP-1 vs. PRP-2 Mean age: 63.30 vs. 63.23 vs. 66.04 years Mean BMI: 28.94 vs. 28.43 vs. 29.61	3 months: 87.4% (83/95)	University

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		in the knee such as rheumatoid arthritis or gout, knee surgery, knee fracture, intra-articular injection of corticosteroids during the previous 2 weeks, intra-articular injection of other drugs such as hyaluronic acid over the previous year, contraindications for intra-articular injection such as thrombocytopenia, coagulopathy, articular infection of knee, skin infection in injection site, impairment of immunity (e.g., acquired immune deficiency syndrome or receiving immunosuppressive medication) and severe intra-articular effusion (intra-articular injection was started after treatment and cure of effusion), Ahlback grade >=3	PRP-2 (n=33): Leukocyte rich; 4-6 ml (platelet conc. NR); 40 mL blood; 2 injections		PRP-2: 2 injections with a 3 week interval		% Female: 70.4% vs. 82.1% vs. 78.6% Ahlback grade: NR Mean symptom duration: NR		
Sdeek, 2021 Egypt	N=200	Inclusion: age 45 to 65, chronic knee pain >=6 months, imaging findings suggesting degenerative knee disorder (KL Score grade 2-3), primary OA	HA (n=94): LMW (500 to 730 kD, Hyalgan); 2.5mL; 3 injections PRP (n=95): Leukocyte-poor; 2.5 ml (platelet	None	HA: 3 injections at 2 week intervals PRP: 3 injections	Cold, acetaminophen	HA vs. PRP Mean age: 59.5 vs. 60.2 years Mean BMI: 27.1 vs. 27.9	36 months: 100%	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Exclusion: Age: <45 or >65; KL grade 1 or 4; Pretreatment VAS <40, rheumatoid arthritis, previous surgery or injection for the knee to be injected; severe mechanical axis deviation (MAD>10°), Knee instability, knee Osteo-Chondral lesion hematological diseases, infections, immunodepression, patients on anticoagulants or antiplatelet therapy, hemoglobin level lower than 11 g/dL or platelet count lower than 150,000/mm³. use of NSAIDs in the 5 days before blood donation	conc. 2,664 ±970 x 10^3/ul; 8.2 x whole blood; 3 injections		at 2 week intervals		% Female: 83.0% vs. 84.2% KL grade 2: 52.1% vs. 45.3% KL grade 3: 47.9% vs. 54.7% Mean symptom duration: ≥6 months[§]		
Wang, 2022 Taiwan	N=100	Inclusion: Age between 35 and 85 years, diagnosis consistent with KOA, KL grade 1-3 (normal hematological examination results Exclusion: Diabetes, hematological or cardiovascular disease or other systemic diseases, infection, hemoglobin level lower than 11 g/dl and platelet count less than	HA (n=50): HMW (620-1,170 kDa, ARTZ (alt name for SUPARTZ)); 25mg/2.5mL; 3 injections PRP (n=50): Leukocyte-rich; 4mL; 40 ml blood, 3 injections	NR	HA: Once weekly for 3 weeks PRP: Once weekly for 3 weeks	NR	HA vs. PRP Mean age: 62.3 vs. 64.9 years Mean BMI: 22.1 vs. 23.4 % Female: 79.1% vs. 73.8%	3 months: NR 6 months: NR Final follow-up: 85% (85/100)	Health Commission of Zhejiang Province

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		150,000/mm^3, use of NSAIDs within 2 weeks before treatment, anticoagulant drugs or immunosuppressants within 3 months					KL grade 1 through 3: 100%§‡‡		

BMI = body mass index; $CaCl^2$ = calcium chloride; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

* Per Costa 2022 Systematic Review.

† per Costa 2022 SR.

‡ Patients were classified as Early OA (KL Grade 0-3), and advanced OA (KL Grade 4).

§ Inclusion criteria.

** N of treatments of interest=118.

†† N of treatments of interest=72.

‡‡ Details NR.

Appendix Table G2. Patient Characteristics of Studies comparing HA to Placebo

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. Placebo									
Hangody, 2018 Poland, Hungary	N=368*	Inclusion: 40 to 75 years of age with a BMI ≤40 kg/m^2, and KL OA grade 1-3 in the index knee as determined by X-ray.15 At baseline, subjects had to have a WOMAC pain score ≥40 mm and ≤90 mm in the affected knee and ≤30 mm in the contralateral knee on a	HA (n=150): Cross-linked (1,000-2,900 kDa, Monovisc); 88mg/4mL; single injection Placebo (saline) (n=69):	None	None	Acetaminophen	HA vs. Placebo Mean age: 59.2 vs. 58.0 years Mean BMI: 28.4 vs. 29.1	3 months: NR 6 months: 96.3% (211/219)	Anika Therapeutics, Inc.

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		100-mm visual ana-log scale (VAS) Exclusion: certain joint disorders, some medical condition(s), or prior knee treatments (including HA or steroid injections in the index knee in the past 6 months); and taking medications that could interfere with the procedure, healing, and/or assessments. A subject was excluded if the synovial fluid aspirate volume was >20 mL or there was visual evidence of cloudiness, crystals, or blood. Pregnant women were also excluded	4mL; single injection				% Female: 66.0% vs. 73.9% KL grade 1: 16.0% vs. 24.6% KL grade 2: 65.3% vs. 55.1% KL grade 3: 18.0% vs. 20.3% KL grade 4: 0.7% vs. 0% Mean symptom duration: NR		
Petterson, 2019 USA	N=369	Inclusion: between 35 and 75 years old, had a BMI between 20 and 40 kg/m^2, and had a diagnosis of idiopathic knee OA as defined by the American College of Rheumatology. Additional inclusion criteria were symptom duration of at least 6 months, confirmed radiographic evidence of	HA (n=184): Cross-linked (1,000-2,900 kDa, Monovisc); 4mL; single injection Placebo (saline) (n=185): 4mL; single injection	None	None	Glucosamine, chondroitin sulphate, acetaminophen	HA vs. Placebo Mean age: 59.5 vs. 58.7 years Mean BMI: 29.9 vs. 30.4 % Female: 59.2% vs. 57.3%	3 months: NR 6 months: 89.7% (331/369)	Anika Therapeutics

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		OA within 6 months of study enrollment, KL grade 2 or 3 OA in the index knee, and a baseline summed WOMAC VAS pain score greater than 200 mm and less than 400 mm out of a maximum 500 mm scoring system Exclusion: intra-articular crystals, neo-plasms, rheumatoid arthritis, fibromyalgia, peripheral neuropathy, vascular insufficiency, immunocompromised or immunosuppressive disorder, systemic bleeding disorder, symptomatic pes anserine bursitis, clinically significant knee deformity that could interfere with the ability to evaluate the effectiveness of the treatment on pain and function, intra-articular HA injection in the index knee within 6 months, intra-articular steroid injection or knee arthroscopy in the index knee within 3 months,					KL grade 2: 57.1% vs. 52.4% KL grade 3: 42.9% vs. 47.6% Mean symptom duration: ≥6 months[†]		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		open surgical procedure in the index knee within 12 months, synovial fluid aspirate greater than 20 ml, and range of motion less than 90° in the index knee. Patients with KL grade 3 or 4 OA in the contralateral knee, a baseline summed WOMAC VAS pain score greater than 150 mm in the contralateral knee, and patients who underwent an open surgical procedure within 3 months in the contralateral knee							
Gel-One SSED (Takamura original study) USA	N=817	Inclusion: Age 40 to 80 years, pain in the target knee for most of the previous 30 days, grade 1 to 3 score on the KL grading scale and had radiographic evidence of one or more of the following features in the target knee by bilateral standing anteroposterior x-ray taken no longer than 90 days prior to screening: osteophytes, joint space	HA (n=407): Cross-linked (>5,000 kDa, Gel-200); mg and mL NR; single injection Placebo (saline) (n=410): mL NR; single injection	NR	None	NR	HA vs. Placebo Mean age: 59.3 vs. 59.8 years Mean BMI: 28.6 vs. 28.8 % Female: 55.0% vs. 57.5%	3 months: NR 6 months: 92.3% (754/817)	Seikagaku Corp

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		narrowing, osteosclerosis, could complete the 50-foot walk test (without assistance, no time constraint), pain score for the target knee of 50 mm to 90 mm (inclusive) recorded on a 100-mm VAS immediately following a 50-foot walk at both screening and Week 0 pre-injection, average pain score for the contralateral knee of less than 30 mm recorded on a 100-mm VAS immediately following a 50-foot walk at screening and Week 0 pre-injection, had been on a stable dose of any allowed, long-term concomitant medications and a stable regimen of non-pharmacological therapies for 30 days prior to screening, including the following: allowed concomitant medications, antidepressants for depression or anxiety,					KL grade 1: 28.1% vs. 27.3% KL grade 2: 40.0% vs. 40.3% KL grade 3: 31.8% vs. 32.4% Mean symptom duration: ≥1 month[†]		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		chondroitin sulfate, oral HA, or/and glucosamine, non-pharmacological therapies (Subjects were encouraged to remain on a stable dose of any of these medications throughout the study. Subjects not meeting this criterion could return after 30 days on a stable dose of these medications to complete the screening process), willing to discontinue use of any of the following prohibited medications: opioids (Morphine, Codeine, Hydromorphone, Hydrocodone, Meperidine, Oxycodone, Oxymorphone, Propoxyphene, Tramadol, Buprenorphine, Butorphanol, Nalbuphine, Pentazocine), long-acting opioid patches (tramadol and fentanyl), long-acting formulations of oral opioids (oxycodone,							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		methadone, and levorphanol), corticosteroids (with the exception of intranasal corticosteroids and steroid-containing ophthalmic solutions) (Subjects who agreed to discontinue use of a prohibited medication could return after 30 days to complete the screening process), willing to switch to using acetaminophen as a rescue medication if currently using other pain medications, such as NSAIDs, or if currently using anticonvulsants exclusively for pain management. A maximum of 1,000 mg/day of acetaminophen was permitted for breakthrough pain control. The use of low-dose aspirin (one to two 81-mg doses/day) for thrombosis prophylaxis was permitted; Willing to suspend the use of all							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		medications for pain including acetaminophen (except antidepressants for depression or anxiety) and non-pharmacologic therapies to treat knee pain (e.g., physical therapy, ice or heat packs) for 24 hours before each study visit. Exclusion: 1) Grade 4 score on the K-L grading scale for the target knee, Grade 3 score on the K-L grading scale for the target knee and exhibited at least one characteristic of a grade 4 on the radiograph (large osteophytes, PMA P080020/S020: FDA Summary of Safety and Effectiveness Data Page 8 marked narrowing of joint space, severe sclerosis, or definite deformity of bone contour), Acute fracture of the lower limb. d. Medical history of severe bone disease (e.g.,							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		osteoporosis, osteonecrosis, joint deformity, meniscal instability, or septic arthritis). 2) Was categorized as grossly obese, defined as body mass index (BMI) greater than 35 kg/m^2 . 3) Had clinically apparent tense effusion of the target knee. 4) Had chondrocyte transplantation or reconstruction of ligaments in the target knee. 5) Had received an intra-articular HA injection(s) for the treatment of OA of either knee within 6 months prior to screening. 6) Had received an intra-articular injection(s) into any joint (e.g., corticosteroids or chondroprotective agents) within 90 days prior to screening. Subjects receiving a corticosteroid injection during the study							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		were withdrawn from the study. 7) Began treatment with or changed the dosage of an allowed concomitant medication within 30 days prior to screening. Subjects could return after 30 days on a stable dose of these medications. 8) Had surgery to the target knee within 12 months or arthroscopy of the target knee within 90 days prior to screening. 9) Had a joint replacement of the target knee at any time. Joint replacement of the contralateral knee was permitted provided it was performed at least 12 months prior to screening. 10) Had significant joint infection in the target knee or inflammatory or skin disorder in the injection area of the target knee. 11) Had symptomatic OA of the hips, spine, or							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		ankle, if it would interfere with the evaluation of the target knee. 12) Had an inflammatory disease of either knee other than OA (e.g., rheumatoid arthritis, septic arthritis). 13) Had another disease that could affect the health of the knee (e.g., chronic hemochromatosis; sickle cell anemia; arthropathies of systemic diseases such as chondrocalcinosis, gout, pseudogout, psoriasis, hemophilia, and infectious diseases of the joints). 14) Had fibromyalgia, anserine bursa, lumbar radiculopathy, neurogenic or vascular claudication, vascular insufficiency of lower limbs, or peripheral neuropathy severe enough to interfere with the study evaluations. 15) Was hospitalized at the time of screening or had a planned hospitalization							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		during the life of the study. 16) Had a known history of allergy to HA products or acetaminophen. 17) Had contraindications to treatment with acetaminophen. 18) Had a history of recurrent, severe allergic or immune-mediated reactions or other autoimmune disorders. 19) Had a malignancy at the time of screening or had received treatment for malignancy within the past 5 years. 20) Had used an investigational drug, device, or biologic in the 90 days prior to screening. 21) Had a systemic or other disease or significant liver function test results from screening that, in the opinion of the investigator, would interfere with study evaluation or have an							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		impact on the balance of benefits and risks of study treatment. a. Diseases that could have interfered: uncontrolled diabetes; immunodeficiency syndrome; significant cardiovascular, renal, or liver disease; severe anemia; severe thrombocytopenia; or severe infectious disease with or without fever. b. Significant liver function test results: aspartate amino transferase (AST) or alanine amino transferase (ALT) greater than 2.5 times the upper limit of normal. 22) Female subjects who were pregnant or lactating. 23) Female subjects of childbearing potential who were not willing to use adequate contraceptive measures to avoid pregnancy. All sexually active							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		subjects agreed to practice an adequate method of birth control during the study. Adequate methods of birth control included the following: a. Hormonal contraception. b. Use of at least one acceptable barrier method. Acceptable barrier methods included diaphragm plus a spermicidal agent or condoms (male or female) plus a spermicidal agent. c. Vasectomy, hysterectomy, bilateral tubal ligation, intrauterine device, and/or an exclusive sexual partner for whom one of these methods applies. Females who had not menstruated within the past 2 years were considered postmenopausal and did not need to practice birth control. 24) Any psychiatric illness or history of alcohol or other substance abuse							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		that would prevent comprehension of the details and nature of the study. 25) Any subject who was receiving worker's compensation or was involved in litigation at the time of screening. 26) Any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.							
Takamura, 2019 Japan	N=311	Inclusion: aged 40 to 80 years with diagnosed knee OA, KL scores grade 1 to 3, and pretreatment pain scores of 50 to 90 mm on a 100-mm VAS in the target knee following a 50-foot walk test were enrolled. Non-posttraumatic OA, K-L grade 2 or 3, WOMAC pain during walking (A1) and WOMAC pain subscores of 40 to 80 mm, ≥3 months' duration of OA pain	HA (n=152): Cross-linked (>5,000 kDa, Gel-200); mg and mL NR; single injection Placebo (saline) (n=159): mL NR; single injection	NR	None	NR	HA vs. Placebo Mean age: 61.0 vs. 62.8 years % Female: 57.9% vs. 62.3% Mean BMI: NR KL grade 2: 55.9% vs. 57.9%	3 months: 100% 6 months: 100%	Seikagaku Corp

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Exclusion: NR					KL grade 3: 44.1% vs. 42.1% Mean symptom duration: ≥3 months[†]		
Strand, 2012 USA	N=379	Inclusion: 40 to 80 years of age, with knee OA, and pain in the affected knee of 4 weeks in duration while standing or walking; KL grade 1-3 by X-ray; WOMAC pain sub-scores >=40 mm in affected knee and <=20 mm in contralateral knee by 100-mm VAS; and willing to dis-continue current OA treatments other than allowed medications, stable for >=4 weeks prior to entry	HA (n=251): Cross-linked (kDa NR, Gel-200); 30mg/3mL; single injection Placebo (phosphate-buffered saline) (n=128): 3mL; single injection	None	None	NSAIDs, non-prescription herbal therapies, chondroprotective agents (e.g., oral HA, glucosamine, chondroitin sulfate, minocycline), intermittent short-acting oral opiates	HA vs. Placebo Mean age: 60.9 vs. 60.3 years Mean BMI: 28.3 vs. 28.7 % Female: 59.5% vs. 60.2% Duration of OA (months): 42.0 vs. 31.2 KL grade 1: 8.5% vs. 14.1% KL grade 2: 38.1% vs. 36.7% KL grade 3: 53.4% vs. 49.2%	3 months: 92.3% (350/379)	Seikagaku Corp

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Strand, 2016 USA	N=308‡	Inclusion: See Strand, 2012	HA retreatment (n=125): Cross-linked (kDa NR, Gel-200); 30mg/3mL; single injection in OG study + 1 inj. In OLE HA non-treatment (n=106): Cross-linked (kDa NR, Gel-200); 30mg/3mL; single injection in OG study	None	HA retreatment: 1 additional injection in OLE	See Strand, 2012	HA Retreatment vs. Non-treatment Mean age: 60.8 vs. 61.4 years Mean BMI: 28.3 vs. 28.4 % Female: 59.2% vs. 58.5% KL grade 1: 8.0% vs. 10.4% KL grade 2: 33.6% vs. 43.4% KL grade 3: 58.4% vs. 46.2%	6 months: NR	Seikagaku Corp
Arden, 2014 Sweden, Germany, UK	N=218	Inclusion: Normally active men and women aged >50 years with the ability to walk 50 meters unaided and with knee pain meeting the American College of Rheumatology criteria for	HA (n=108): NASHA (90,000 kDa Durolane); 60mg/3mL; single injection Placebo (saline)	None	None	Acetaminophen	HA vs. Placebo Mean age: 64.5 vs. 60.9 years	6 weeks: 79.8% (174/218)	Q-Med AB, industry (specific authors)

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		the diagnosis of OA (KL grade 2/3); WOMAC pain score of 7–17 at baseline visit Exclusion: pain during the previous 3 months in the non-study knee, radio-graphically verified OA of the non-study knee (KL grade 4), OA or clinically significant pain from any part of the musculoskeletal system other than the study knee, previous IA steroid injection into the study knee within the last 3 months, previous IA HA injection into the study knee within the last 9 months, use of systemic steroids (excluding inhaled steroids) within the last3 months, and arthroscopy or other surgical procedures in the study knee within the last 12 months	(n=110): 3mL; single injection				Mean BMI (female): 26.4 vs. 26.9 Mean BMI (male): 28.2 vs. 28.1 % Female: 55% vs. 46% KL grade 2: 30.6% vs. 36.4% KL grade 3: 29.4% vs. 63.6%		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Bao, 2018 China	N=60[§]	Inclusion: mentally intact, i.e., able to follow 2-step commands; (ii) radiographic OA severity grade 2 or above for the knee joint on the KL scale and pain visual analogue scale score ≥6 after walking a distance of 100 m continuously on level ground; (iii) failure of physical therapy and/or medical treatment in the last 3 months; (iv) involvement of unilateral knee joint through clinical check and bilateral X-ray of the knees Exclusion: patients who had received an IA injection in the affected knee within 3 months prior to the initial evaluation; (ii) disease complications, such as rheumatoid arthritis, tumors and any non-arthritic trauma to the affected knee, in the last 3 months; (iii) severe cardiac, liver or kidney dysfunction that had	HA (n=20): LMW (620-1,170 kDa, ARTZ (alt name for SUPARTZ)); mg/mL NR; 5 injections Placebo (saline) (n=20): 2.5mL; single injection	Ultrasound	HA: 5 injections, once weekly	Exercise therapy, ice	HA vs. Placebo Mean age: 66.0 vs. 65.3 years % Female: 35% vs. 55% Mean BMI: NR Time since OA (months): 31.8 vs. 33.6 KL grade 2: 60% vs. 70% KL grade 3: 40% vs. 30%	2 months: 100%	Yue Bei People's Hospital

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		caused hospitalization in the last 3 months							
Ke, 2021 China	N=440	Inclusion: aged 40 to 80 years, with grade I to III KL OA of the knee, confirmed by standard X-ray up to 3 months before screening. Patients were required to meet the ACR criteria for knee OA, had a WOMAC A1 Numerical Rating Scale score of between 4.0and 8.0 at baseline, and failed to respond to non-pharmacologic therapy and/or simple analgesics Exclusion: moderately severe or severe depression as indicated by PHQ-9 total score of≥15 or a score of > 0 on item # 9, severe anxiety, or severe insomnia as indicated by a score from four questionnaires (pain DETECT, Patient Health Questionnaire-9, Generalized Anxiety	HA (n=218): HMW (6,000 kDa, Hylan GF-20, Synvisc formulation but maybe not brand); 48mg/6mL; single injection Placebo (phosphate-buffered saline) (n=220): 6mL; single injection	NR	None	Acetaminophen (500 mg, up to 3000 mg/day), Acetaminophen (325mg)/oxycodone (5 mg, up to 1 tablet 4 times daily), or Acetaminophen (325 mg)/tramadol (37.5 mg, up to 1 tablet 6 times daily)	HA vs. Placebo Mean age: 61.5 vs. 61.6 years Mean BMI: 25.57 vs. 25.39 % Female: 77.3% vs. 78.2% KL grade 1: 14.1% vs. 10.9% KL grade 2: 47.7% vs. 52.7% KL grade 3: 38.2% vs. 36.4%	3 months: NR 6 months: 98.0%	Sanofi

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Disorder-7, and Insomnia Severity Index) at the screening visit. Patients who had prior knee surgery, or previous IA treatment with corticosteroids, local anesthetic agents or viscosupplementation agents to the target knee were excluded. Patients with scores of contralateral knee pain (if present) greater than 3.0 numerical rating scale, or those with ipsilateral hip OA, concomitant inflammatory disease, or other conditions that affected the joints							
Farr, 2019 USA	N=200 N of treatments of interest=132	Inclusion: older than 18 years with a BMI <40 kg/m^2, diagnosed with moderate knee OA (grade2 or 3 on the KL score), and a 7-day average pain score of 4 or greater on a scale of 1 to 10. Female patients were abstinent, actively practicing an accepted contraceptive method,	HA (n=64): Cross-linked (1,000-2,900 kDa, Monovisc); 88mg/4mL; single injection Placebo (saline) (n=68): 4mL, single injection	None	None	NR/None	HA vs. Placebo Mean age: 55.4 vs. 54.9 years Mean BMI: 28.2 vs. 28.5 % Female: 48.4% vs. 45.6%	3 months: 95.5% (126/132) 6 months: 25.0% (33/132)	Organogenesis. Inc.

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		surgically sterilized, or postmenopausal. Exclusion: taken pain medication <15 days prior to the injection, receive pain medicine other than acetaminophen for conditions unrelated to OA of the index knee, regularly use anticoagulants, history of substance abuse, or failure to agree not to take additional knee symptom-modifying drugs during the course of the study without reporting the use to the study team. Physical or IA injection exclusion criteria included frank mechanical symptoms such as locking, intermittent block to range of motion, or loose body sensations (meniscal displacement or IA loose body), corticosteroid or viscosupplementation injection into the index knee within 3 months, knee surgery on index knee within 12 months or on contralateral knee					KL grade 2: 45.3% vs. 38.2% KL grade 3: 54.7% vs. 61.8%		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		within 6 months, or acute injury to the knee within 3 months. Additional exclusion criteria included workers' compensation patients, history of solid organ or hematologic transplantation, rheumatoid arthritis and other autoimmune disorders, current immunosuppressive treatment, diagnosis of non-basal cell malignancy within preceding 5 years, or infection requiring antibiotic treatment within the preceding 3 months. Female patients were excluded if they were pregnant or had a desire to become pregnant during the study							
Gomoll, 2021 USA	N=200 N of treatments of interest=132	Inclusion: older than 18 years with a body mass index (BMI) <40 kg/m^2, diagnosed with moderate knee OA (grade2 or 3 on the KL score), and a 7-day average pain score of 4 or greater on a scale of 1 to 10. Female patients were abstinent, actively practicing an accepted	HA (n=64): Cross-linked (1,000-2,900 kDa, Monovisc); 88mg/4mL; single injection Placebo (saline) (n=68):	None	None	NR/None	HA vs. PLacebo Mean age: 55.4 vs. 54.9 years Mean BMI: 28.2 vs. 28.5	3 months: 95.5% (126/132) 6 months: 25.0% (33/132) 12 months:	Organogenesis. Inc.

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		contraceptive method, surgically sterilized, or postmenopausal. Exclusion: taken pain medication <15 days prior to the injection, receive pain medicine other than acetaminophen for conditions unrelated to OA of the index knee, regularly use anticoagulants, history of substance abuse, or failure to agree not to take additional knee symptom-modifying drugs during the course of the study without reporting the use to the study team. Physical or IA injection exclusion criteria included frank mechanical symptoms such as locking, intermittent block to range of motion, or loose body sensations (meniscal displacement or IA loose body), corticosteroid or viscosupplementation injection into the index knee within 3 months, knee surgery on index knee within 12 months or	4mL, single injection				% Female: 48.4% vs. 45.6% KL grade 2: 45.3% vs. 38.2% KL grade 3: 54.7% vs. 61.8%	22.0% (29/132))	

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		on contralateral knee within 6 months, or acute injury to the knee within 3 months. Additional exclusion criteria included workers' compensation patients, history of solid organ or hematologic transplantation, rheumatoid arthritis and other autoimmune disorders, current immunosuppressive treatment, diagnosis of non-basal cell malignancy within preceding 5 years, or infection requiring antibiotic treatment within the preceding 3 months. Female patients were excluded if they were pregnant or had a desire to become pregnant during the study							

AMR = American College of Rheumatology; BMI = body mass index; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PHQ-9 = Patient Health Questionnaire-9; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Appendix Table G3. Patient Characteristics of Studies comparing HA to Steroids

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. Steroid									

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Vaishya, 2017 India	N=82	Inclusion: moderate OA knee (KL grade 2 and 3) Exclusion: systemic disorders such as diabetes and thyroid disorder, inflammatory arthritis, major axial deviation at knee joint (varus>5, valgus>5), hematological diseases, e.g., coagulopathy, severe cardiovascular diseases, any infective foci anywhere in the body, immunosuppression, malignancy, age>80 years, case with history of previous IA injection	HA (n=42): HMW (6,000, Synvisc-One); 48mg/6mL; single injection Steroid (n=40): Triamcinolone hexa-acetate; 40mg; single injection	None	None	None	HA vs. Steroid Mean age: NR Mean BMI: NR % Female: 69% vs. 62.5% KL grade 2: 43% vs. 55% KL grade 3: 57% vs. 45%	3 months: 100% 6 months: 100%	None
Askari, 2016 Iran	N=140	Inclusion: 5 to 80 years who were suffering from knee OA for at least 3 months, along with radiographic OA KL grade 2 and 3 Exclusion: History or presence of trauma or surgery or cancer or malignant tumors, infections and sores on the target knee, history of vasovagal shock, use of NSAIDs in 2 days prior to injection, any receiving corticosteroids injection in the knee in the last 6 months, pregnancy and lactation	HA (n=71): LMW (500-730 kDa, Hyalgan Dist by Fidia); 2mL; single injection Steroid (n=69): Type NR; 40mg; single injection	None	None	None	HA vs. Steroid Mean age: 58.5 vs. 57.0 years % Female: 87.3% vs. 82.6% Mean BMI: NR Mean symptom duration: ≥3 months[†]	3 months: 100%	Fasa University of Medical Sciences

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Bissichia, 2016 Italy	N=150	Inclusion: walking patients older than 45, with a single symptomatic knee. Patients were included if they had a KL grade 2–3 knee osteoarthritis and a VAS for pain ≥3 Exclusion: grade 1 or 4 osteoarthritis according to KL, symptoms in both knees, a varus or valgus deformity greater than 10 degrees, flexion contracture greater that 15 degrees, ligamentous instability, or meniscal tears, NSAIDSs used in the last 30 days, intra-articular injections in the last 12 months; septic, inflammatory or crystal arthritis, previous surgeries in the last 6 months, physical therapy in the last 30 days	HA (n=75): LMW (500-730 kDa, HYADD 4 (Hymovis)); Dose NR; 2 injections Steroid (n=75): Type/Dose NR; 2 injections	None	HA: 2 injections, once weekly Steroid: 2 injections, once weekly	NSAIDs, acetaminophen	HA vs. Steroid Mean age: 71.5 vs. 68.6 years % Female: 70.7% vs. 66.7% Mean BMI: NR KL Grade 2 or 3: 100%**	3 months: 100% 6 months: 90.7% (136/150) 12 months: 85.3% (128/150)	None
Tammachote, 2016 Thailand	N=110	Inclusion: symptomatic primary knee osteoarthritis according to the American Rheumatism Association classification criteria for knee osteoarthritis, dissatisfaction with conservative treatment (NSAIDs, oral analgesic drugs, physical therapy, or brace), no lumbar spondylosis with radiculopathy, good cognition,	HA (n=55): HMW (6,000 kDa, Hylan GF-20 (Synvisc)); 6mL; single injection Steroid (n=55): Triamcinolone acetonide + Lidocaine + Epinephrine;	None	None	35mg orphenadrine citrate, 500mg acetaminophen	HA vs. Steroid Mean age: 62.6 vs. 61 years % Female: 86% vs. 73.5% Mean BMI: 26.3 vs. 25.8	3 months: NR 6 months: 90.0% (99/110)	Thammasat University

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		and the ability to understand the study protocol Exclusion: allergy to any of the medications used in this study, bone-on-bone arthritis appearing on any radiograph, varus or valgus deformity of >5°from the mechanical axis of the knee, previous fracture or surgical procedure of the investigational knee, previous intra-articular injection in the ipsilateral knee in the past 6 months, and current infection in the affected limb	1mL 40mg CS + 5mL 1% Lido w/ 1:100000 Epi; single injection				KL grade 1: 20% vs. 24.5% KL grade 2: 22% vs. 22.4% KL grade 3: 44% vs. 38.8% KL grade 4: 14% vs. 14.3% Mean symptom duration: NR		
Leighton, 2014 Canada, UK, Sweden	N=442	Inclusion: aged 35 to 80 with a body mass index of <=40 kg/m^2, the ability to walk 50m unaided, unilateral knee pain meeting he American College of Rheumatology criteria for the diagnosis of OA, WOMAC pain score of 7 to 17 in the study knee, and radio-graphically verified OA of the study knee (KL grade II or II) Exclusion: clinically detectable knee effusion, clinically significant contralateral knee OA (WOMAC pain score>3),clinically significant pain in joints other than the	HA (n=221): NASHA (90,000 kDa Durolane); 60mg/3mL; single injection Steroid (n=221): Methylprednisolone; 40mg/1mL; single injection	None	None	Acetaminophen	HA vs. Steroid Mean age: 61.9 vs. 61.5 years Mean BMI: 28.2 vs. 28.3 % Female: 51% vs. 47% Duration of OA (years): 4.7 vs. 4.9 KL grade 2: 32.6% vs. 39.5%	3 months: 87.3% (386/442) 6 months: 77.8% (344/442)	Q-Med AB, Smith & Nephew, UK Ltd

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		knee, IA steroid injection into the study knee within the preceding 3 months, IA HA injection into the study knee within the preceding 9 months, use of systemic glucocorticosteroids (excluding inhaled steroids) within the preceding 3 months and arthroscopy or other surgical procedure in the study knee within the preceding 12 months					KL grade 3: 67.4% vs. 60.5%		
Campos, 2017 Brazil	N=120	Inclusion: currently wait-listed for total knee arthroplasty, treatment adherence Exclusion: intra-articular injection in the past six months, were allergic to any of the substances used in the study, or had a history of knee infection	HA (n=50): HMW (6,000 kDa, Hylan GF-20 (Synvisc)); 6mL; single injection Steroid (n=53): Triamcinolone acetonide; 20mg/1mL; single injection	None	None	None	HA vs. Steroid Mean age: NR % Female: 73.3% Mean BMI: NR KL Grade: NR Mean symptom duration: NR	3 months: 75.7% (78/103) 6 months: 71.8% (74/103)	None

BMI = body mass index; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

* N of treatments of interest=219.

† Inclusion criteria.

‡ N of treatments of interest=231.

§ N of treatments of interest=40.

** Details NR.

Appendix Table G4. Patient Characteristics of Studies comparing HA to Oral Analgesics

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. Oral Analgesics									
Guner, 2016 Turkey	N=62	Inclusion: aged 50–70 years, standard radiographic criteria for symptomatic mild or moderate knee OA (KL 2 and 3), and pain with the regular use of NSAIDs or other analgesics Exclusion: biochemical analysis abnormality, active peptic ulcer, pregnancy, secondary arthritis, hypertension, previous knee surgery, sensitivity to HA or other NSAIDs, a history of chronic infection, such as hepatitis, other systemic diseases, such as severe cardiac, renal, or hepatic diseases, a history of allergies, asthma, cardiac or renal failure, or a history of drug or alcohol abuse	HA (n=31): HMW (1,000-2,900 kDa, Orthovisc); 30mg/2mL; 3 injections NSAID (n=31): Etofenamate (Flexo ampule); 100mg/2mL; 7 IM injections	None	HA: 3 injections, once weekly NSAID: 7 injections, once daily	NSAID: Proton pump inhibitor when necessary	HA vs. NSAID Mean age: 62.5 vs. 61.3 years Mean BMI: 27.54 vs. 28.73 % Female: 90.0% vs. 82.8% KL grade 2: 50% vs. 58.6% KL grade 3: 50% vs. 41.4% Mean symptom duration: NR	6 months: 98.4% (61/62) 12 months: 95.2% (59/62))	None

BMI = body mass index; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Appendix Table G5. Patient Characteristics of Studies comparing HA to Usual Care

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. Usual Care									

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Hermans, 2019 Netherlands	N=156	Inclusion: age was set between 18 and 65 years, the latter being the pensionable age in The Netherlands at the inclusion period. Inclusion criteria were: pain > 3 months, mean pain severity≥2 on the numeric rating scale, KL grade 1-3 in medial and/or lateral compartment Exclusion: intra-articular HA injections <1 year, intra-articular steroid injection < 3 months, arthroscopy < 6 months, tibial osteotomy < 1 year, synovectomy, scheduled knee surgery < 1 year, varus/valgus deformity > 12 degrees, chondrocalcinosis, dermatologic knee disorders, allergy to HMW-HA components, (planned) pregnancy or lactation, inflammatory arthritis, severe hip OA, non-knee related regular analgesic use, daily oral steroid therapy, poor general health, conditions interfering with functional assessments, alcoholism, patients unable to attend follow-up	HA + Usual Care (n=77): HMW (6,000 kDa, Hylan GF-20, Synvisc formulation but maybe not brand); Dose NR; 3 injections, once weekly Usual Care (n=79): pain medication (e.g., acetaminophen or NSAIDs), physical therapy and lifestyle recommendation	None	HA: 3 injections, once weekly	Allowed when deemed appropriate	HA + Usual Care vs. Usual Care Mean age: 53.6 vs. 54.8 years Mean BMI: 28.9 vs. 29.2 % Female: 48% vs. 51% KL grade 1-2: 57% vs. 59% KL grade 3: 43% vs. 41% Mean symptom duration: ≥3 months*	3 months: NR 9 months: NR 12 months: 96.2% (150/156)	ZonMW (Dutch Ministry of Health, Welfare and Sport and the Netherlands Organization for Scientific Research)

BMI = body mass index; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
* Inclusion criteria.

Appendix Table G6. Patient Characteristics of Studies comparing HA to Physical Therapy and Prolotherapy

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. Physical Therapy vs. Prolotherapy									
Rezasoltani, 2020 Iran	N=120*	Inclusion: established diagnosis of chronic knee osteoarthritis Exclusion: Desire to change group assignment during research period	HA (n=30): LMW (500-730 kDa, Hyalgan); 2mL; 3 injections Physical Therapy (n=30): Heat, ENS, Pulse ultrasound Prolotherapy (n=30): 20% Dextrose sol.+2% Lidocaine; 8mL+2mL; 3 injections	Ultrasonic	HA: 3 injections, once weekly Prolotherapy: 3 injections, once weekly	Exercise Program	HA vs. PT vs. Prolotherapy Mean age: 66.1 vs. 70.0 vs. 64.8 years Mean BMI: 32.6 vs. 33.2 vs. 32.4 % Female: 53.3% vs. 60% vs. 63.3% KL grade: NR Pain duration (months): 75.1 vs. 70.2 vs. 75.4	3 months: 92.2% (83/90)	None

BMI = body mass index; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
* N of treatments of interest=90.

Appendix Table G7. Patient Characteristics of Studies comparing HA to Exercise

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. Exercise									

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Saccomano, 2016 Italy	N=165	Inclusion: aged 18 years or older in good general health with knee OA according to the ACR diagnostic criteria were eligible for inclusion. Knee malalignment (varus or valgus deformity) and OA were confirmed by radiographic examinations in different views: weight-bearing anteroposterior, weight-bearing posteroanterior according to Rosenberg, standard lateral view and axial patella view at 30° of flexion. Radiographic evidence of knee OA was graded according to the KL classification for the tibiofemoral OA and according to Iwano et al for the patellofemoral OA Exclusion: no radiographic evidence of knee OA or with severe OA (grade IV according to KL and/or stage IV according to Iwano et al.) were excluded. Other exclusion criteria were: inability or unwillingness to sign informed consent, intra-articular injections with steroids or hyaluronic acid in prior 6 months, physio-therapy for knee problems in prior 6 months, congenital or acquired inflammatory or neurological (systemic or local) diseases involving the knee, chronic	HA (n=55): HMW (1,000-2,900 kDa, Orthovisc); 30mg/2mL; 3 injections Exercise (n=55): Knee Exercises (Compartment-targeting); 20 sessions, 5 times weekly (4 weeks total) HA + Exercise (n-55): HMW (1,000-2,900 kDa, Orthovisc)+Knee Exercises (Compartment-targeting); 30mg/2mL; 3 injections, every 2 weeks; 20 sessions, 5 times weekly (4 weeks total)	None	HA: 3 injections every 2 weeks HA + Exercise: 3 injections every 2 weeks	None	HA vs. Exercise vs. HA + Exercise Mean age: 62.8 vs. 61.2 vs. 62.4 years BMI (median): 27.5 vs. 27.5 vs. 28.9 % Female: 79.2% vs. 64.7% vs. 71.7% Symptom duration (months, median): 24 vs. 24 vs. 36 KL grade 1: 65.8% vs. 67.6% vs. 66.7% KL grade 2: 13.2% vs. 23.5% vs. 22.2% KL grade 3: 21.1% vs. 8.8% vs. 11.1%	3 months: 95.2% (157/165) 6 months: 95.2% (157/165)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		treatment with steroids or NSAIDs and cognitive or psychiatric disorders							

BMI = body mass index; f/u = follow-up; FDA = Food and Drug Administration; HA = hyaluronic acid; HMW = high molecular weight; IA = intra-articular; KL = Kellgren-Lawrence; LMW = low molecular weight; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = Non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PMA = Pre-market approval; PRP = platelet-rich plasma; RCT = randomized control trial; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Appendix Table G8. Patient Characteristics of Studies comparing HA to Other Treatments for Hip Osteoarthritis

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
HA vs. PRP									
Villanova-Lopez 2020 Spain	N=74	Inclusion: >30 years, diagnose with OA which didn't respond to NSAIDs for 6 months, voluntarily express intention to participate with informed consent, not pregnant during participation Exclusion: treatment with injections 3 months prior to injection, NSAIDs within 24 hours of	HA (N=36) Hialano G-F, Synvisc-One; 6 mL; single injection PRP (N=38) 6 mL, platelet count 586216 ± 153208 x 10^3; single injection	Ultrasound	None (single injection)	NR	HA vs. PRP Mean age: 61 vs. 51 years % Female: 47.2% vs. 63.2% Mean BMI: 28.4 vs. 28.6 KL grade 1: 36.1% vs. 36.8%	12 months: 91.9% (68/74)	Spanish Orthopedic Surgery Society

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		injection, previous surgical treatment on affected hip, HBV background, diabetics, serious heart, kidney, or liver disease, allergy to HA or NSAIDs, history of crystal arthropathy, inflammatory arthritis or neuropathic arthropathy, serious protrusive OA, background of infectious arthritis, excessive deformity, active bacterial infection, autoimmune disease.					KL grade 2: 52.8% vs. 47.4% KL grade 3 or 4: 11.1% vs. 15.8% Symptom duration: ≥6 vs. ≥6 months (inclusion criteria)		
HA vs. Placebo									
Qvistgaard 2016 Denmark	N=69*	Inclusion: Hip OA as defined by American College of Rheumatology, age over 18 years, stable medication for at least 3 weeks prior to inclusion, written informed consent.	HA (N=33) Hyalgan; 2 mL; 3 injections Placebo (saline) (N=36) 2 mL; 3 injection	Ultrasound	3 injections, 14 day intervals	Normal analgesic consumption	HA vs. Placebo Mean age: 65 vs. 64 years % Female: 61% vs. 61% BMI: NR	3 months: 89.9% (62/69)	Oak Foundation and The Erna Hamilton Foundation

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Exclusion: radiographic signs of osteonecrosis of the hip, pain demanding morphine or incompatibility with long-term observation, pain-free at randomization, participation in other medical trials, previous intra-articular injection in the hip joint within last 3 months, defects or other skin changes in the injection area with resultant increased risk of infection, inflammatory or neurological diseases, poultry allergy, anticoagulation treatment, pregnancy, language or intellectual problems, suspected potential non-compliance with protocol.					KL grade 1 or 2: 50% vs. 65% KL grade 3 or 4: 50% vs. 35% Symptom duration: NR		

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Brander 2019 USA, Canada	N=357	Inclusion: KL grade 2 or 3, previous use of analgesics or NSAIDs for hip OA pain with completion of pain and OA medication washout period, hip pain as demonstrated by a WOMAC A1 score of 5 to 8 on 0-11 scale, age over 35 years, willingness to receive image-guided injections. Exclusion: WOMAC A1 score under 5 or 9-10 at screening, symptomatic contralateral hip OA, decrease in WOMAC A1 >1 point from screening to baseline, presence of comorbidities that may affect the target joint or impact measurement of efficacy, surgeries or procedures to the hip or lower extremities within 26 weeks of	HA (N=182) Hylan G-F 20; 6 mL; single injection Placebo (saline) (N=175) 6 mL; single injection	Ultrasound or fluoroscopy	None (single injection)	Acetaminophen, NSAIDs (not to be used for first 2 days after each study visit)	HA vs. Placebo Mean age: 61 vs. 60 % Male: 58.2% vs. 60% % Race, white: 91.2% vs. 93.7% % Race, black: 7.7% vs. 5.7% % race, unknown: 0.5% vs. 0.6% Mean BMI: 30.9 vs. 29.1 KL grade 0: 0% vs. 0.6% KL grade 1: 0% vs. 0% KL grade 2: 39% vs. 36% KL grade 3: 61% vs. 63.4%	6 months: 74.8% (267/357)	Sanofi Biosurgery, LLC

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		screening, 1A corticosteroid injection within 12 weeks of screening.					KL grade 4: 28% vs. 25.7% Symptom duration: NR Fibromyalgia: 1.6% vs. 1.1% Back pain: 19.2% vs. 16% Intervertebral disc degeneration: 4.9% vs. 4.6% Intervertebral disc disorder: 0% vs. 1.1% Intervertebral disc protrusion: 4.9% vs. 5.7% Lumbar spinal stenosis: 2.2% vs. 1.1% Neuropathy peripheral: 1.6% vs. 1.7%		

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
							Sciatica: 0.5% vs. 1.7%		
HA vs. Steroid									
Qvistgaard 2016 Denmark	N=65[†]	Inclusion: Hip OA as defined by American College of Rheumatology, age over 18 years, stable medication for at least 3 weeks prior to inclusion, written informed consent. Exclusion: radiographic signs of osteonecrosis of the hip, pain demanding morphine or incompatibility with long-term observation, pain-free at randomization, participation in other medical trials, previous intra-articular injection in the hip joint within last 3 months, defects or other skin changes in the injection area with resultant increased risk of infection,	HA (N=33) Hyalgan; 2 mL; 3 injections Steroid (N=32) Dep-medrol; 1 mL; 1 injection	Ultrasound	HA: 3 injections, 14 day intervals Steroid: None (single injection)	Normal analgesic consumption	HA vs. Steroid Mean age: 65 vs. 69 years % Female: 61% vs. 72% BMI: NR KL grade 1 or 2: 50% vs. 54% KL grade 3 or 4: 50% vs. 46% Symptom duration: NR	3 months: 95.4% (62/65)	Oak Foundation and The Erna Hamilton Foundation

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		inflammatory or neurological diseases, poultry allergy, anticoagulation treatment, pregnancy, language or intellectual problems, suspected potential non-compliance with protocol.							

BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
* Study also includes a steroid group (N=32).
† Study also includes a placebo group (N=36).

Appendix Table G9. Patient Characteristics of Studies comparing PRP to Placebo

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. Placebo									
Görmeli, 2017 Turkey	N=136*	Inclusion: History of chronic pain or swelling, KL grades 1 to 4. Exclusion: previous lower extremity surgery, systemic disorders, generalized OA, undergoing anti-	LR-PRP (N=45) 5 mL; platelets 5.2× (1118,000 µL); 1 injection LR-PRP (N=46) 5 mL; platelets 5.2× (1118,000 µL); 3 injections	NR	1 injection PRP: None 3 injection PRP: 3 injections, weekly	Paracetamol	1 LR-PRP vs. 3 LR-PRP vs. Placebo Mean age: 54 vs. 54 vs. 53 years	6 months: 90.4% (123/136)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		coagulant or antiaggregant therapy, use of NSAIDs in the 5 days before injection, hemoglobin ≤11 g/dL and platelet <150,00/mm^3.	Placebo (saline) (N=45) mL NR; 3 injections		Placebo: 3 injections, weekly		% Female: 56.8% vs. 58.9% vs. 50% Mean BMI: 28.4 vs. 28.7 vs. 29.5 Early OA[†]: 68.1% vs. 66.7% vs. 67.5% Advanced OA[†]: 31.8% vs. 33.3% vs. 32.5% Symptom duration: ≥4 vs. ≥4 vs. ≥4 months (inclusion criteria)		
Bennell, 2021 Australia	N=288	Inclusion: Age ≥50, knee pain most days of past month, average knee pain score ≥4 on 11 point scale, mild to moderate radiographic tibiofemoral OA. Exclusion: Radiographic lateral joint space narrowing that was greater than medial,	LP-PRP (N=144) 5 mL; Platelets 325 x $10^3/mm^3$; 3 injections Placebo (saline) (N=144); 5 mL; 3 injections	Ultrasound	LP-PRP: 3 injections over 3 weeks Placebo: 3 injections over 3 weeks	Acetaminophen	LP-PRP vs. Placebo Mean age: 62.2 vs. 61.6 years % female: 59% vs. 58.3% BMI: 29 vs. 29.6	2 months: 98.3% (283/288) 12 months: 97.6% (281/288)	NHMRC project grant

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		systemic or inflammatory disease, injection of a glucocorticoid in past 3 months or HA in past 6 months, past treatments with autologous blood product or stem cell preparation, platelet count of $150x10^3$ or lower, bleeding disorder, or ongoing anticoagulation therapy.					KL grade 2: 47.9% vs. 50% KL grade 3: 52.1% vs. 50% Symptom duration: 5 vs. 6 years		
Elik, 2020 Turkey	N=60	Inclusion: Between 50 and 75 years old, knee pain in the previous year, VAS >4, KL grade 1 to 3, no pathologies in the laboratory and coagulation parameters. Exclusion: Rheumatological disease other than OA, systemic active infectious disease or tumor, IA injection to the knee and physical treatment practices in the last 3 months, NSAID usage in the last	LR-PRP + exercise (N=30) 4 mL, platelets NR; 3 injections. Exercises included joint mobility range exercises and stretching, and later on, strength. Placebo (saline) + exercise (see above), (N=30) 4 mL; 3 injections	Ultrasound	LR-PRP: 3 injections over 3 weeks Placebo: 3 injections over 3 weeks	Paracetamol	PRP + exercise vs. placebo + exercise Mean age: 61.3 vs. 60.2 years % Female: 96.7% vs. 88.9% BMI: 30.4 vs. 30.7 KL grade 1: 6% vs. 11.1%	1 month: NR 6 month: 95% (57/60)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		7 days, previous history of knee joint surgery, severe mental retardation, blood thrombocyte count equal to or lower than 150,000/microliters before treatment and or/bleeding disorder, hepatitis B, C, or HIV, previous history of traumatic knee cartilage injury.					KL grade 2: 46.7% vs. 48.1% KL grade 3: 46.7% vs. 40.7% Symptom duration: NR		
Patel, 2013 India	N=78	Inclusion: Bilateral knee OA as diagnosed by American College of Rheumatology criteria and staged as per Ahlback radiological grading (grade 1 or 2) in patients who volunteered and signed a detailed informed consent form. Exclusion: IA secondary to join inflammatory diseases, generalized OA, metabolic diseases of the bone, coexisting backache, advanced staged of OA, received intra-articular	LP-PRP (N=27) 8 mL; platelet count 310.14 × 10^3/mL, mean platelet quantity injected 238.56 × 10^7; single injection LP-PRP (N=25) 8 mL; platelet count 310.14 × 10^3/mL, mean platelet quantity injected 238.56 × 10^7; single injection; 2 injections	NR	PRP group 1: none (single injection) PRP group 2: 2 injections (3 weeks apart)	None	Single injection PRP vs. 2 injection PRP vs. placebo Mean age: 53 vs. 52 vs. 54 % Female: 59% vs. 80% vs. 74% Mean BMI: 26.3 vs. 25.8 vs. 26.2 Ahlback grade 1: 71% vs. 72% vs. 54%	6 months: 94.9% (74/78)	Professor D.S. Grewal Memorial Orthopedics Society and the Indian Arthroplasty Association

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		injections within 1 year or were receiving anticoagulant therapy, hemoglobin level less than 10 gm% or associated comorbidities, infection, tumor, crystal arthropathies, or tense joint effusion.	Placebo (saline) (N=26) 8 mL; 1 injection				Ahlback grade 2: 21% vs. 20% vs. 39% Ahlback grade 3: 4% vs. 4% vs. 7% Symptom duration: NR		
Dório, 2021 Brazil	N=41‡	Inclusion: Men and women aged 45 to 80, fulfill criteria for KOA of the American College of Rheumatology, radiographic KL grade 2 or 3 in at least 1 knee, VAS pain 3 to 8 on 0-10 scale in at least one knee in the last week. Exclusion: Use of analgesics, NSAIDs, myorelaxants and systemic glucocorticoids within 1 week to allocation, use of slow acting drugs for OA started within 8 weeks to allocation, corticosteroids or HA intra-articular injection	LP-PRP (N=20) 1.4 to 4 mL; platelets 1 x 10^6; 2 injections§ Placebo (saline) (N=21) mL NR; 2 injections§	Ultrasound	LP-PRP: 2 injections, 2 weeks apart Placebo: 2 injections, 2 weeks apart	None	LP-PRP vs. placebo Mean age: 66.4 vs. 62.5 years % Female: 95% vs. 90% Mean BMI: 28.3 vs. 28 comorbidities: 80% vs. 86% KL grade 2 or 3: 100%** Mean duration of symptoms: 8.4 vs. 7.1 years	5.5 months: 87.8% (36/41)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		in the index knee within 6 months to allocation, intra-articular injection of any drug in any other join within 1 month of allocation, introduction of any medical or physical intervention for the locomotor system within the last 3 months, KL 4 in any of the knees, BMI ≥35, fibromyalgia and inflammatory arthropathies such as rheumatoid arthritis, connective tissue diseases, microcrystalline arthropathies, spondyloarthropathies, and infectious arthropathies, symptomatic OA of hips or feet, previous surgery in the index knee, difference in length of lower limbs >1 cm, skin lesion on index knee surface, any blood dyscrasia or use of anticoagulants, other diseases, severe							

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		depression, non-controlled diabetes, decompensated cardiovascular disease, infection, immunosuppression, systemic infectious disease, symptomatic lower limb vascular disease, neurological diseases, cancer or any other conditions believed to interfere with results, any sick leave or similar due to KOA.							
Yurtbay, 2022 Turkey	N=267	Inclusion: KL grade 1, 2, or 3, aged 18 to 80, mean VAS pain score >4 over the course of 7 days. Exclusion: OA secondary to joint inflammatory disease, metabolic bone disease, coexisting backache, presence of hematological disease, bilateral symptomatic lesions, advanced stage OA, intra-articular injection made within previous 3 months, or	LR-PRP (N=67) 5 mL; platelets 128 x 10^5 µl; 1 injection LR-PRP (N=66) 5 mL; platelets 128 x 10^5 µl; 3 injections injection Placebo (saline) (N=69) 5 mL; 1 injection Placebo (saline) (N=65) 5 mL; 3 injection	NR	3 injection groups: 1 month intervals	Paracetamol as needed	1 injection PRP vs. 3 injection PRP vs. 1 injection placebo vs. 3 injection placebo Mean age: 53 vs. 57 vs. 56 vs. 53 years % Female: 33.8% vs. 14.3% vs. 18.6% vs. 40%	1, 3, 6, 12, 24 months 93% (237/267)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		arthroscopic lavage in previous year, use of immunosuppressive drugs, current use of anti-coagulant medications or NSAIDs in the 5 days before blood sampling, major axis deviation of the knee, hemoglobin level <11.5 g/dK and platelet level <100,000 or associated comorbidities, infection ,tumor, crystal arthropathies, anemia, intense joint effusion, or known or possible pregnancy.					BMI: 31.09 vs. 30.68 vs. 30.67 vs. 29.22 KL grade 1: 11.3% vs. 3.2% vs. 5.1% vs. 5.7% KL grade 2: 69.4% vs. 60.3% vs. 78% vs. 83% KL grade 3 : 19.4% vs. 36.5% vs. 16.9% vs. 11.3% Symptom duration: NR		
Chu, 2022 China	N=644	Inclusion: Age between 18 and 80, knee pain on most days in the previous month, unilateral symptoms, damage to articular cartilage seen on weight-bearing radiographs or MIR, ability to provide informed consent. Exclusion: KL grade 4 tibiofemoral OA on x-	LR-PRP (N=322) 5 mL; platelets 832.1 ± 269.3 × 10^9 /L; 3 injections Placebo (saline) (N=322) 5 mL; 3 injections	ultrasound	LR-PRP: 3 injections, weekly Placebo: 3 injections, weekly	None	LR-PRP vs. placebo Mean age: 53.9 vs. 54.5 % Female: 60.1% vs. 57.9% Mean BMI: 27.5 vs. 27.9	60 months: 94.7% (610/644)	National Natural Science Foundation of China, National Clinical Research Center for Orthopedics, sports Medicine & Rehabilitation and Jiangsu

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		ray, recent intra-articular injection of glucocorticoid in the past 3 months or HA in past 6 months, knee instability, bilateral symptomatic lesions, BMI >40 kg/m2, systemic disorders such as rheumatoid arthritis, diabetes, hematological diseases, osteoporosis, immunodeficiencies, infections, pregnancy, use of NSAIDs in past week.					Smoking history: 29.6% vs. 24.8% KL grade 1: 27.6% vs. 29.5% KL grade 2: 42.2% vs. 40.1% KL grade 3: 25.8% vs. 24.2% Symptom duration: ≥1 vs. ≥1 months (inclusion criteria)		China-Israel Industrial Technical Research Institute Foundation
Lewis, 2022 Australia	N=102	Inclusion: ≥18 years, demonstrated history of more than 4 months of pain and/or swelling in the knees with early radiological evidence of tibiofemoral OA, KL grade 0, 1, 2. Exclusion: Evidence of advanced OA of the knee, previous open knee surgery, anticoagulation, or any systemic disorder, such as rheumatological	LP-PRP + Placebo (saline) (N=47) 4 to 6 mL; platelets NR; 1 injection PRP + 2 injections placebo LP-PRP (N=27) 4 to 6 mL; platelets NR; 3 injections	NR	3 injections: 1 injection weekly	NR	LP-PRP + placebo vs. LP-PRP (3 injections) vs. placebo Mean age: 55 vs. 59 vs. 60 years % Female: 57% vs. 67% vs. 57% Mean BMI: 29.3 vs. 29.7 vs. 29.9	3 months: 83.3% (85/102) 6 months: 90.2% (92/102) 12 months: 88.2% (90/102)	Clifford Craig Foundation

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		disease, severe cardiovascular disease, hematological disease, or infection.	Placebo (saline) (N=28) 5 mL; 3 injections				KL grade 0: 8.5% vs. 3.7% vs. 0% KL grade 1: 23.4% vs. 29.6% vs. 28.6% KL grade 2:48.9% vs. 48.1% vs. 60.7% Mean symptom duration: 56 vs. 55.7 vs. 52.7 months		
Nunes-Tamashiro, 2022 Brazil	N=67[††]	Inclusion: Primary bilateral knee OA, age between 40 and 85, diagnosis of primary and symptomatic bilateral knee OA through diagnosis of KL 2 or 3, pain more than 3 months, pain on VAS between 4 and 8 which interfered with the function on most days of the week, agreement and	PRP (N=34) (leukocyte count not performed), mL NR; platelets 152,930 per mm^3; 1 injection[‡‡] Placebo (saline) (N=33) 2 mL; 1 injection	NR	None (single injection)	NR[§§]	PRP vs. placebo Mean age: 68 vs. 68 years % Female: 88.2% vs. 90.9% Race, white: 76.5% vs. 90.9% Race, nonwhite: 23.5% vs. 9.1%	12 months: 100% (67/67)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		signature of the informed consent form. Exclusion: secondary knee OA, cutaneous knee injury, intra-articular injection with corticosteroids or HA in the knee in the last 6 months, use of corticosteroids in the last 30 days, inflammatory arthritis, gout or pseudogout, presence of oncologic disease, previous surgery on the knee, cardiovascular or respiratory disease interfering with functional status, pregnancy, breast-feeding, severe clotting disorder, suspected bacterial infection of any kind, any condition interfering with gait, use of antiplatelet agents and/or NSAIDs in previous 14 days, presence of thrombocytopenia.					Mean BMI: 29.22 vs. 30.23 KL grade 2: 41.2% vs. 48.5% KL grade 3: 58.8% vs. 51.5% Mean duration of symptoms: 10.3 vs. 7.8 years		

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.
* Study also included HA group (N=46).
† Patients were classified as Early OA (KL Grade 0-3), and advanced OA (KL Grade 4).
‡ Study also includes a plasma intervention group (N=21). Plasma was explicitly excluded from the present report.
§ In bilateral cases the knee selected for treatment was the one reported with higher pain score as reported by the participant.
** No further details on proportion of each grade.
†† Study also includes a triamcinolone hexacetonide intervention group (N=33).
‡‡ All bilateral knee OA. Only a single intra-articular injection was performed on the most symptomatic knee according to the patient perception.
§§ Patients were instructed to avoid any other type of treatment such as exercise program, physical modalities, or knee brace. But nothing reported on other surgeries or medications.

Appendix Table G10. Patient Characteristics of Studies comparing PRP to Steroids

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. Steroid									
Huang, 2019 China	N=80*	Inclusion: early stage OA (KL grade 1 and 2), ages 40 to 65, BMI <30, stable knees without malalignment or maltracking of the patella, pain with no relief using anti-inflammatory agents even after 3 months, normal blood results and coagulation profile, not undergone any surgery on the affected knee with 2 years prior to first injection and zero traces or 1+ effusion	LP-PRP (N=40) 4 mL, platelets 2x baseline; 3 injections Steroid (N=40) 1 mL; 3 injections	NR	3 injections, weekly interval	NR	LP-PRP vs. Steroid Mean age: 54 vs. 55 % Female: 82.5% vs, 79.2% Mean BMI: 24.6 vs. 25.3 Hypertension: 4.2% vs. 2.5% Diabetes: 0.8% vs. 1.7%	12 months: 100% (80/80)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		on the grading scale based on the Stroke test. Exclusion: Diagnosed with tricompartmental OA, rheumatoid arthritis or concomitant hip OA. Previous high tibial osteotomy or cartilage transplantation procedure, grade 2+ and 3+ effusion in the knee joint based on the Stroke test, blood diseases, systemic metabolic disorders, immunodeficiency, hepatitis B or C, HIV positive status, local or systemic infection, ingestion of anti-platelet medication within 7 days prior to injection and treatment with IA or oral corticosteroid in the 3 months prior to the first injection.					KL grade 1 or 2[†]: 100% vs. 100% Symptom duration: NR		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Elksniņš-Finogejevs, 2020 Latvia	N=40	Inclusion: Over 55 years, chronic pain history, swelling, and/or reduced range of motion in the knee joint, KL grade 2 or 3. Exclusion: Post-traumatic knee OA, pregnancy, breastfeeding, oncological diseases, endocrine disease, autoimmune diseases, acute/chronic infectious disease, blood clotting disorders, previous interventions on the knee joint, and previous consistent hormonal therapy, or NSAIDs within 10 days prior to intervention.	LP-PRP (N=20) 8 mL; platelets NR; single injection Steroid (N=20) 1 mL triamcinolone + 5 mL lidocaine; single injection	NR	None (single injection)	NSAIDs (prohibited for the first 10 days)	PRP vs. corticosteroid Mean age: 66 vs. 70 years % Female: 15% vs. 25% Mean BMI: 28.6 vs. 30.5 KL grade 2: 25% vs. 30% KL grade 3: 75% vs. 70% Symptom duration: NR	13 months: 90% (36/40)	None
Freire, 2020 Brazil	N=50	Inclusion: Age 30 to 90, presence of KL grade 2 to 4, absence of other rheumatic inflammatory diseases, absence of previous treatment	PRP (N=25) 5 mL; platelets NR; 1 injection Steroid (N=25) 2 mL	NR	None (single injection)	NR	PRP vs corticosteroid Mean age: 64 vs 60 years	6 months: 100% (50/50)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		with intravenous, injectable or oral corticosteroids during the last 12 months, and signature of the informed consent form. Exclusion: Disease preventing follow-up, loss at follow-up, use of oral or intravenous corticosteroids during the follow-up period, hemoglobin level lower than 11 g/dL and platelet count lower than 150,000/mm^3	triamcinolone; 1 injection				% Female: 84%‡ Mean BMI: NR KL grade 1: 0% vs. 4% KL grade 2: 40% vs. 40% KL grade 3: 44% vs. 56% KL grade 4: 16% vs. 0% Symptom duration: NR Obesity: 76% vs. 88% Hypertension: 64% vs. 68% Diabetic: 24% vs. 16%		
Khan, 2018 Pakistan	N=103§	Inclusion: Knee pain in patients ages ≥40 years, either gender, KL grade 2, fulfilling American College of Rheumatology	PRP (N=51) 5 mL; platelets NR; injections unclear**	NR	Details NR	NR	PRP vs. Steroid Mean age: 52 vs. 51 years	NR	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		criteria of OA, failed to respond to conservative treatment for past 3 months; Exclusion: Past history of acute trauma, tumor involving knee joint.	Steroid (N=52) 1 mL triamcinolone + 4 mL lidocaine; injections unclear**				% Female: 77% vs. 75% KL grade 2: 100% vs. 100% Mean BMI: 26 vs. 28 Symptom duration: NR		
Nabi, 2018 Iran	N=72	Inclusion: Age 30 to 75, KL grade 2 or 3, debilitating knee pain for ≥3 months, not responding to different treatments, pain causing dysfunction. Exclusion: Knee joint deformities, cancer, rheumatoid lesions, BMI >35 kg/m2, pregnancy, breastfeeding, acute infection, hemoglobin <11 g/dL, platelets <150,000 x 10^9/l, blood disorders, hemoglobinopathies, uncontrolled	PRP (N=36) 5 mL; platelets 4 to 6x baseline; 3 injections Steroid (N=36) 40 mg triamcinolone; 3 injections	Ultrasound	PRP: 3 injections, once a month for three months Steroid: 3 injections, once a month for three months	Acetaminophen	PRP vs. Steroid Mean age: 59 vs. 59 years % Female: 85% vs. 79% Mean BMI: 28.4 vs. 27.8 KL grade 2: 32.4% vs. 27.3% KL grade 3: 67.6% vs. 72.7% Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)	6 months: 93% (67/72)	Anesthesiology research center at Guilan University of Medical Sciences

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		diabetes, acute knee pain, history of knee surgery, serious neurologic or psychological disorders, sciatica pain, history of treatment with anticoagulants, treatment of coagulation disorders, corticosteroid consumption within last 3 months.							
Phul, 2018 Pakistan	N=80	Inclusion: Age 40 to 75, BMI ≤33 kg/m^2, primary OA with KL grade 2 to 4, history of knee pain or swelling for at least 4 months. Exclusion: Already treated with steroids and anti-coagulant or anti-platelet aggregation, history of infectious, systemic diseases, immune deficiency and coagulation disorders and collagen vascular	PRP (N=40) 4 to 6 mL; platelets NR; 2 injection Steroid (N=40) 2 mL; Triamcinolone + bupivacaine; 2 injections	PRP: NR Steroid: fluoroscopically	2 injections (4 week interval)	Acetaminophen-codeine[††]	PRP vs. placebo Mean age:54 vs. 58 % Female: 70% vs. 65% BMI: <3 kg/m^{2‡‡} KL grade 2 to 4: 100%[†] Symptom duration: 1.93 vs. 2.03 years	NR	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		disorders, infection or active wound, current history of harsh trauma to knee, history of knee articular injections of corticosteroids, hemodynamic instability or septicemia, hemoglobin ≤11, platelet ≤150,000/mm^3, genu varum >10 degrees or Gen valgum 10 degrees relative contraindications to PRP knee injections and cancer, particularly of bone or blood.							
Jubert, 2017 Spain	N=65[§§]	Inclusion: Age 40 to 80 years, knee OA, eligibility for TKA, walking ability with or without external support, VAS >60, informed consent obtained Exclusion: Inability to obtain informed consent, received intra-articular	LP-PRP (N=35) 4 mL; platelets 0.99 x 10^6 platelets/mL; single injection Steroid (N=30) 2 mL betamethasone; single injection	NR	None (single injection)	Painkillers and NSAIDs Routine clinical practices	PRP vs. steroid Mean age: 66 vs. 68 years % Female: 65.7% vs. 80% Mean BMI: 31.2 vs. 31	6 months: 98.5% (64/65)	Ministry of Health, Social Policy, and Equality of Spain

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		injections of steroids, anesthetic, or HA in past year, underwent arthroscopic surgery in past 3 months, received open surgery on occasion, compromised bone metabolism, fibromyalgia, chronic fatigue syndrome, liver disease, clotting deficiency, thrombocytopenia, anticoagulants, active infection, cancer, neuromuscular disease, severe cardiovascular disease, immunosuppression, pregnancy, severe damage of homolateral hip or ankle, rheumatoid arthritis, inflammatory diseases of the connective tissue, involved in proceedings for legal incapacitation or						Smoker: 17% vs. 13% KL grade 3: 28.6% vs. 56.6% KL grade 4: 71.4% vs. 43.4% Symptom duration: NR		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		financial compensation, documented history of allergy to steroids, bupivacaine, valgus deformity >15 degress or varus deforming >20 degrees, severe ligamentous instability of the knee joint, limitation of knee range of movement, positive serology.							
Forogh, 2015 Iran	N=41 (48 knees)	Inclusion: VAS ≥60, knee pain for more than 3 months, residing in Tehran and its suburbs, history of undergoing but not benefiting from at least two OA treatments (lifestyle changes, weight loss, oral medications, physiotherapy, acupuncture, laser, using insole, cane, or orthotic devise), KL grade 2 or 3.	LR-PRP (N=24 knees) 5 mL; platelets $1500x10^3$; single injection*** Steroid (N=24 knees) 1 mL corticosteroid; single injection***	NR	Details NR	Range of motion exercises, walking in water and on flat surfaces, oral analgesics.	PRP vs. steroid Mean age: 59 vs. 61 years % Female: 29.2% vs. 37.5% Mean BMI: 28.9 vs. 29.2 % Smoker: 0% vs. 12.5% KL grade 2: 29.5% vs. 33.3%	6 months: 81.2% (39/48 knees)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Exclusion: History of collagen vascular or severe cardiovascular and hematopoietic disease, diabetes mellitus, history or presence of cancer, malignant disorders or immunosuppression, hepatitis B or C, HIV, any active infection or wound of the knee, history of any knee articular injections, infection, arthroscopy or surgery during the previous 6 months, active lumbosacral radiculopathy and/or drug abuse.					KL grade 3: 70.8% vs. 66.7% Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)		
Nunes-Tamashiro, 2022 Brazil	N=67[†††]	Inclusion: Primary bilateral knee OA, age between 40 and 85, diagnosis of primary and symptomatic bilateral knee OA through diagnosis of KL 2 or 3, pain more than 3 months, pain on VAS between 4	PRP (N=34) (leukocyte count not performed), mL NR; platelets 152,930 per mm^3; single injection[‡‡] Steroid (N=33) 2 mL	NR	None (single injection)	NR[‡‡‡]	PRP vs. Steroid Mean age: 68 vs. 66 years % Female: 88.2% vs. 90.9%	12 months: 100% (67/67)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		and 8 which interfered with the function on most days of the week, agreement and signature of the informed consent form. Exclusion: secondary knee OA, cutaneous knee injury, intra-articular injection with corticosteroids or HA in the knee in the last 6 months, use of corticosteroids in the last 30 days, inflammatory arthritis, gout or pseudogout, presence of oncologic disease, previous surgery on the knee, cardiovascular or respiratory disease interfering with functional status, pregnancy, breast-feeding, severe clotting disorder, suspected bacterial	Triamcinolone Hexacetonide; single injection‡‡				Race, white: 76.5% vs. 81.8% Race, nonwhite: 23.5% vs. 18.2% Mean BMI: 29.22 vs. 29.59 KL grade 2: 41.2% vs. 48.5% KL grade 3: 58.8% vs. 51.5% Mean duration of symptoms: 10.3 vs. 6.3 years		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		infection of any kind, any condition interfering with gait, use of antiplatelet agents and/or NSAIDs in previous 14 days, presence of thrombocytopenia.							

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.
* Study also includes HA group (N=40).
† Details not reported.
‡ Whole population only.
§ Authors report randomizing 150 patients, but later report on (51 vs. 52) patients, but say N=101. Other tables seem to add up to 102. Unclear what happened to missing patients or if this is an error.
** Authors report that injections were given "between 2 and 6 months", unclear how many.
†† Provided to all patients two hours after injection.
‡‡ Inclusion criteria.
§§ Authors report N=75 in the abstract; text and consort diagram report N=65 and (PRP) n=35 versus (steroid) n=30.
*** Bilateral - each knee (in same patient) received same injection (either PRP or steroid).
††† Study also includes a placebo intervention group (N=33).
‡‡‡ Patients were instructed to avoid any other type of treatment such as exercise program, physical modalities, or knee brace. But nothing reported on other surgeries or medications.

Appendix Table G11. Patient Characteristics of Studies comparing PRP to Other Treatments for Oral analgesics

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. Oral analgesics									
Buendía-López, 2019 Spain	N=70*	Inclusion: Symptomatic knee OA as defined by the Spanish Society of	LP-PRP (N=35) 5 mL, platelets 1,095,000 ±	NR	LP-PRP: None (single injection)	Omeprazole	LP-PRP vs. NSAIDs	12 months: 94.3% 66/70	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Rheumatology, KL grade 1 or 2. Exclusion: Varus deformity, recent trauma, inflammatory arthritis, history of gastrointestinal or cardiovascular disease, concomitant medications of potent analgesics, corticosteroid, NSAID, anticoagulant or anti-platelet therapy within 12 months of study enrollment, previous surgery to the limb or spine; previous injection to study joint or any active local or systemic infection; systemic disorders with restrictions for the use of NSAID (diabetes) or potential effect on the knee.	23,200/mm^3; single injection NSAIDs (N=35) etoricoxib; 60 mg		NSAIDs: daily for 52 weeks		Mean age: 56 vs. 57 years % Female: 48.6% vs. 48.6% Mean BMI: 24.9 vs. 25.2 KL grade 1: 51.4% vs. 48.6% KL grade 2: 42.9% vs. 45.7% Symptom duration: NR		
Simental-Mendia, 2016 Mexico	N=75	Inclusion: Male or female >18 years, pain, inflammation, or any other symptom related to knee OA lasting at least 3	LP-PRP (N=33[†]) 3 mL; platelets NR; 3 injections[‡]	NR	LP-PRP: 3 injections over 6 weeks (1 every 2 weeks)	Cold therapy	LP-PRP vs. acetaminophen Mean age: 57 vs. 56 years	5.5 months: 86.7% (65/75)	Consejo Nacional de Ciencia y Tecnologiía Mexico

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		months, no use of NSAIDs, radiologic signs of KL grade 1 or 2. Exclusion: Any surgical intervention of the knee, pregnancy, rheumatic disease, hepatological disease, liver disease, severe cardiovascular disease, diabetes, coagulation, infection, immunodepression, anticoagulant therapy, an Hb value <11 g/dL and platelet value <150,00/uL.	APAP (N=32) 500 mg		APAP: 500 mg every 8 hours for 6 weeks		% Female: 33% vs. 38% Mean BMI: 29.5 vs. 32.2 KL grade 1: 33% vs. 37% KL grade 2: 67% vs. 63% Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)		
Reyes-Sosa, 2020 Mexico	N=60	Inclusion: KL grade 2 or 3. Exclusion: Systemic pathologies, uncontrolled diabetes mellitus, rheumatoid arthritis, axial deviation, hematologic disorders, cardiovascular diseases, infection, immunosuppression, patients with	LP-PRP (N=30) 3 mL; platelets NR; 2 injections[§] celecoxib (N=30) 200 mg[§]	NR	LP-PRP: 2 injections, once every 15 days celecoxib: Every day for 12 months	None	PRP vs. NSAID Mean age: 54 vs. 53 years % Female: 86.7% vs. 70% BMI: NR KL grade 2: 43.3% vs. 60%	12 months: 100% (60/60)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		anticoagulant treatment or antiplatelet agents, allergy to celecoxib.					KL grade 3: 56.7% vs. 40% Duration of symptoms: NR		

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.
* Study also includes HA group (N=36).
† n=33 + n=32 is the final follow-up N=65. 75 patients were randomized but 13.3% (10/75) were lost during follow-up. Unclear which intervention group they belonged to.
‡ In patients with bilateral OA, only the knee with more significant symptoms was considered.
§ Both unilateral (38%, n=23) and bilateral (62%, n=37). Both knees treated in patients with bilateral knee OA: n=19 PRP vs. n=18 steroid (63% vs. 60%).

Appendix Table G12. Patient Characteristics of Studies comparing PRP to Exercise

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. exercise									
Raeissadat, 2020 Iran	N=46 knees (23 patients)*	Inclusion: History of pain for previous 3 months, KL grades 1, 2, or 3. Exclusion: Any contraindications for performing an MRI including aneurism clips, pacemakers, non MRI-compatible metallic devices in the body and	LR-PRP + exercise (N=23) mL NR; 2 injections Exercise (N=23) Multi-angle isometric exercise + stretching	NR	LR-PRP: 2 injections, every 4 weeks Exercise: 3 times per day, 10 times for each move and 10 seconds each time. After 4 weeks, strengthening	Paracetamol, codeine	Whole population Mean age: 58 years % Female: 100% Mean BMI: 28.49 KL grade 1: 26.3%	8 months: 91.3% (42/46 knees)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		claustrophobia, any form of knee injection in previous 3 months, arthroscopic or open surgery in previous 6 months, immunodeficiency, autoimmune disease, collagen vascular disease, or diabetes, history of cancer, infection or inflamed lesion in the knee, platelet disorder or disease, use of anticoagulant or anti-platelet medication 10 days before injection, use of NSAIDs 2 days before injection, corticosteroid knee injection 3 weeks before injection or use of systemic corticosteroids 2 weeks before the injection, hemoglobin level less than 12 g/dL and platelets less than 150,000/mL, history of severe knee trauma, age of less than 45 and higher than 65, history of vasovagal			exercises were taught.		KL grade 2: 52.6% KL grade 3: 21.1% Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		shock, pregnancy and lactation, genu valgum or genu varum more than 20 degrees.							
Akan, 2018 Turkey	N=62	Inclusion: Age 40 to 75, moderate to severe knee pain scores ≥4 VAS, diagnostic criteria of ACR as knee OA, radiologically had grade 4 knee OA, not responded to conservative therapy for ≥3 months. Exclusion: Uncontrolled systemic disorder, history of rheumatic disease, active malignancy, another symptomatic joint or asymptomatic OA in >3 joints, history of acute trauma, acute meniscopathy, anterior-posterior cruciate ligaments or collateral ligament injury or tear in the affected knee, history of surgery, manipulation, mobilization or	LR-PRP + exercise (N=30) mL NR; platelets NR; 3 injections Exercise (N=30) home exercise consisting of knee ROM, isometric strengthening, and quadriceps strengthening exercises	NR	PRP: 3 injections, 1 every 3 weeks Exercise: 3 days per week	Paracetamol	PRP + exercise vs. exercise Mean age: 61 vs. 56 years % Female: 80% vs. 96.7% Mean BMI: 33.6 vs. 32.7 Comorbidities[†]: 70% vs. 63.3% KL grade 4: 100% vs. 100% Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)	6 months: 96.8% (60/62)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		arthroscopy in the affected knee, history of steroid, local anesthetics or HA injection, kinesiotaping, prolotherapy or neural therapy over last 3 months, reflex sympathetic dystrophy or neurodeficit of the affected extremity, anemia or thrombocytopenia, bleeding disorders, anticoagulants, history of medication use over past 10 days, infection or suspicious of infection, serious psychiatric disorder.							
Angoorani, 2015 Iran	N=54	Inclusion: Knee OA as diagnoses by American College of Rheumatology criteria, KL grade 1, 2, or 3, no history of corticosteroid injection or consumption within 6 months, no history of peripheral vascular disease, spinal	LR-PRP (N=27) 6 mL; platelets 3x baseline; single injection TENS + exercise (N=27)	NR	LR-PRP: None (single injection) TENS + Exercise: 10 sections of TENS, twice a week + exercise daily	Paracetamol for first 72 hours	PRP vs. TENS Mean age: 62 vs. 62 years % Female: 81.5% vs. 92.6% Mean BMI: 28.5 vs. 29.2	2 months: 92.6% (50/54)	Iran University of Medical Sciences

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		stenosis, severe disabilities, inflammatory and metabolic diseases and lack of history of anticoagulative drugs. Exclusion: Consumption of intra-articular injection of corticosteroids during the study, anticoagulative drugs during the study, patient request for leaving the study.					KL grade 1, 2, or 3[†]: 100% vs. 100% Symptom duration: NR		
Rayegani, 2014 Iran	N=65	Inclusion: Arthralgia in past 3 months, KL grade 1 through 4. Exclusion: Age over 75 years, history of diabetes mellitus, immunosuppressive and collagen vascular disorders, history or presence of cancer or malignant disorders, any infection or active wound of the knee, recent history of severe trauma to the knee, autoimmune and platelet disorders,	LR-PRP + exercise (N=32) 4 to 6 mL; platelets NR; 2 injections Exercise (N=33) details NR	NR	LR-PRP: details NR Exercise: 3 times a day	Acetaminophen, (if pain is persistent then acetaminophen-codeine)	PRP vs. exercise Mean age: 58 vs. 55 years % Female: 93.5% vs. 93.5% Mean BMI: 28.2 vs. 27.3 KL grade: NR[‡] Symptoms 3-12 months: 16.7% vs. 25.8%	6 months: 95.4% (62/65)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		treatment with anticoagulant and anti-platelet medications 10 days before injection, use of NSAIDs 3 days before injection, history of knee articular injections of corticosteroids during previous 3 weeks or use of systemic corticosteroids 2 weeks before injection, hemoglobin measures < 12 g/dL and platelet counts <150,00/mL, history of vasovagal shock, pregnancy or breastfeeding and genu valgum/varum >20 degrees.					Symptoms ≥12 months: 83.3% vs. 74.2%		

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.

* Bilateral OA. Each patient had one knee each randomized to intervention and control.

† Details not reported.

‡ Inclusion criteria included patients with KL grades 1 through 4. Authors report grades 1-4 for tibiofemoral OA and grades 1-4 for patellofemoral OA, but not overall KL grade.

Appendix Table G13. Patient Characteristics of Studies comparing PRP to Physiotherapy

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. PT									
Gaballa, 2019 Egypt	N=40*	Inclusion: Patients fitting American College of Rheumatology criteria for knee OA. Exclusion: Systemic or metabolic diseases, on immunosuppressive or anticoagulant treatment, with history of previous invasive procedure or intra-articular steroid injection to the knee during the preceding 12 months.	PRP (N=20) mL NR; platelets NR; 2 injections Rehabilitation (N=20) Infrared, TENS, strength training	NR	PRP: 2 injections, one every two weeks Rehabilitation: 3 sessions per week for 1 month	NR	PRP vs. PT Mean age: 54 vs. 55 years % Female: 75% vs. 75% Mean BMI: NR Mean symptom duration: 5.4 vs. 6.4 years KL grade 1: 10% (whole population) KL grade 2: 53.3% (whole population) KL grade 3: 36.7% (whole population)	NR	None

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.
* Study also includes a group for Ozone (N=20), but this intervention is explicitly excluded.

Appendix Table G14. Patient Characteristics of Studies comparing PRP to Prolotherapy

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. prolotherapy									
Pishgahi, 2020 Egypt	N=60*	Inclusion: Inflammation, pain, or any other symptom related to knee OA lasting at least 3 months, radiologic signs of grade 2, 3, or 4 knee OA, no use of NSAIDs. Exclusion: Rheumatic disease, any surgical intervention of the knee, infection ,liver disease, diabetes, severe cardiovascular disease, coagulopathy, anticoagulant therapy, pregnancy.	LP-PRP (N=30) mL NR; platelets NR; 2 injections Dextrose (N=30) 50% dextrose (2 mL), bacteriostatic water (2 mL), and 2% lidocaine (1 mL); 3 injections	Ultrasound	LP-PRP: 2 injections, once per week for two weeks Dextrose: 1 injection per week for 3 weeks	NR	PRP vs. Dextrose Mean age: 59 vs. 58 years % Female: 46.7% vs. 50% % Overweight (BMI 25.01 to 30): 43.3% vs. 46.7% % Obese (BMI ≥30.01): 46.7% vs. 56.7% KL grade 2: 16.7% vs. 23.3% KL grade 3: 53.3% vs. 40% KL grade 4: 30% vs. 36.7% Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)	6 months: 100% (60/60)	Physical Medicine and Rehabilitation Research Center Tabriz University of Medical Sciences

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
Rahimzadeh, 2018 Iran	N=42	Inclusion: Age range 40 to 70, KL grade 1 or 2. Exclusion: Rheumatoid arthritis or hemophilia, previous history of knee surgery, drug or alcohol addiction, use of anticoagulant or NSAIDs in the previous 7 days.	PRP (N=21) 7 mL; platelets NR; 2 injections Dextrose (N=21) 7 mL dextrose (25%); 2 injections	Ultrasound	PRP: 2 injections, one per month Dextrose: 2 injections, one per month	Paracetamol	PRP vs. Dextrose Mean age: 66 vs. 64 years % Female: 55% vs. 50% Mean BMI: 28.6 vs. 28.3 Mean KL score: 2.47 vs. 2.42 Symptom duration: NR	NR	NR

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.
* Study also includes an autologous conditioned serum intervention group (N=32). This was explicitly excluded from the current SR.

Appendix Table G15. Patient Characteristics of Studies comparing PRP to other Quantities of PRP

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. PRP									
Görmeli, 2017 Turkey	N=91*	Inclusion: History of chronic pain or swelling, KL grades 1 to 4.	LR-PRP (N=45) 5 mL; platelets 5.2× (1118,000 µL); single injection	NR	1 injection PRP: None 3 injection PRP: 3	Paracetamol	1 LR-PRP vs. 3 LR-PRP Mean age: 54 vs. 54 years	6 months: 91.2% (83/91)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		Exclusion: previous lower extremity surgery, systemic disorders, generalized OA, undergoing anti-coagulant or antiaggregant therapy, use of NSAIDs in the 5 days before injection, hemoglobin ≤11 g/dL and platelet <150,00/mm^3.	PRP (N=46) 5 mL; platelets 5.2× (1118,000 µL); 3 injections		injections, weekly		% Female: 56.8% vs. 58.9% Mean BMI: 28.4 vs. 28.7 Early OA[†]: 68.1% vs. 66.7% Advanced OA[†]: 31.8% vs. 33.3% Symptom duration: ≥4 vs. ≥4months (inclusion criteria)		
Kavadar, 2015 Turkey	N=102	Inclusion: Age 40 to 75, single knee pain for ≥6 months. Exclusion: Bilateral symptomatic knee OA, age older than 75 years, receiving physical therapy, intra-articular steroid, HA or PRP injection in the last 6 months, recent history of severe trauma of the affected knee, active injection,	LR-PRP (N=34) mL NR; platelets NR; single injection LR-PRP (N=34) mL NR; platelets NR; 2 injections LR-PRP (N=34) mL NR; platelets NR; 3 injections	NR	All injections 2 weeks apart	Acetaminophen with codeine	LR-PRP (1 injection) vs. LR-PRP (2 injections) vs. LR-PRP (3 injections) Mean age: 54 vs. 55 vs. 55 % Female: 84.7%[†] Mean BMI: 24.9 vs. 25.1 vs. 25.5	6 months: 96.1% (98/102)	NR

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		inflammation or tumor existence around the knee, history of diabetes mellitus, severe cardiovascular disease, coagulopathies, malignant immunosuppressive, collagen vascular or autoimmune disorders, Hb values of <11 g/dL or platelet values of <150,000/mL, receiving treatment with anticoagulant or antiplatelet medications or systemic corticosteroids 10 days before injection, or use of NSAIDs 5 days before injection, genu varum or valgus >5 degrees, pregnancy, or breastfeeding.					KL grade 3: 100% vs. 100% vs. 100% Symptom duration: ≥6 vs. ≥6 months vs. ≥6 months (inclusion criteria)		
Yaradilmis, 2020 Turkey	N=70‡	Inclusion: KL grade 2 or 3 symptomatic knee OA, aged 38 to	LP-PRP (N=34) mL NR; platelets mean 486.71 ± 65.75	NR	3 injections, weekly intervals	NSAIDs	LP-PRP vs. LR-PRP	12 months: 85.7% (60/70)	Hospital's education planning committee

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		80 years and stable knees. Exclusion: Inflammatory diseases, major malalignment of the knee, hematologic diseases, anemia, severe cardiac diseases.	X 10^9/L; 3 injections LR-PRP (N=36) mL NR; platelets mean 577.83 ± 71.76 X 10^9/L; 3 injections				Mean age: 59 vs. 60 % Female: 90% vs. 86.7% Mean BMI: 32.53 vs. 31.27 Comorbidities (hypertension & diabetes): 20% vs. 33.3% KL grade 2 or 3[§]: 100% vs. 100% Symptom duration: NR		
Zhou, 2023 China	N=60	Inclusion: Between 18 and 75, MRI clearly indicated articular cartilage injury, KL 1 to 3, obvious knee pain or discomfort lasting more than 3 months, willing to participate and signed informed consent form, articular cartilage injury diagnosed by arthroscopy and who	Pure PRP (N=30) 5 mL; platelets 486.71 ± 65.75 x 10^9/L; 3 injections Leukocyte PRP (N=30) 5 mL; platelets 577.83 ± 71.76 x 10^9/L; 3 injections	NR	All injections within 14 days of each other	None	Pure PRP vs. L-PRP Mean age: 62 vs. 62 % Female: 76.6% vs. 70% Mean BMI: 25.45 vs. 25.6 KL grade: NR	12 months: 88.3% (53/60)	National Natural Science Foundation of China and Chine PLA General Hospital

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		did not receive targeted treatment. Exclusion: Other surgical procedures to treat articular cartilage, history of intra-articular injection or peri-articular invasive treatments and procedures within 3 months, symptoms and imaging findings localized in the patellofemoral joint, suffering from malignant neoplasms, active infection, pregnant, lactating, or preparing for pregnancy, cartilage lesions caused by infectious or gouty arthritis, autoimmune diseases, diabetes, generally in poor condition and unable to tolerate surgery, severe diseases such as cerebral hemorrhage, pneumonia, or multiple organ					Symptom duration: ≥3 vs. ≥3 months (inclusion criteria)		

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		dysfunction, Charcot joint, conditions that might increase risk or influence the results of the research, other reasons making the patient unsuitable.							
Yurtbay, 2022 Turkey	N=133**	Inclusion: KL grade 1, 2, or 3, aged 18 to 80, mean VAS pain score >4 over the course of 7 days. Exclusion: OA secondary to joint inflammatory disease, metabolic bone disease, coexisting backache, presence of hematological disease, bilateral symptomatic lesions, advanced stage OA, intra-articular injection made within previous 3 months, or arthroscopic lavage in previous year, use of immunosuppressive drugs, current use of anti-coagulant medications or NSAIDs in the 5 days before blood sampling, major	LR-PRP (N=67) 5 mL; platelets 128 x 10^5 µl; single injection†† LR-PRP (N=66) 5 mL; platelets 128 x 10^5 µl; 3 injections††	NR	3 injection groups: 1 month intervals	Paracetamol if needed	1 injection PRP vs. 3 injection PRP Mean age: 53 vs. 57 % Female: 33.8% vs. 14.3% BMI: 31.09 vs. 30.68 KL grade 1: 11.3% vs. 3.2% KL grade 2: 69.4% vs. 60.3% KL grade 3 : 19.4% vs. 36.5% Symptom duration: NR	24 months 94% (125/133)	None

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		axis deviation of the knee, hemoglobin level <11.5 g/dK and platelet level <100,000 or associated comorbidities, infection ,tumor, crystal arthropathies, anemia, intense joint effusion, or known or possible pregnancy.							
Lewis, 2022 Australia	N=74[‡‡]	Inclusion: ≥18 years, demonstrated history of more than 4 months of pain and/or swelling in the knees with early radiological evidence of tibiofemoral OA, KL grade 0, 1, 2. Exclusion: Evidence of advanced OA of the knee, previous open knee surgery, anticoagulation, or any systemic disorder, such as rheumatological disease, severe cardiovascular disease, hematological disease, or infection.	LP-PRP + Placebo (saline) (N=47) 4 to 6 mL; platelets NR; single injection PRP + 2 injections placebo LP-PRP (N=27) 4 to 6 mL; platelets NR; 3 injections	NR	3 injections: 1 injection weekly	NR	LP-PRP + placebo vs. LP-PRP (3 injections) Mean age: 55 vs. 59 % Female: 57% vs. 67% Mean BMI: 29.3 vs. 29.7 KL grade 0: 8.5% vs. 3.7% KL grade 1: 23.4% vs. 29.6% KL grade 2:48.9% vs. 48.1%	3 months: 82.7% (62/75) 6 months: 93.3% (70/75) 12 months: 89.3% (67/75)	Clifford Craig Foundation

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
							Mean symptom duration: 56 vs. 55.7 months		
Patel, 2013 India	N=52[§§]	Inclusion: Bilateral knee OA as diagnosed by American College of Rheumatology criteria and staged as per Ahlback radiological grading (grade 1 or 22) in patients who volunteered and signed a detailed informed consent form. Exclusion: IA secondary to join inflammatory diseases, generalized OA, metabolic diseases of the bone, coexisting backache, advanced staged of OA, received intra-articular injections within 1 year o were receiving anticoagulant therapy,	LP-PRP (N=27) 8 mL; platelet count 310.14 × 10^3/mL, mean platelet quantity injected 238.56 × 10^7; single injection LP-PRP (N=25) 8 mL; platelet count 310.14 × 10^3/mL, mean platelet quantity injected 238.56 × 10^7; single injection; 2 injections	NR	PRP group 1: none (single injection) PRP group 2: 2 injections (3 weeks apart)	None	Single injection PRP vs. 2 injection PRP Mean age: 53 vs. 52 years % Female: 59% vs. 80% Mean BMI: 26.3 vs. 25.8 Ahlback grade 1: 71% vs. 72% Ahlback grade 2: 21% vs. 20% Ahlback grade 3: 4% vs. 4% Symptom duration: NR	6 months: 98.1% (51/52)	Professor D.S. Grewal Memorial Orthopaedics Society and the Indian Arthroplasty Association

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		hemoglobin level less than 10 gm% or associated comorbidities, infection, tumor, crystal arthropathies, or tense joint effusion.							
Tavassoli, 2019	N=64***	Inclusion: Diagnosis of knee OA defined by the criteria of the American College of Rheumatology, staged using the Ahlback radiological grading, bilateral knee OA with the same Ahlback grade, and all knees with full range of motion. Exclusion: History of diabetes, other joint diseases in the knee such as rheumatoid arthritis or gout, knee surgery, knee fracture, intra-articular injection of corticosteroids during the previous 2 weeks, intra-articular injection of other drugs such as hyaluronic acid over	PRP-1 (n=31): Leukocyte rich; 4-6 ml (platelet conc. NR); 40 mL blood, double centrifugation: 1500 rpm for 15 minutes, 3500 rpm for 7 minutes; single injection PRP-2 (n=33): Leukocyte rich; 4-6 ml (platelet conc. NR); 40 mL blood, double centrifugation: 1500 rpm for 15 minutes, 3500 rpm for 7 minutes; 2 injections with a 3 week interval	None	PRP-1: 1 injection PRP-2: 2 injections with a 3 week interval	Acetaminophen	PRP-1 vs. PRP-2 Age: 63.23 vs. 66.04 BMI: 28.43 vs. 29.61 % Female: 82.1% vs. 78.6%	3 months: 87.5% (56/64))	University

RCT (Country)	N	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		the previous year, contraindications for intra-articular injection such as thrombocytopenia, coagulopathy, articular infection of knee, skin infection in injection site, impairment of immunity (e.g., acquired immune deficiency syndrome or receiving immunosuppressive medication) and severe intra-articular effusion (intra-articular injection was started after treatment and cure of effusion), Ahlback grade >=3							

APAP = Acetaminophen; BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized control trial; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.

* Study also included HA group (N=46) and placebo (N=45).

† Whole population only.

‡ Study included HA group (N=35).

§ Details not reported.

** Study also includes a 1 injection placebo group (N=69) and 3 injection placebo group (N=65).

†† Unilateral only; bilateral injection was not applied to any patient.

‡‡ Study also includes a 3 injection placebo group (N=27).

§§ Study also includes a placebo group (N=26).

*** Study also include HA group (n=31).

Appendix Table G16. Patient Characteristics of Studies comparing PRP to Other Treatments for Knee Osteoarthritis (Knees Randomized)

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
PRP vs. Placebo									
Lin, 2019 Taiwan	N=NR[*] (58 knees)	Inclusion: Age 20 to 80, ability to provide informed consent, unilateral or bilateral knee VAS ≥4, ≥4 months symptoms duration, diagnosis of Ahlback OA stage 1 to 3, no prior PRP injection in knee, no prior surgical procedure in participating knee. Exclusion: Ahlback OA stage 4, major axial deviation, any concomitant symptomatic knee disorders, systemic inflammatory arthropathy, hematologic disease, severe cardiovascular disease, neurologic disorder, active infection, immunocompromised, therapy with anticoagulant or antiaggregant, use of NSAID and/or	LP-PRP (N=31 knees) 2 ml; platelet concentration 1.81 ± 0.34 x baseline value; 3 injections[†] Placebo (saline) (N=27 knees) 2 mL; 3 injections[†]	NR	3 injections, weekly	Paracetamol[‡]	LP-PRP vs. Placebo Mean age: 61 vs. 62 years % Female: 70.97% vs. 62.96% Mean BMI: 23.98 vs. 24.98 Ahlback stage 1: 16.12% vs. 14.81% Ahlback stage 2: 51.61% vs. 44.44% Ahlback stage 3: 32.25% vs. 40.74% Symptom duration: ≥4 vs. ≥4 months (inclusion criteria)	12 months: 100% (N=NR[§])	Kaohsiung Veterans General Hospital Research Grant

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		chondroprotective supplement, reent intra-articular injection of corticosteroid (30 days) and prior treatment with HA in past 6 months, Hb level <11 g/dL, platelet count <150,000/mm^3.							
Wu, 2018 Taiwan	N=20 (20 knees to each intervention)	Inclusion: Radiological diagnosis of degenerative join disease of both knees equivalent to Ahlback Stage I-II, age 50 to 75, pain in both knees lasting for at least 6 months, same OA grade in both knees, bilateral pain level during walking ≥4. Exclusion: Intra-articular injections (HA/steroids) in the knee joint 6 months before study, anti-inflammatory tumors, previous knee surgery, any other connective tissue disorder affecting the knee joint, use of	LP-PRP (N=20 knees) 4 mL; platelets NR; single injection Placebo (saline) (N=20 knees) 4 mL; single injection	NR	No (single injection)	Acetaminophen (500 mg, up to 4 g/d)	Whole populations Mean age: 63 years % Female: 75% Mean BMI: 24.14 Ahlback stage 1: 70% Ahlback stage 2: 30% Symptom duration: 65 vs. 60 months.	3 months: 100% (20/20) 6 months: 100% (20/20)	Ministry of Science and Technology, Taiwan

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		anticoagulants, liver disease, cancer history, and inability to undergo muscle strength testing.							
Ghai, 2020 India	N=20 (20 knees to each intervention)	Inclusion: Between 30 and 65 years with bilateral OA knees of either gender, history of pain or swelling in the knee >4 months, imaging findings (x-ray or MRI) of degenerative changes of the joint without significant deformity (KL 1 or 2). Exclusion: History of diabetes, immunosuppressive drugs, collagen vascular disorders, cancer or malignant disorders and those with active infection/wound of the knee, autoimmune and platelet disorders, treatment with anticoagulant and antiplatelet medications 10 days before injection or use	LR-PRP (N=20 knees) 8 mL, 14 × 10^3/mL, mean platelet quantity injected 238.56 × 10^7; single injection Placebo (saline) (N=20 knees) 4 mL; single injection	Ultrasound	No (single injection)	Conservative management (defined as adjuvant drugs, NSAIDs, and/or therapeutic exercise programs). Pain medications were to stop if they showed substantial improvement with study intervention; in others, dosages were increased or continued.	Whole population Mean age: 49.8 years % Female: 75% BMI: NR KL Grade 1 or 2: 100%** Symptom duration: NR (>4 months, per inclusion criteria)	3 months: 100% (20/20) 6 months: 100% (20/20)	NR

RCT (Country)	N*	Inclusion & Exclusion Criteria	Interventions	Imaging Guidance	Repeat injections	Co-interventions	Patient Characteristics	Length, % f/u	Funding
		of NSAIDS 2 days before injection, history of knee articular injection of corticosteroid during previous 3 months or use of systemic corticosteroids 2 weeks before injection, genu valgum/varum greater than 20 degrees, HIV, Hepatitis B or C, venereal disease, or Research Laboratory virus positive cases.							

BMI = body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; LP = leukocyte-poor; LR = leukocyte-rich; MRI = magnetic resonance imaging; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma.
* 53 patients were randomized in total, with 87 knees included. 29 knees were randomized to HA.
† Some bilateral, not all; bilateral knees randomized to different treatments. There were 53 patients with 87 knees, estimating that 19 patients were unilateral and 34 patients were bilateral (i.e., 68 knees) (68+19 = 87).
‡ Had to be discontinued 72 hours before each follow-up assessment.
§ There were no withdrawals, but 1 knee in PRP group missed the 2-month follow-up and 1 knee in the placebo group missed the 6-month follow-up.
** No further details on proportion of each grade.

Appendix Table G17a. Patient Summary Demographics in Studies Comparing HA to PRP for Knee Osteoarthritis (1-3 of 11)

	Buendía-López, 2019		Görmeli, 2017			Raeissadat, 2021	
	HA	PRP	HA	PRP	PRP	HA	PRP
n	36	35	39	46	45	59	59
Patient characteristics							
Age, yrs (mean)	56.63	56.15	53.5	53.7	53.8	57.91	56.01
BMI (mean)	24.9	24.9	29.7	28.7	28.4	27.46	27.41
% Female	53.1%	51.5%	56.4%	58.9%	56.8%	75.5%	75.0%

Minimum Duration of Symptoms	NR	NR	4 months	4 months	4 months	3 months	3 months
Duration of symptoms (mean)	NR	NR	NR	NR	NR	3.86 years	4.44 years
Previous nonoperative %	100%	100%	100%	100%	100%	NR	NR
Previous operative %	0%	0%	0%	0%	0%	NR	NR
Bilateral/Unilateral	Unilateral		Unilateral			NR	
Kellgren-Lawrence							
Grade 1	56.3%	54.5%	NR	NR	NR	-	-
Grade 2	43.7%	45.5%	NR	NR	NR	55.1%	50.0%
Grade 3	-	-	NR	NR	NR	44.9%	50.0%
Grade 4	-	-	NR	NR	NR	-	-
Procedural Characteristics							
Formulation	Durolane	-	Orthovisc	-	-	Hyalgan	
Dose/Platelet Count	60mg	1,095,000 ± 23,200/mm^3	30mg	5.2× (1118,000 µL)	5.2× (1118,000 µL)	20mg	5 times normal concentration
Volume	2mL	5mL	2mL	5mL	5mL	2mL	3.5mL
High/Low Molecular Weight (Reported in KDa)	High (100,000kDa)	-	High (1,000-2,900kDa)	-	-	Low (500-730kDa)	-
Leukocyte Rich/Poor (Leukocyte Count)	-	Poor	-	Rich	Rich	-	Rich
Activating Agent	-	Calcium chloride	-	Calcium chloride	Calcium chloride	-	Epinephrine, calcium chloride
Local Anesthetic	NR	NR	NR	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR	NR
Imaging Guidance	None		None			None	
Number of Injections	1	1	3	3	1 PRP, 2 Placebo	3	2
Injection Frequency	-	-	Weekly	Weekly	Weekly	Weekly	3 weeks
Funding	None		None			Non-Industry	
Quality	**Fair**		**Fair**			**Poor**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported; PRP = platelet-rich plasma.

Appendix Table G17b. Patient Summary Demographics in Studies Comparing HA to PRP for Knee Osteoarthritis (4-6 of 11)

	Lisi, 2018		Cole, 2017		Lana, 2016	
	HA	PRP	HA	PRP	HA	PRP
n	28	30	59	52	36	36
Patient characteristics						
Age, yrs (mean)	57.1	53.5	56.8	55.9	60.0	60.9
BMI (mean)	NR	NR	29.0	27.4	28.24	27.42
% Female	43%	33%	60.0%	42.9%	91.7%	80.6%
Minimum Duration of Symptoms	NR	NR	NR	NR	4 months	4 months
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	NR	NR	NR	NR	100%	100%
Previous operative %	NR	NR	NR	NR	0%	0%
Bilateral/Unilateral	Bilateral (both knees received same treatment)		Unilateral		NR	
Kellgren-Lawrence						
Grade 1	Shahriaree: 0%	Shahriaree: 0%	0%	6.1%	25%	25%
Grade 2	NR	NR	54.0%	53.1%	44%	39%
Grade 3	NR	NR	44.0%	40.8%	31%	36%
Grade 4	Shahriaree: 0%	Shahriaree: 0%	2.0%	0%	-	-
Procedural Characteristics						
Formulation	Hyalgan	-	Synvisc	-	Eufflexa	-
Dose/Platelet Count	20mg	NR	16mg	PRP-to-peripheral blood ratio of platelets 1.73 (SD 0.05)	20mg	800,000 to 1,600,000 per mm^3, 5-8x basal concentration
Volume	2mL	NR	2mL	4mL	2mL	5mL
High/Low Molecular Weight (Reported in KDa)	Low (500-730kDa)	-	High (6,000kDa)	-	High (2,400-3,000kDa)	-
Leukocyte Rich/Poor (Leukocyte Count)	-	NR	-	Poor	-	Poor (NR)
Activating Agent	-	Calcium gluconate	-	NR	-	Serum
Local Anesthetic	NR	NR	NR	NR	Lidocaine 2% with epinephrine	Lidocaine 2% with epinephrine

Other injectate	NR	NR	NR	NR	Sodium bicarbonate	Sodium bicarbonate
Imaging Guidance	Ultrasound		Ultrasound		Ultrasound	
Number of Injections	3	3	3	3	3	3
Injection Frequency	Monthly	Monthly	Weekly	Weekly	2 weeks	2 weeks
Funding	Non-Industry		Industry		None	
Quality	**Fair**		**Fair**		**Fair**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported; PRP = platelet-rich plasma; SD = standard deviation.

Appendix Table G17c. Patient Summary Demographics in Studies Comparing HA to PRP for Knee Osteoarthritis (7-9 of 11)

	Louis, 2018		Raeissadat, 2015		Tavassoli, 2019		
	HA	PRP	HA	PRP	HA	PRP	PRP
n	28	28	73	87	31	31	33
Patient characteristics							
Age, yrs (mean)	48.5	53.2	61.13	56.85	63.30	63.23	66.04
BMI (mean)	27.0	25.6	27.03	28.20	28.94	28.43	29.61
% Female	54.2%	41.7%	75.8%	89.6%	70.4%	82.1%	78.6%
Minimum Duration of Symptoms	NR	NR	3 months	3 months	NR	NR	NR
Duration of symptoms (mean)	100.2 months	99.5 months	NR	NR	NR	NR	NR
Previous nonoperative %	NR	NR	NR	NR	NR	NR	NR
Previous operative %	NR	NR	NR	NR	NR	NR	NR
Bilateral/Unilateral	NR		NR		Bilateral*		
Kellgren-Lawrence							
Grade 1	-	-	0%	6%	Ahlback: 37.5%†	Ahlback: 30.4%†	Ahlback: 40.7%†
Grade 2	100%	100%	47%	44%	Ahlback: 62.5%†	Ahlback: 69.6%†	Ahlback: 59.3%†
Grade 3	-	-	37%	38%	-	-	-
Grade 4	-	-	16%	12%	-	-	-
Procedural Characteristics							
Formulation	Durolane	-	Hyalgan	-	Hyalgan	-	-
Dose/Platelet Count	60mg	platelets >2 but < 4 compared with blood	20mg	platelet concentration 5 x normal values	30mg	NR	NR
Volume	3mL	3mL	2mL	4-6mL	2mL	4-6mL	4-6mL

High/Low Molecular Weight (Reported in KDa)	High (100,000kDa)	-	Low (500-730kDa)	-	Low (500-730kDa)	-	-
Leukocyte Rich/Poor (Leukocyte Count)	-	Poor (NR)	-	Rich (NR)	-	Rich (NR)	Rich (NR)
Activating Agent	-	NR	-	None	-	NR	NR
Local Anesthetic	NR	NR	None	None	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR	NR
Imaging Guidance	Echographic		None		None		
Number of Injections	1	1	3	2	3	1	2
Injection Frequency	-	-	Weekly	4 weeks	Weekly	-	3 weeks
Funding	Industry		None		Non-industry		
Quality	**Good**		**Poor**		**Poor**		

BMI = body mass index; HA = hyaluronic acid; NR = not reported; PRP = platelet-rich plasma.
* Both knees received the same treatment.
† By knees, not individuals.

Appendix Table G17d. Patient Summary Demographics in Studies Comparing HA to PRP for Knee Osteoarthritis (10-11 of 11)

	Sdeek, 2021		Wang, 2022	
	HA	PRP	HA	PRP
n	94	95	50	50
Patient characteristics				
Age, yrs (mean)	59.5	60.2	62.3	64.9
BMI (mean)	27.1	27.9	22.1	23.4
% Female	83.0%	84.2%	79.1%	73.8%
Minimum Duration of Symptoms	6 months	6 months	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR
Previous nonoperative %	100%	100%	NR	NR
Previous operative %	0%	0%	NR	NR
Bilateral/Unilateral	Unilateral		NR	
Kellgren-Lawrence				
Grade 1	-	-	-	-
Grade 2	52.1%	45.3%	-	-
Grade 3	47.9%	54.7%	100%	100%
Grade 4	-	-	-	-
Procedural Characteristics				

Formulation	Hyalgan	-	Supartz	-
Dose/Platelet Count	NR	2,664 ±970 x 10^3/ul	25mg	NR
Volume	2.5mL	2.5mL	2.5mL	4mL
High/Low Molecular Weight (Reported in KDa)	Low (500-730kDa)	-	High (620-1,170kDa)	-
Leukocyte Rich/Poor (Leukocyte Count)	-	Poor (NR)	-	Rich (NR)
Activating Agent	-	NR	-	Calcium Chloride
Local Anesthetic	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR
Imaging Guidance	None		NR	
Number of Injections	3	3	3	3
Injection Frequency	2 weeks	2 weeks	Weekly	Weekly
Funding	None		Non-Industry	
Quality	**Poor**		**Poor**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported; PRP = platelet-rich plasma.

Appendix Table G18a. Patient Summary Demographics in Studies Comparing HA to Placebo for Knee Osteoarthritis (1-3 of 9)

	Hangody, 2018		Petterson, 2019		Takamura SSED	
	HA	Placebo	HA	Placebo	HA	Placebo
n	150	69	184	185	407	410
Patient characteristics						
Age, yrs (mean)	59.2	58.0	59.5	58.7	59.3	59.8
BMI (mean)	28.4	29.1	29.9	30.4	28.6	28.8
% Female	66.0%	73.9%	59.2%	57.3%	55.0%	57.5%
Minimum Duration of Symptoms	NR	NR	6 months	6 months	30 days	30 days
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	NR	NR	100% within 12 months	100% within 12 months	100%	100%
Previous operative %	NR	NR	0% within 12 months	0% within 12 months	0%	0%
Bilateral/Unilateral	Unilateral		Unilateral		Unilateral	
Kellgren-Lawrence						
Grade 1	16.0%	24.6%	-	-	28.1%	27.3%
Grade 2	65.3%	55.1%	57.1%	52.4%	40.0%	40.3%
Grade 3	18.0%	20.3%	42.9%	47.6%	31.8%	32.4%
Grade 4	0.7%	0%	-	-	-	-

Procedural Characteristics						
Formulation	Monovisc	-	Monovisc	-	Gel-One	-
Dose/Platelet Count	88mg	-	NR	-	NR	-
Volume	4mL	4mL	4mL	4mL	NR	NR
High/Low Molecular Weight (Reported in KDa)	High (1,000-2,900kDa)	-	High (1,000-2,900kDa	-	High (>5,000kDa)	-
Local Anesthetic	NR	NR	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	None		None		NR	
Number of Injections	1	1	1	1	1	1
Injection Frequency	-	-	-	-	-	-
Funding	Industry		Industry		Industry	
Quality	**Good**		**Good**		**Fair**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported.

Appendix Table G18b. Patient Summary Demographics in Studies Comparing HA to Placebo for Knee Osteoarthritis (4-6 of 9)

	Strand, 2012		**Bao, 2018**		**Arden, 2014**	
	HA	Placebo	HA	Placebo	HA	Placebo
n	251	108	20	20	110	128
Patient characteristics						
Age, yrs (mean)	60.9	64.5	66.0	65.3	60.9	60.3
BMI (mean)	28.3	26.4 (female), 28.2 (male)	NR	NR	26.9 (female), 28.1 (male)	28.7
% Female	59.5%	55%	35%	55%	46%	60.2%
Minimum Duration of Symptoms	4 weeks	4 weeks	NR	NR	NR	NR
Duration of symptoms (mean)	NR	NR	31.8 months	33.6 months	NR	NR
Previous nonoperative %	NR	NR	100% within 12 months	100% within 12 months	NR	NR
Previous operative %	NR	NR	0% within 12 months	0% within 12 months	NR	NR
Bilateral/Unilateral	NR		NR		NR	
Kellgren-Lawrence						
Grade 1	8.5%	10.4%	-	-	-	-
Grade 2	38.1%	30.6%	60%	70%	36.4%	36.7%
Grade 3	53.4%	69.4%	40%	30%	63.6%	49.2%

Grade 4	-	-	-	-	-	-
Procedural Characteristics						
Formulation	Gel-200	-	Durolane	-	Supartz	-
Dose/Platelet Count	30mg	-	60mg	-	NR	-
Volume	3mL	3mL	3mL	2.5mL	NR	3mL
High/Low Molecular Weight (Reported in KDa)	NR	-	High (90,000kDa)	-	High (620-1,170kDa)	-
Local Anesthetic	NR	NR	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	None		None		Ultrasound	
Number of Injections	1	1	5	1	1	1
Injection Frequency	-	-	Weekly	-	-	-
Funding	Industry		Industry		Non-industry	
Quality	**Good**		**Good**		**Poor**	

Appendix Table G18c. Patient Summary Demographics in Studies Comparing HA to Placebo for Knee Osteoarthritis (7-9 of 9)

	Görmeli, 2017		**Ke, 2021**		**Farr, 2019**	
	HA	Placebo	HA	Placebo	HA	Placebo
n	39	45	218	220	64	68
Patient characteristics						
Age, yrs (mean)	53.5	52.8	61.5	61.6	55.4	54.9
BMI (mean)	29.7	29.5	25.57	25.39	28.2	28.5
% Female	56.4%	50.0%	77.3%	78.2%	48.4%	45.6%
Minimum Duration of Symptoms	4 months	4 months	NR	NR	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	100%	100%	100%	100%	100% within 12 months	100% within 12 months
Previous operative %	0%	0%	0%	0%	0% within 12 months	0% within 12 months
Bilateral/Unilateral	Unilateral				Bilateral*	
Kellgren-Lawrence						
Grade 1	NR	NR	14.1%	10.9%	-	-
Grade 2	NR	NR	47.7%	52.7%	45.3%	38.2%
Grade 3	NR	NR	38.2%	36.4%	54.7%	61.8%
Grade 4	NR	NR	-	-	-	-

Procedural Characteristics						
Formulation	Orthovisc	-	Hylan GF-20	-	Monovisc	-
Dose/Platelet Count	30mg	-	48mg	-	88mg	-
Volume	2mL	NR	6mL	6mL	4mL	4mL
High/Low Molecular Weight (Reported in KDa)	High (1,000-2,900kDa)	-	High (6,000kDa)	-	High (1,000-2,900kDa)	-
Local Anesthetic	NR	NR	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	None		NR		None	
Number of Injections	3	3	1	1	1	1
Injection Frequency	Weekly	Weekly	-	-	1	1
Funding	None		Industry		Industry	
Quality	**Fair**		**Good**		**Poor**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported.

* Patients had bilateral knee OA, but only one knee was randomized.

Appendix Table G19a. Patient Summary Demographics in Studies Comparing HA to Steroid for Knee Osteoarthritis (1-3 of 6)

	Vaishya, 2017		**Askari, 2016**		**Bissichia, 2016**	
	HA	Steroid	HA	Steroid	HA	Steroid
n	42	40	71	69	75	75
Patient characteristics						
Age, yrs (mean)	NR	NR	58.5	57.0	71.5	68.6
BMI (mean)	NR	NR	NR	NR	NR	NR
% Female	69.0%	62.5%	87.3%	82.6%	70.7%	66.7%
Minimum Duration of Symptoms	NR	NR	3 months	3 months	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	NR	NR	100%	100%	100% within 6 months	100% within 6 months
Previous operative %	NR	NR	0%	0%	0% within 6 months	0% within 6 months
Bilateral/Unilateral	Bilateral*		NR		Unilateral	
Kellgren-Lawrence						
Grade 1	-	-	-	-	-	-
Grade 2	43%	55%	NR	NR	NR	NR
Grade 3	57%	45%	NR	NR	NR	NR
Grade 4	-	-	-	-	-	-

Procedural Characteristics						
Formulation	Synvisc-One	Triamcinolone hexa-acetate	Hyalgan	NR	Hymovis	NR
Dose/Platelet Count	48mg	40mg	NR	40mg	NR	NR
Volume	6mL	NR	2mL	NR	NR	NR
High/Low Molecular Weight (Reported in KDa)	High (6,000KDa)	-	Low (500-730KDa)	-	Low (500-730KDa)	-
Local Anesthetic	NR	NR	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	None	None	None	None	None	None
Number of Injections	1	1	1	1	2	2
Injection Frequency	-	-	-	-	Weekly	Weekly
Funding	None		Non-Industry		None	
Quality	**Poor**		**Good**		**Fair (3 mos.) Poor (6, 12 mos.)**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported.

* Bilateral knees injected simultaneously but no specification on treatment in methods.

Appendix Table G19b. Patient Summary Demographics in Studies Comparing HA to Steroid for Knee Osteoarthritis (4-6 of 6)

	Tammachote, 2016		**Leighton, 2014**		**Campos, 2017**	
	HA	Steroid	HA	Steroid	HA	Steroid
n	55	55	221	221	50 (knees)	53 (knees)
Patient characteristics						
Age, yrs (mean)	62.6	61.0	61.9	61.5	NR	NR
BMI (mean)	26.3	25.8	28.2	28.3	NR	NR
% Female	86.0%	73.5%	51%	49%	73.3%	
Minimum Duration of Symptoms	NR	NR	NR	NR	NR	NR
Duration of symptoms (mean)	NR	NR	4.7 years	4.9 years	NR	NR
Previous nonoperative %	100%	100%	100% within 12 months	100% within 12 months	NR	NR
Previous operative %	0%	0%	0% within 12 months	0% within 12 months	NR	NR’
Bilateral/Unilateral	NR		Unilateral		Bilateral*	
Kellgren-Lawrence						
Grade 1	20.0%	24.5%	-	-	NR	NR
Grade 2	22.0%	22.4%	32.6%	39.5%	NR	NR

Grade 3	44.0%	38.8%	67.4%	60.5%	NR	NR
Grade 4	14.0%	14.3%	-	-	NR	NR
Procedural Characteristics						
Formulation	Synvisc	Triamcinolone Acetonide	Durolane	Methylprednisolone	Synvisc	Triamcinolone acetonide
Dose/Platelet Count	NR	40mg	60mg	40mg	NR	20mg
Volume	6mL	1mL (6mL with injectates)	3mL	1mL	6mL	1mL
High/Low Molecular Weight (Reported in KDa)	High (6,000kDa)	-	High (90,000kDa)	-	High (6,000kDa)	-
Local Anesthetic	2% lidocaine hydrochloride with 1:80,000 epi-nephrine	2% lidocaine hydrochloride with 1:80,000 epi-nephrine	1% lidocaine, 2mL	1% lidocaine, 2mL	NR	NR
Other injectate	NR	Lidocaine 1% with Epinephrine 1:100,000 (5mL)	NR	NR	NR	NR
Imaging Guidance	None	None	None	None	None	None
Number of Injections	1	1	1	1	1	1
Injection Frequency	-	-	-	-	-	-
Funding	Non-industry		Industry		None	
Quality	**Fair**		**Fair**		**Poor**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported.
* Bilater knee OA. Knees randomized individually.

Appendix Table G20. Patient Summary Demographics in Studies Comparing HA to NSAIDs for Knee Osteoarthritis (1-2 of 2)

	Buendía-López, 2019		Guner, 2016	
	HA	NSAID	HA	NSAID
n	36	35	31	31
Patient characteristics				
Age, yrs (mean)	56.63	57.42	62.5	61.3
BMI (mean)	24.9	25.2	27.54	28.73
% Female	53.1%	51.5%	90.0%	82.8%
Minimum Duration of Symptoms	NR	NR	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR
Previous nonoperative %	100%	100%	100%	100%
Previous operative %	0%	0%	0%	0%

Bilateral/Unilateral	Unilateral		NR	
Kellgren-Lawrence				
Grade 1	56.3%	51.5%	-	-
Grade 2	43.7%	48.5%	50.0%	58.6%
Grade 3	-	-	50.0%	41.4%
Grade 4	-	-	-	-
Procedural Characteristics				
Formulation	Durolane	Etoricoxib	Orthovisc	Etofenamate (Flexo ampule)
Dose/Platelet Count	60mg	NR	30mg	100mg
Volume	2mL	60mg	2mL	2mL
High/Low Molecular Weight (Reported in KDa)	High (100,000kDa)	-	High (1,000-2,900kDa)	-
Local Anesthetic	NR	-	Lidocaine	-
Other injectate	NR	-	NR	lansoprazole 30 mg/day*
Imaging Guidance	None	-	None	None
Number of Injections	1	-	3	7 (IM)
Injection Frequency	-	Daily	Weekly†	Daily‡
Funding	None		None	
Quality	**Fair**		**Fair**	

BMI = body mass index; HA = hyaluronic acid; NR = not reported.

* Proton pump inhibitor (lansoprazole 30 mg/day) given only to patients with gastrointestinal system problems.

† Weekly injections for 3 weeks.

‡ Daily injections for 1 week.

Appendix Table G21a. Patient Summary Demographics in Studies Comparing PRP to Placebo for Knee Osteoarthritis (1-3 of 9)

	Bennel, 2021		Chu, 2022		Dório, 2021	
	PRP	Placebo	PRP	Placebo	PRP	Placebo
n	144	144	322	322	20	21
Patient characteristics						
Age, yrs (mean)	62	62	54	55	66	63
BMI (mean)	29	29.6	27.5	27.9	28.3	28
% Female	59%	58.3%	60.1%	57.9%	95%	90%
Minimum Duration of Symptoms	1 month		1 month		1 week	
Duration of symptoms (mean)	5 years	6 years	≥1 month	≥1 month	8.4 years	7.1 years
Previous nonoperative %	NR	NR	NR	NR	100%†	100%†

Previous operative %	NR	NR	NR	NR	0%	0%
Bilateral/Unilateral	Bilateral		Unilateral		Both‡	
Kellgren-Lawrence						
Grade 1	-	-	27.6%	29.5%	-	-
Grade 2	47.9%	50%	42.2%	40.1%	NR	NR
Grade 3	52.1%	50%	25.8%	24.2%	NR§	NR§
Grade 4	-	-	-	-	-	-
Procedural Characteristics						
Dose/Platelet Count	235 x 10^3/mm^3	-	832.1 ± 269.3 × 10^9/L	-	1 x 10^6	-
Volume	5 mL	5 mL	5 mL	5 mL	1.4 to 4 mL	NR
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Poor	-	Rich	-	Poor	-
Activating Agent	None	-	NR	-	None	-
Local Anesthetic	Yes*	Yes*	NR	NR	Yes	Yes
Other injectate	None	None	NR	NR	NR	NR
Imaging Guidance	Ultrasound	Ultrasound	Ultrasound	Ultrasound	Ultrasound	Ultrasound
Number of Injections	3	3	3	3	2	2
Injection Frequency	Weekly	Weekly	Weekly	Weekly	2 week intervals	2 week intervals
Funding	Non-industry		Non-industry		None	
Quality	**Good**		**Good**		**Good**	

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.
* Optional before injection.
† Exclusion criteria.
‡ In bilateral cases, the knee selected for treatment was the one reported with higher pain score as reported by the participant.
§ All patients were either KL grade 2 or 3, but authors did not report details

Appendix Table G21b. Patient Summary Demographics in Studies Comparing PRP to Placebo for Knee Osteoarthritis (4-5 of 9)

	Elik, 2020		Görmeli, 2017		
	PRP	Placebo	PRP	PRP	Placebo
n	30	30	45	46	45
Patient characteristics					
Age, yrs (mean)	61	60	54	54	53
BMI (mean)	30.4	30.7	28.4	28.7	29.5
% Female	96.7%	88.9%	56.8%	58.9%	50%

Minimum Duration of Symptoms	NR	NR	≥4 months	≥4 months	≥4 months
Duration of symptoms (mean)	NR	NR	≥4 months†	≥4 months†	≥4 months†
Previous nonoperative %	100%*	100%*	100%*	100%*	100%*
Previous operative %	0%	0%	0%	0%	0%
Bilateral/Unilateral	Bilateral		Both		
Kellgren-Lawrence					
Grade 1	6%	11.1%	NR	NR	NR
Grade 2	46.7%	48.1%	NR	NR	NR
Grade 3	46.7%	40.7%	NR‡	NR‡	NR‡
Grade 4	-	-	31.8%	33.3%	32.5%
Procedural Characteristics					
Dose/Platelet Count	NR	-	5.2× (1118,000 µL);	5.2× (1118,000 µL);	-
Volume	4 mL	4 mL	5 mL	5 mL	NR
High/Low Molecular Weight	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	-	Rich	Rich	-
Activating Agent	NR	-	Calcium chloride	Calcium chloride	-
Local Anesthetic	NR	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR	NR
Imaging Guidance	Ultrasound	Ultrasound	NR	NR	NR
Number of Injections	3	3	1	3	3
Injection Frequency	Weekly	Weekly	-	Weekly	Weekly
Funding	None		NR		
Quality	**Fair**		**Fair**		

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* Exclusion criteria.

† Inclusion criteria.

‡ Patients were classified as Early OA (KL Grade 0-3), and advanced OA (KL Grade 4).

Appendix Table G21c. Patient Summary Demographics in Studies Comparing PRP to Placebo for Knee Osteoarthritis (6-7 of 9)

	Nunes-Tamashiro, 2022		Patel, 2013		
	PRP	Placebo	PRP	PRP	Placebo
n	34	33	27	25	26
Patient characteristics					
Age, yrs (mean)	68	68	53	52	54
BMI (mean)	29.22	30.23	26.3	25.8	26.2
% Female	88.2%	90.9%	59%	80%	74%

Minimum Duration of Symptoms	3 months	3 months	NR	NR	NR
Duration of symptoms (mean)	10.3 years	7.8 years	NR	NR	NR
Previous nonoperative %	100%*	100%*	NR	NR	NR
Previous operative %	0%	0%	NR	NR	NR
Bilateral/Unilateral	Bilateral†		Bilateral		
Kellgren-Lawrence/Ahlback					
Grade 1	-	-	Ahlback: 71%	Ahlback: 72%	Ahlback: 54%
Grade 2	41.2%	48.5%	Ahlback: 21%	Ahlback: 20%	Ahlback: 39%
Grade 3	58.8%	51.5%	Ahlback: 4%	Ahlback: 4%	Ahlback: 7%
Grade 4	-	-	-	-	-
Procedural Characteristics					
Dose/Platelet Count	152,930 per mm^3	-	310.14 × 10^3/mL	310.14 × 10^3/mL	-
Volume	NR	2 mL	8 mL	8 mL	8 mL
High/Low Molecular Weight	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	NR	-	Poor	Poor	-
Activating Agent	None	-	Calcium chloride	Calcium chloride	-
Local Anesthetic	Yes	Yes	No	No	No
Other injectate	NR	NR	NR	NR	NR
Imaging Guidance	NR	NR	NR	NR	NR
Number of Injections	1‡	1‡	1	2	1
Injection Frequency	-	-	-	2 week interval	-
Funding	None		Non-industry		
Quality	**Fair**		**Fair**		

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* Exclusion criteria.

† All bilateral knee OA. Only a single IA injection was performed on the most symptomatic knee according to the patient perception.

‡ Injected into the most symptomatic knee.

Appendix Table G21d. Patient Summary Demographics in Studies Comparing PRP to Placebo for Knee Osteoarthritis (8 of 9)

	Lewis, 2022		
	PRP + Placebo	PRP	Placebo
n	47	27	28
Patient characteristics			
Age, yrs (mean)	55	59	60
BMI (mean)	29.3	29.7	29.9

% Female	57%	67%	57%
Minimum Duration of Symptoms	4 months	4 months	4 months
Duration of symptoms (mean)	56 months	55.7 months	52.7 months
Previous nonoperative %	100%	100%	100%
Previous operative %	0%*	0%*	0%*
Bilateral/Unilateral	NR		
Kellgren-Lawrence/Ahlback			
Grade 1	23.4%	29.6%	28.6%
Grade 2	48.9%	48.1%	60.7%
Grade 3	-	-	-
Grade 4	-	-	-
Procedural Characteristics			
Dose/Platelet Count	NR	NR	-
Volume	4 to 6 mL	4 to 6 mL	5 mL
High/Low Molecular Weight	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Poor	Poor	-
Activating Agent	NR	NR	NR
Local Anesthetic	NR	NR	NR
Other injectate	NR	NR	NR
Imaging Guidance	NR	NR	NR
Number of Injections	3†	3	3
Injection Frequency	Weekly	Weekly	Weekly
Funding	Non-industry		
Quality	**Fair**		

BMI = body mass index; KL = Kellgren-Lawrence; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

Appendix Table G21e. Patient Summary Demographics in Studies Comparing PRP to Placebo for Knee Osteoarthritis (9 of 9)

	Yurtbay, 2022			
	PRP	PRP	Placebo	Placebo
Patient characteristics	67	66	69	65
Age, yrs (mean)	53	57	56	53
BMI (mean)	31.09	30.68	30.67	29.22
% Female	33.8%	14.3%	18.6%	40%
Minimum Duration of Symptoms	1 week	1 week	1 week	1 week
Duration of symptoms (mean)	NR	NR	NR	NR
Previous nonoperative %	NR	NR	NR	NR

Previous operative %	NR	NR	NR	NR
Bilateral/Unilateral	Unilateral			
Kellgren-Lawrence/Ahlback				
Grade 1	11.3%	3.2%	5.1%	5.7%
Grade 2	69.4%	60.3%	78%	83%
Grade 3	19.4%	36.5%	16.9%	11.3%
Grade 4	-	-	-	-
Procedural Characteristics				
Dose/Platelet Count	128 x 10^5 µl	128 x 10^5 µl	-	-
Volume	5 mL	5 mL	5 mL	5 mL
High/Low Molecular Weight	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	Rich	-	-
Activating Agent	NR	NR	NR	NR
Local Anesthetic	NR	NR	NR	NR
Other injectate	NR	NR	NR	NR
Imaging Guidance	NR	NR	NR	NR
Number of Injections	1	3	1	3
Injection Frequency	-	1 month interval	-	1 month interval
Funding	None			
Quality	**Fair**			

BMI = body mass index; KL = Kellgren-Lawrence; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

Appendix Table G22. Patient Summary Demographics in Studies Comparing PRP to Placebo for Knee Osteoarthritis (1-3 of 3) (Knees Randomized)

	Ghai, 2019*		Wu, 2018*		Lin, 2019**	
	PRP	Placebo	PRP	Placebo	PRP	Placebo
n	20 knees	20 knees	20 knees	20 knees	31 knees	27 knees
Patient characteristics						
Age, yrs (mean)	49.8		63		61	62
BMI (mean)	NR		24.14		23.98	24.98
% Female	75%		75%		70.97%	62.96%
Minimum Duration of Symptoms	4 months		6 months		4 months	4 months
Duration of symptoms (mean)	NR		65 months‡	60 months‡	NR	NR
Previous nonoperative %	NR		100%§		100%	

Previous operative %	NR		0%		0%††	
Bilateral/Unilateral	Bilateral		Bilateral		Both‡‡	
Kellgren-Lawrence/Ahlback						
Grade 1	-		Ahlback: 70%		Ahlback: 16.12%	Ahlback: 14.81%
Grade 2	NR†		Ahlback: 30%		Ahlback: 51.61%	Ahlback: 44.44%
Grade 3	NR		-		Ahlback: 32.25%	Ahlback: 40.74%
Grade 4	-		-		-	-
Procedural Characteristics						
Dose/Platelet Count	14×10^3/mL	-	NR	-	1.81 ± 0.34 x baseline value	-
Volume	8 mL	4 mL	4 mL	4 mL	2 mL	2 mL
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	-	Poor	-	Poor	-
Activating Agent	Calcium chloride	-	NR	NR	NR	NR
Local Anesthetic	NR	NR	NR	NR	None	None
Other injectate	NR	NR	None	None	NR	NR
Imaging Guidance	Ultrasound		NR	NR	NR	NR
Number of Injections	1	1	1	1	3	3
Injection Frequency	-	-	-	-	Weekly	Weekly
Funding	NR		Non-industry		Non-industry	
Quality	**Fair**		**Fair**		**Fair**	

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.
* Study randomized by knee, not patient. So each patient was randomly assigned one knee to PRP and the other to placebo.
† Authors do not report details, but all patients were either KL Grade 1 or 2.
‡ Reported according to knees randomized to intervention, not patients.
§ Exclusion criteria.
** Unclear how many patients were randomized, authors only report number of knees randomized. Some patients may have had both knees randomized to different interventions.
†† Inclusion criteria.
‡‡ Some bilateral, not all; bilateral knees randomized to different treatments. There were 53 patients with 87 knees…estimating that 19 patients were unilateral and 34 patients were bilateral (i.e., 68 knees) (68+19 = 87).

Appendix Table G23a. Patient Summary Demographics in Studies Comparing PRP to Steroid for Knee Osteoarthritis (1-3 of 9)

	Elksniņš-Finogejevs, 2020		Forogh, 2016		Freire, 2020	
	PRP	Steroid	PRP	Steroid	PRP	Steroid
n	20	20	24 knees	24 knees	25	25
Patient characteristics						

Age, yrs (mean)	66	70	59	61	64	60
BMI (mean)	28.6	30.5	28.9	29.2	NR	NR
% Female	15%	25%	29.2%	37.5%	84%††	
Minimum Duration of Symptoms	NR	NR	3 months	3 months	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	100%*	100%*	NR	NR	NR	NR
Previous operative %	0%	0%	NR§	NR§	2%††	
Bilateral/Unilateral	Unilateral†		Both**		NR	
Kellgren-Lawrence/Ahlback						
Grade 1	-	-	-	-	0%	4%
Grade 2	25%	30%	29.5%	33.3%	40%	40%
Grade 3	75%	70%	70.8%	66.7%	44%	56%
Grade 4	-	-	-	-	16%	0%
Procedural Characteristics						
Dose/Platelet Count	NR	-	$1500x10^3$	-	NR	-
Volume	8 mL	6 mL‡	5 mL	1 mL	5 mL	2 mL
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Poor	-	Rich	-	NR	-
Activating Agent	NR	-	Calcium gluconate	-	None	-
Local Anesthetic	No	Yes	NR	NR	Yes	Yes
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	NR	NR	NR	NR	NR	NR
Number of Injections	1	1	1	1	1	1
Injection Frequency	-	-	-	-	-	-
Funding	None		None		NR	
Quality	**Poor**		**Poor**		**Fair**	

BMI = body mass index; KL = Kellgren-Lawrence; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* Exclusion criteria include previous interventions on the knee joint. This is assumed to include any operation.

† Authors report in table 1 the number of patients as left or right knee, assumed unilateral because total number is the same as total number for each group.

‡ 1 mL triamcinolone + 5 mL lidocaine.

§ Exclusion criteria include previous surgery or arthroscopy in previous 6 months.

** Bilateral - each knee (in same patient) received same injection (either PRP or steroid).

†† Only reported for whole population.

Appendix Table G23b. Patient Summary Demographics in Studies Comparing PRP to Steroid for Knee Osteoarthritis (4-6 of 9)

	Huang, 2019		Jubert, 2017		Khan, 2018	
	PRP	Steroid	PRP	Steroid	PRP	Steroid
n	40	40	35	30	51	52
Patient characteristics						
Age, yrs (mean)	54	55	66	68	52	51
BMI (mean)	24.6	25.3	31.2	31	26	28
% Female	82.5%	79.2%	65.7%	80%	77%	75%
Minimum Duration of Symptoms	NR	NR	NR	NR	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	NR	NR	NR[§]	NR[§]	NR	NR
Previous operative %	NR[*]	NR[*]	NR	NR	NR	NR
Bilateral/Unilateral	Unilateral		Both		NR	
Kellgren-Lawrence/Ahlback						
Grade 1	NR	NR	-	-	-	-
Grade 2	NR[†]	NR[†]	-	-	100%	100%
Grade 3	-	-	28.6%	56.6%	-	-
Grade 4	-	-	71.4%	43.4%	-	-
Procedural Characteristics						
Dose/Platelet Count	2x baseline	-	0.99 x 10^6/mL	-	NR	-
Volume	4 mL	1 mL	4 mL	2 mL	5 mL	5 mL[**]
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Poor	-	Poor	-	NR	-
Activating Agent	NR[‡]	-	None	-	NR	-
Local Anesthetic	Yes	Yes	None	None	None	Yes
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	NR	NR	NR	NR	NR	NR
Number of Injections	3	3	1	1	Unclear[††]	Unclear[††]
Injection Frequency	Weekly	Weekly	-	-	NR	NR
Funding	NR		Non-industry		NR	
Quality	**Poor**		**Fair**		**Poor**	

BMI = body mass index; KL = Kellgren-Lawrence; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* No surgeries allowed within past 2 years.

† All patients were either KL grade 1 or 2. Details not reported.

‡ Details NR. Authors report that platelets were activated in vivo when exposed to collagen or von Willebrand factor, leading to aggregation.
§ Exclusion criteria include arthroscopy surgery in past 3 months.
** 1 mL triamcinolone + 4 mL lidocaine.
†† Unclear how many injections were received. Authors report that injections were given "between 2 and 6 months", but do not give more details.

Appendix Table G23c. Patient Summary Demographics in Studies Comparing PRP to Steroid for Knee Osteoarthritis (7-9 of 9)

	Nabi, 2018		Nunes-Tamashiro, 2022		Phul, 2018	
	PRP	Steroid	PRP	Steroid	PRP	Steroid
n	36	36	34	33	40	40
Patient characteristics						
Age, yrs (mean)	59	59	68	66	54	58
BMI (mean)	28.4	27.8	29.22	29.59	NR§	NR§
% Female	85%	79%	88.2%	90.9%	70%	65%
Minimum Duration of Symptoms	3 months	3 months	3 months	3 months	4 months	4 months
Duration of symptoms (mean)	NR	NR	10.3 years	6.3 years	1.93 years	2.03 years
Previous nonoperative %	100%*	100%*	100%	100%	NR	NR
Previous operative %	0%	0%	0%	0%	NR	NR
Bilateral/Unilateral	NR		Bilateral‡		NR	
Kellgren-Lawrence/Ahlback						
Grade 1	-	-	-	-	-	-
Grade 2	32.4%	27.3%	41.2%	48.5%	NR	NR
Grade 3	67.6%	72.7%	58.8%	51.5%	NR	NR
Grade 4	-	-	-	-	NR**	NR**
Procedural Characteristics						
Dose/Platelet Count	4-6x baseline	-	152,930 per mm^3	-	NR	-
Volume	5 mL	40 mg	NR	2 mL	4 to 6 mL	60 mg††
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	NR	-	NR	-	NR	-

Activating Agent	NR	-	None	-	NR	-
Local Anesthetic	NR†	NR	Yes	Yes	NR	Yes
Other injectate	NR	NR	NR	NR	acetaminophen-codeine‡‡	acetaminophen-codeine‡‡
Imaging Guidance	Ultrasound	Ultrasound	NR	NR	NR	fluoroscope
Number of Injections	3	3	1	1	2	2
Injection Frequency	4 week intervals	4 week intervals	-	-	4 week intervals	4 week intervals
Funding	Non-industry		None		NR	
Quality	**Poor**		**Fair**		**Poor**	

BMI = body mass index; KL = Kellgren-Lawrence; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.
* Exclusion criteria.
† An anesthesiologist was present and performed flexion and extension movements, but authors do not report if anesthetic was given.
‡ All bilateral knee OA. Only a single IA injection was performed on the most symptomatic knee according to the patient perception.
§ Inclusion criteria included BMI <3 kg/m2.
** Inclusion criteria included patients with KL Grade 2 through 4. Details NR.
†† 10 mg bipuvicaine + 40 mg triamcinolone hexacetonide.
‡‡ All patients received acetaminophen-codeine 2 hours prior to intervention injection.

Appendix Table G24. Patient Summary Demographics in Studies Comparing PRP to Oral Analgesics for Knee Osteoarthritis (1-3 of 3)

	Buendía-López, 2019		Reyes-Sosa, 2020		Simental-Mendía, 2016	
	PRP	NSAIDs	PRP	celecoxib	PRP	APAP
n	35	35	30	30	33†	32†
Patient characteristics						
Age, yrs (mean)	56	57	54	53	57	56
BMI (mean)	24.9	25.2	NR	NR	29.5	32.2
% Female	51.5%	48.6%	86.7%	70%	33%	38%
Minimum Duration of Symptoms	NR	NR	NR	NR	3 months	3 months
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	100%	100%	NR	NR	100%	100%
Previous operative %	0%*	0%*	NR	NR	0%*	0%*
Bilateral/Unilateral	Both		Both		Both	
Kellgren-Lawrence/Ahlback						
Grade 1	54.5%	48.6%	-	-	33%	37%
Grade 2	45.5%	45.7%	43.3%	60%	67%	63%
Grade 3	-	-	56.7%	40%	-	-

Grade 4	-	-	-	-	-	-
Procedural Characteristics						
Dose/Platelet Count	1,095,000 ± 23,200/mm^3	-	NR	-	NR	-
Volume	5 mL	60 mg	3 mL	200 mg	3 mL	500 mg
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Poor	-	Poor	-	Poor	-
Activating Agent	Calcium chloride	-	Calcium chloride	-	Calcium gluconate	-
Local Anesthetic	NR	NR	NR	NR	Yes	Yes
Other injectate	NR	NR	NR	NR	None	None
Imaging Guidance	NR	NR	NR	NR	NR	NR
Number of Injections	1	-	2	-	3	-
Injection Frequency	-	-	15 day intervals	-	2 week intervals	-
Funding	None		NR		Non-industry	
Quality	**Fair**		**Fair**		**Poor**	

APAP = acetaminophen; BMI = body mass index; NR = not reported; NSAIDs = non-steroid anti-inflammatory drugs; PRP = platelet-rich plasma; RCT = randomized control trial.
* Exclusion criteria.
† n=33 + n=32 is the final follow-up N=65. 75 patients were randomized but 13.3% (10/75) were lost during follow-up. Unclear which intervention group they belonged to.

Appendix Table G25. Patient Summary Demographics in Studies Comparing PRP to Exercise for Knee Osteoarthritis (1-3 of 3)

	Akan, 2018		Angoorani, 2015		Rayegani, 2014	
	PRP	Exercise	PRP	Exercise	PRP	Exercise
n	30	30	27	27	32	33
Patient characteristics						
Age, yrs (mean)	61	56	62	62	58	55
BMI (mean)	33.6	32.7	28.5	29.2	28.2	27.3
% Female	80%	96.7%	81.5%	92.6%	93.5%	93.5%
Minimum Duration of Symptoms	3 months	3 months	NR	NR	3 months	3 months
Duration of symptoms (mean)	NR	NR	NR	NR	3-12 months: 16.7% >12 months: 83.3%	3-12 months: 25.8% >12 months: 73.2%
Previous nonoperative %	100%	100%	NR	NR	NR	NR
Previous operative %	0%*	0%*	NR	NR	NR	NR
Bilateral/Unilateral	NR		NR		NR	

Kellgren-Lawrence/Ahlback						
Grade 1	-	-	NR	NR	NR	NR
Grade 2	-	-	NR	NR	NR	NR
Grade 3	-	-	NR†	NR†	NR	NR
Grade 4	100%	100%	-	-	NR‡	NR‡
Procedural Characteristics						
Dose/Platelet Count	NR	-	3x baseline	-	NR	-
Volume	NR	-	6 mL	-	4 to 6 mL	-
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	-	Rich	-	Rich	-
Activating Agent	Calcium chloride	-	Calcium gluconate	-	None	-
Local Anesthetic	None	-	None	-	None	-
Other injectate	NR	NR	NR	NR	Acetaminophen-codeine§	NR
Imaging Guidance	NR	-	NR	-	NR	-
Number of Injections	3	-	1	-	2	-
Injection Frequency	3 week intervals	-	-	-	NR	-
Funding	NR		Non-industry		NR	
Quality	**Fair**		**Fair**		**Fair**	

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.
* Exclusion criteria.
† Inclusion criteria included patients with KL Grade 1 through 3. Details not reported.
‡ Inclusion criteria included patients with KL Grade 1 through 4. Details not reported.
§ All patients were given acetaminophen-codeine 2 hours before injection instead of anesthesia.

Appendix Table G26. Patient Summary Demographics in Studies Comparing PRP to Exercise for Knee Osteoarthritis (1 of 1) (Knees Randomized)

	Raeissadat, 2020	
	PRP	Exercise
n	23	23
Patient characteristics		
Age, yrs (mean)	58	
BMI (mean)	28.49	
% Female	100%	

Minimum Duration of Symptoms	3 months	
Duration of symptoms (mean)	NR	
Previous nonoperative %	NR	
Previous operative %	NR*	
Bilateral/Unilateral	Bilateral†	
Kellgren-Lawrence/Ahlback		
Grade 1	26.3%	
Grade 2	52.6%	
Grade 3	21.1%	
Grade 4	-	
Procedural Characteristics		
Dose/Platelet Count	NR	-
Volume	NR	-
High/Low Molecular Weight	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	-
Activating Agent	NR	NR
Local Anesthetic	NR	NR
Other injectate	NR	NR
Imaging Guidance	NR	NR
Number of Injections	2	-
Injection Frequency	4 week interval	-
Funding	NR	
Quality	**Poor**	

BMI = body mass index; KL = Kellgren-Lawrence; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* Patients were excluded if they had had knee surgery in the previous 6 months.

† Study randomized patients knees. All patients received PRP to one knee, and exercise to both. Further details unclear.

Appendix Table G27a. Patient Summary Demographics in Studies Comparing PRP to PRP by Number of Injections for Knee Osteoarthritis (1-3 of 6)

	Görmeli, 2017		Kavadar, 2015			Lewis, 2022	
	PRP	PRP	PRP	PRP	PRP	PRP + Placebo	PRP
n	45	46	34	34	34	47	27
Patient characteristics							
Age, yrs (mean)	54	54	54	55	55	55	59
BMI (mean)	28.4	28.7	24.9	25.1	25.5	29.3	29.7
% Female	56.8%	58.9%	84.7%§			57%	67%

Minimum Duration of Symptoms	≥4 months	≥4 months	6 months	6 months	6 months	4 months	4 months
Duration of symptoms (mean)	≥4 months*	≥4 months*	NR	NR	NR	56 months	55.7 months
Previous nonoperative %	100%†	100%†	NR	NR	NR	100%	100%
Previous operative %	0%	0%	NR	NR	NR	0%	0%
Bilateral/Unilateral	Both		Unilateral			NR	
Kellgren-Lawrence/Ahlback							
Grade 1	NR	NR	-	-	-	23.4%	29.6%
Grade 2	NR	NR	-	-	-	48.9%	48.1%
Grade 3	NR	NR	100%	100%	100%	-	-
Grade 4	31.8%‡	33.3%‡	-	-	-	-	-
Procedural Characteristics							
Dose/Platelet Count	5.2× (1118,000 µL)	5.2× (1118,000 µL)	NR	NR	NR	NR	NR
Volume	5 mL	5 mL	NR	NR	NR	4 to 6 mL	4 to 6 mL
High/Low Molecular Weight	-	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	Rich	Rich	Rich	Rich	Poor	Poor
Activating Agent	Calcium chloride	Calcium chloride	Calcium chloride	Calcium chloride	Calcium chloride	NR	NR
Local Anesthetic	NR	NR	None	None	None	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR	NR
Imaging Guidance	NR	NR	NR	NR	NR	NR	NR
Number of Injections	1	3	1	2	3	3**	3
Injection Frequency	-	Weekly	-	2 week interval	2 week interval	Weekly	Weekly
Funding	NR		NR			Non-industry	
Quality	**Fair**		**Fair**			**Fair**	

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* Inclusion criteria.

† Exclusion criteria.

‡ Patients were classified as Early OA (KL Grade 0-3), and advanced OA (KL Grade 4).

§ Whole population only.

** 1 injection PRP + 2 injections placebo.

Appendix Table G27b. Patient Summary Demographics in Studies Comparing PRP to PRP by Number of Injections for Knee Osteoarthritis (4-6 of 6)

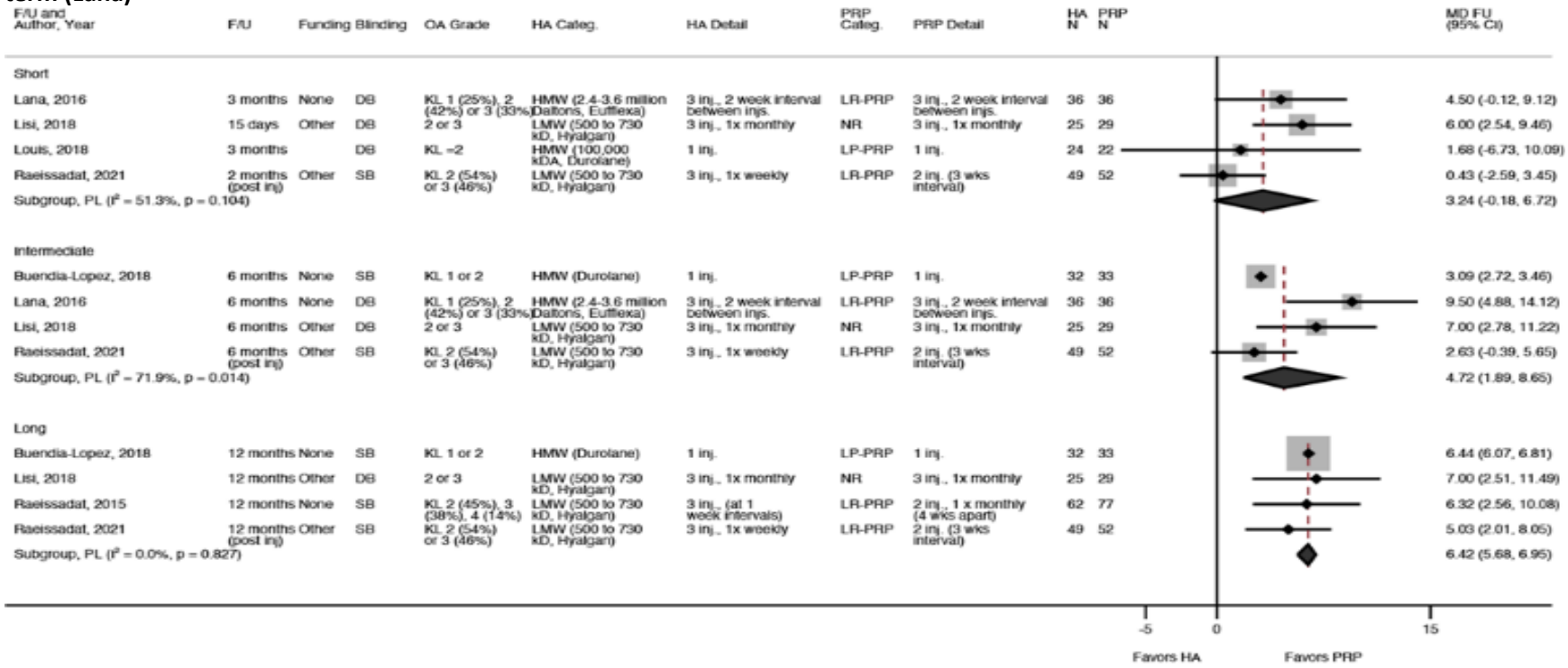
	Yurtbay, 2022		Patel, 2013		Tavassoli, 2019	
	PRP	PRP	PRP	PRP	PRP	PRP
n	67	66	27	25	31	33
Patient characteristics						
Age, yrs (mean)	53	57	53	52	63	66
BMI (mean)	31.09	30.68	26.3	25.8	28.43	29.61
% Female	33.8%	14.3%	59%	80%	82.1%	78.6%
Minimum Duration of Symptoms	1 week	1 week	NR	NR	NR	NR
Duration of symptoms (mean)	NR	NR	NR	NR	NR	NR
Previous nonoperative %	NR	NR	NR	NR	NR	NR
Previous operative %	NR	NR	NR	NR	NR	NR
Bilateral/Unilateral	Unilateral		Bilateral		Bilateral	
Kellgren-Lawrence/Ahlback						
Grade 1	11.3%	3.2%	Ahlback: 71%	Ahlback: 72%	Ahlback: 37.5%*	Ahlback: 30.4%*
Grade 2	69.4%	60.3%	Ahlback: 21%	Ahlback: 20%	Ahlback: 62.5%	Ahlback: 69.6%
Grade 3	19.4%	36.5%	Ahlback: 4%	Ahlback: 4%	-	-
Grade 4	-	-	-	-	-	-
Procedural Characteristics						
Dose/Platelet Count	128 x 10^5 µl	128 x 10^5 µl	310.14 × 103/mL	310.14 × 103/mL	NR	NR
Volume	5 mL	5 mL	8 mL	8 mL	4 to 6 mL	4 to 6 mL
High/Low Molecular Weight	-	-	-	-	-	-
Leukocyte Rich/Poor (Leukocyte Count)	Rich	Rich	Poor	Poor	Rich	Rich
Activating Agent	NR	NR	Calcium chloride	Calcium chloride	NR	NR
Local Anesthetic	NR	NR	No	No	NR	NR
Other injectate	NR	NR	NR	NR	NR	NR
Imaging Guidance	NR	NR	NR	NR	NR	NR
Number of Injections	1	3	1	2	1	2
Injection Frequency	-	1 month interval	-	2 week interval	-	3 week interval
Funding	None		Non-industry		Non-industry	
Quality	**Fair**		**Fair**		**Poor**	

BMI = body mass index; NR = not reported; PRP = platelet-rich plasma; RCT = randomized control trial.

* Ahback grade reported by number of knees (N=56 knees) for each group.

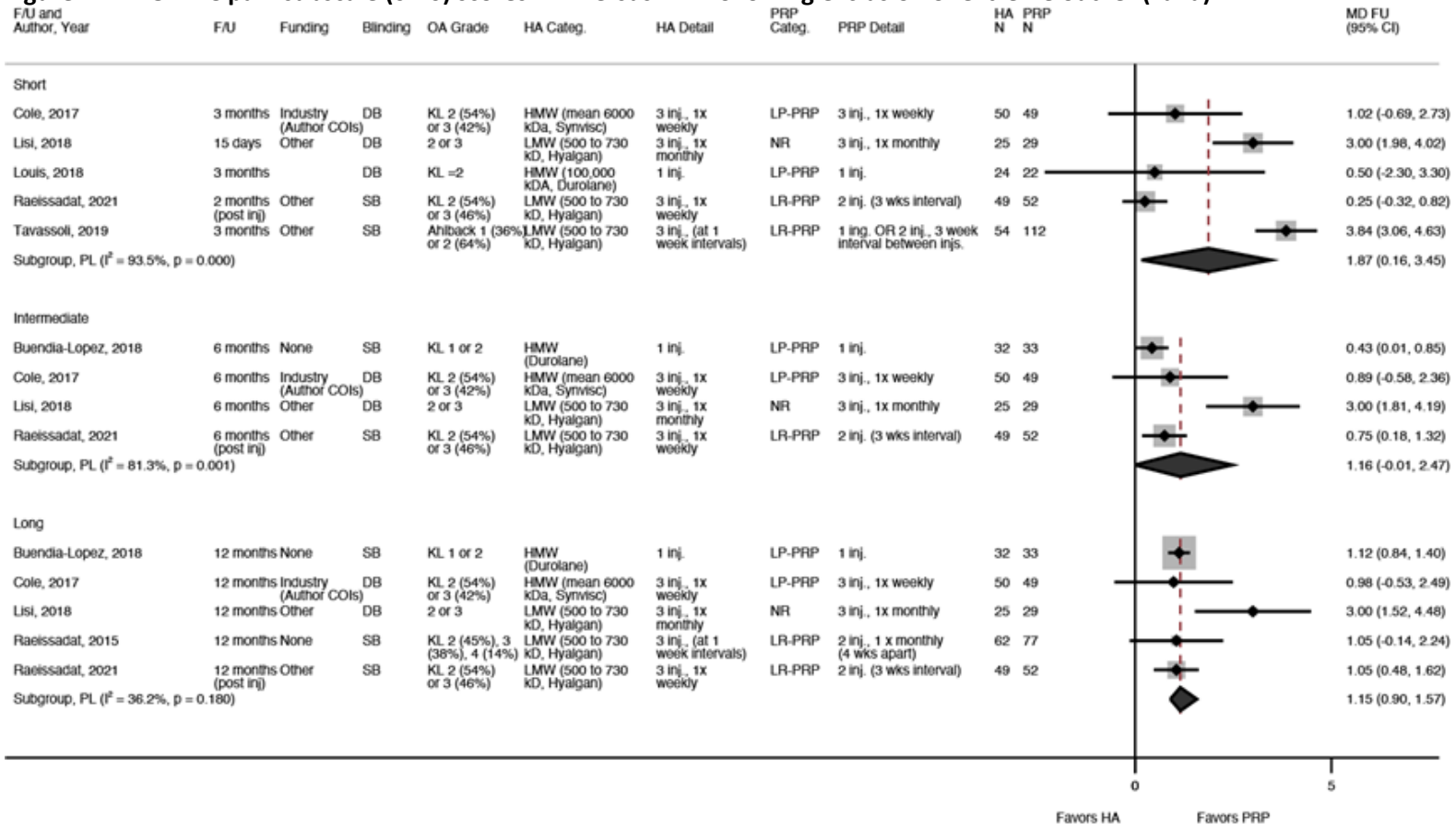
APPENDIX H. Additional Forest Plots

Figure H1. WOMAC physical function scores (0-68 scale): Comparison of HA and PRP excluding Outliers at short term (Tavassoli) and Long term (Lana)



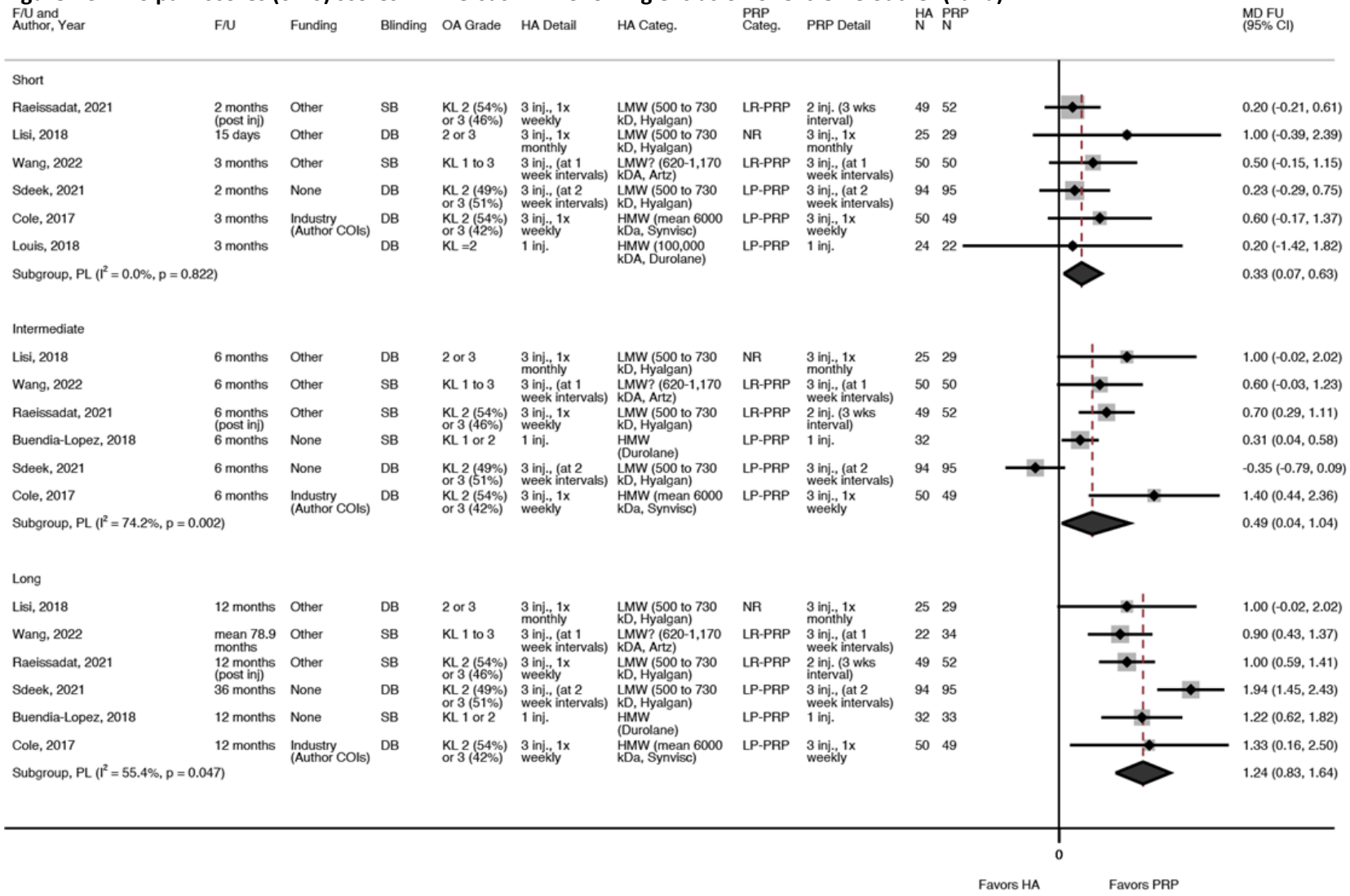
CI = confidence interval; DB = double blind; F/U = Follow-up; HA = hyaluronic acid; HMW = high molecular weight; KL = Kellgren-Lawrence; LMW = low molecular weight; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Figure H2. WOMAC pain subscale (0-20) scores: HA versus PRP following exclusion of extreme outlier (Lana)



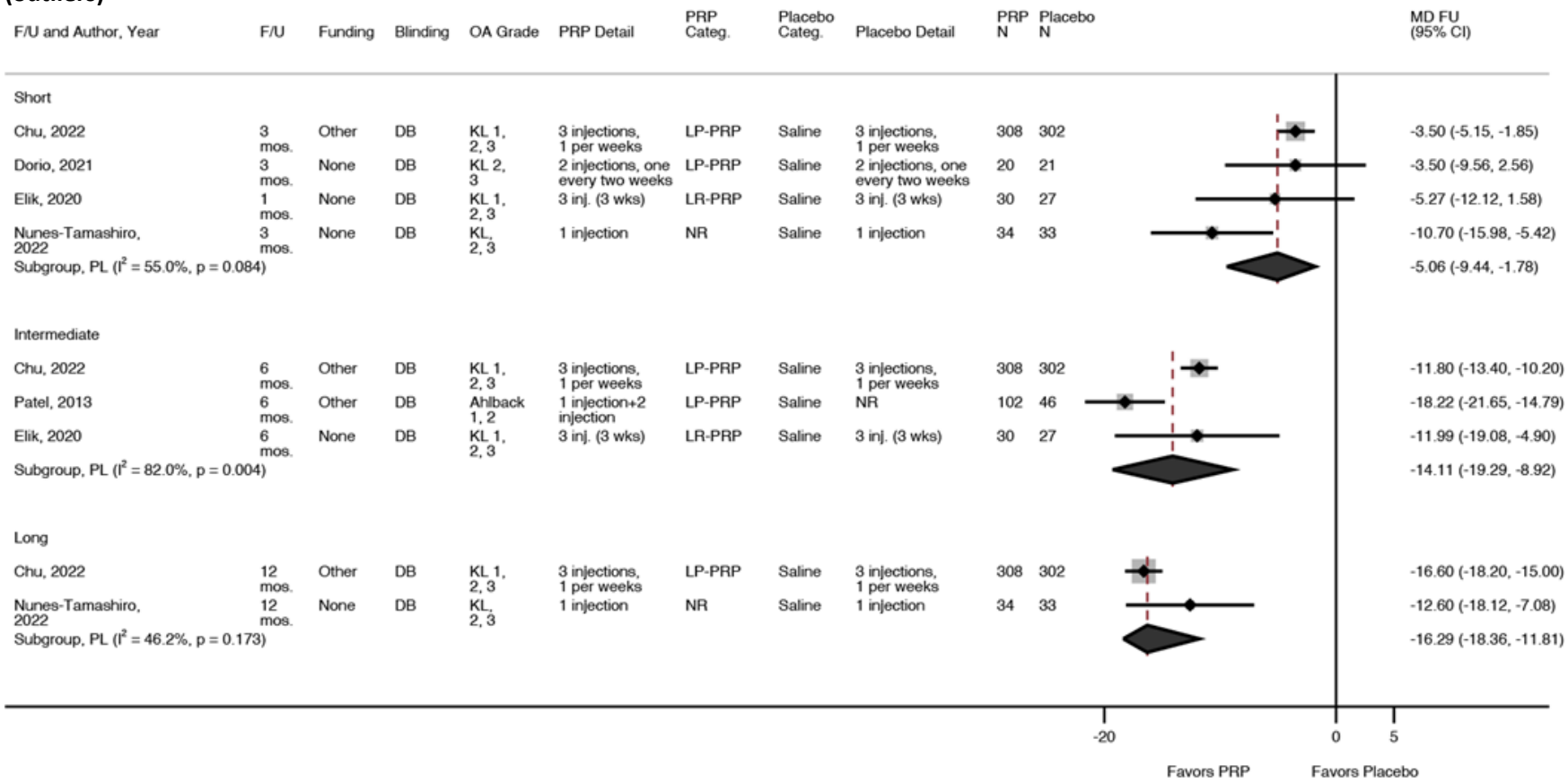
CI = confidence interval; COI = conflict of interest; DB = double blind; F/U = Follow-up; HA = hyaluronic acid; HMW = high molecular weight; KL = Kellgren-Lawrence; LMW = low molecular weight; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Figure H3. VAS pain scores (0-10) scores: HA versus PRP following exclusion of extreme outlier (Lana)



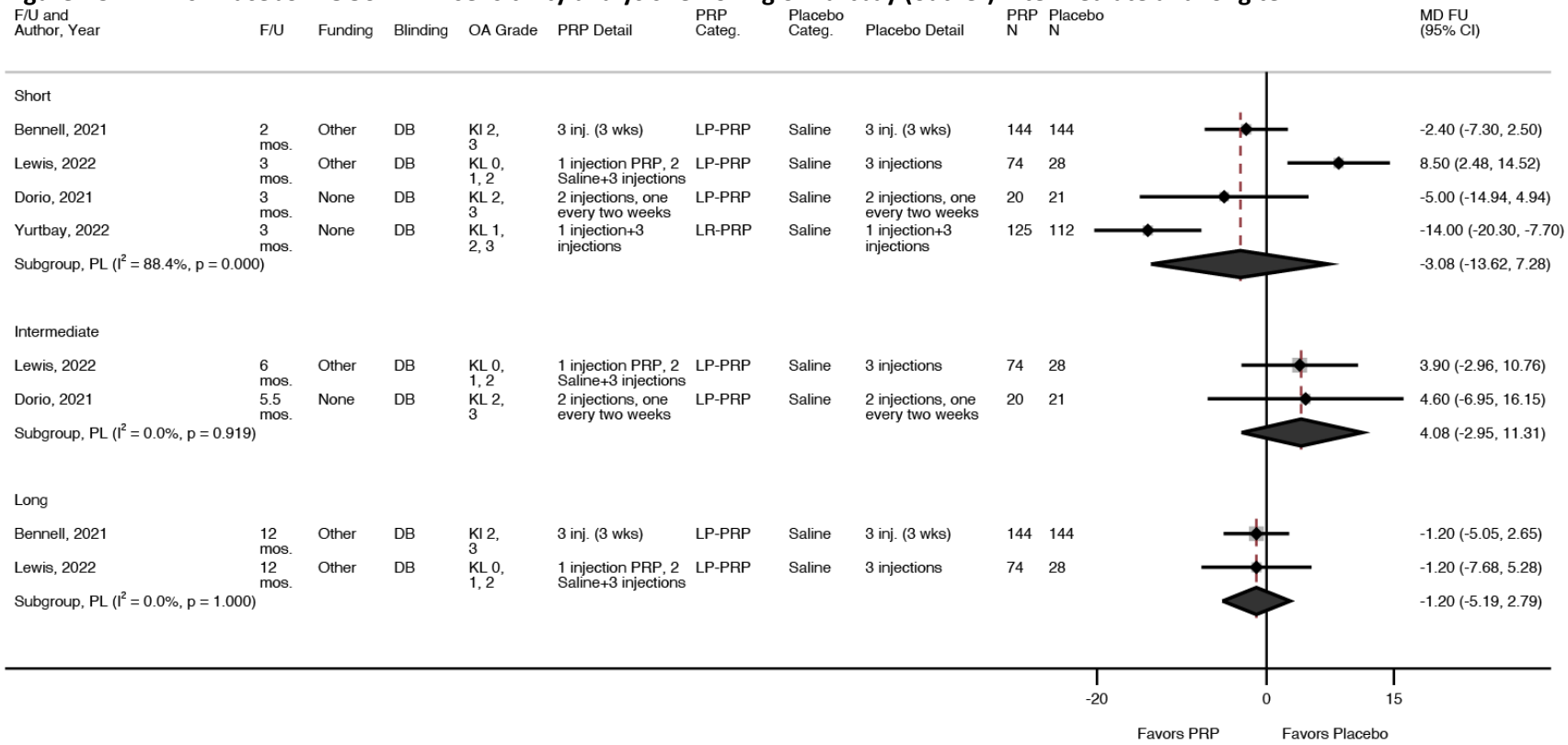
CI = confidence interval; COI = conflict of interest; DB = double blind; F/U = Follow-up; HA = hyaluronic acid; HMW = high molecular weight; KL = Kellgren-Lawrence; LMW = low molecular weight; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind; VAS = visual analogue scale.

Figure H4. PRP vs. Placebo: WOMAC physical function – sensitivity analysis removing of Patel short term and Dório intermediate term (outliers)



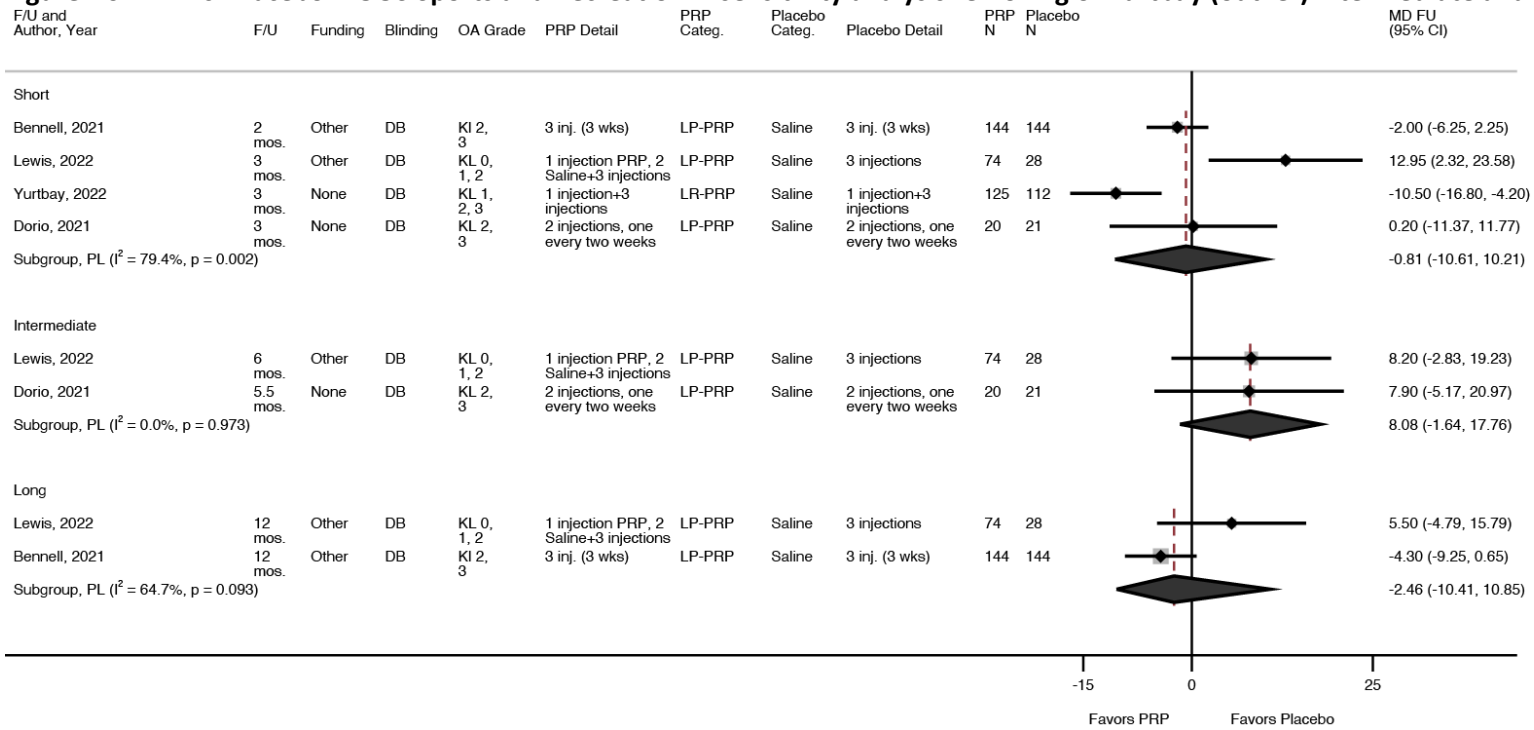
CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Figure H5. PRP vs. Placebo: KOOS ADL – sensitivity analysis removing of Yurtbay (outlier) intermediate and long term



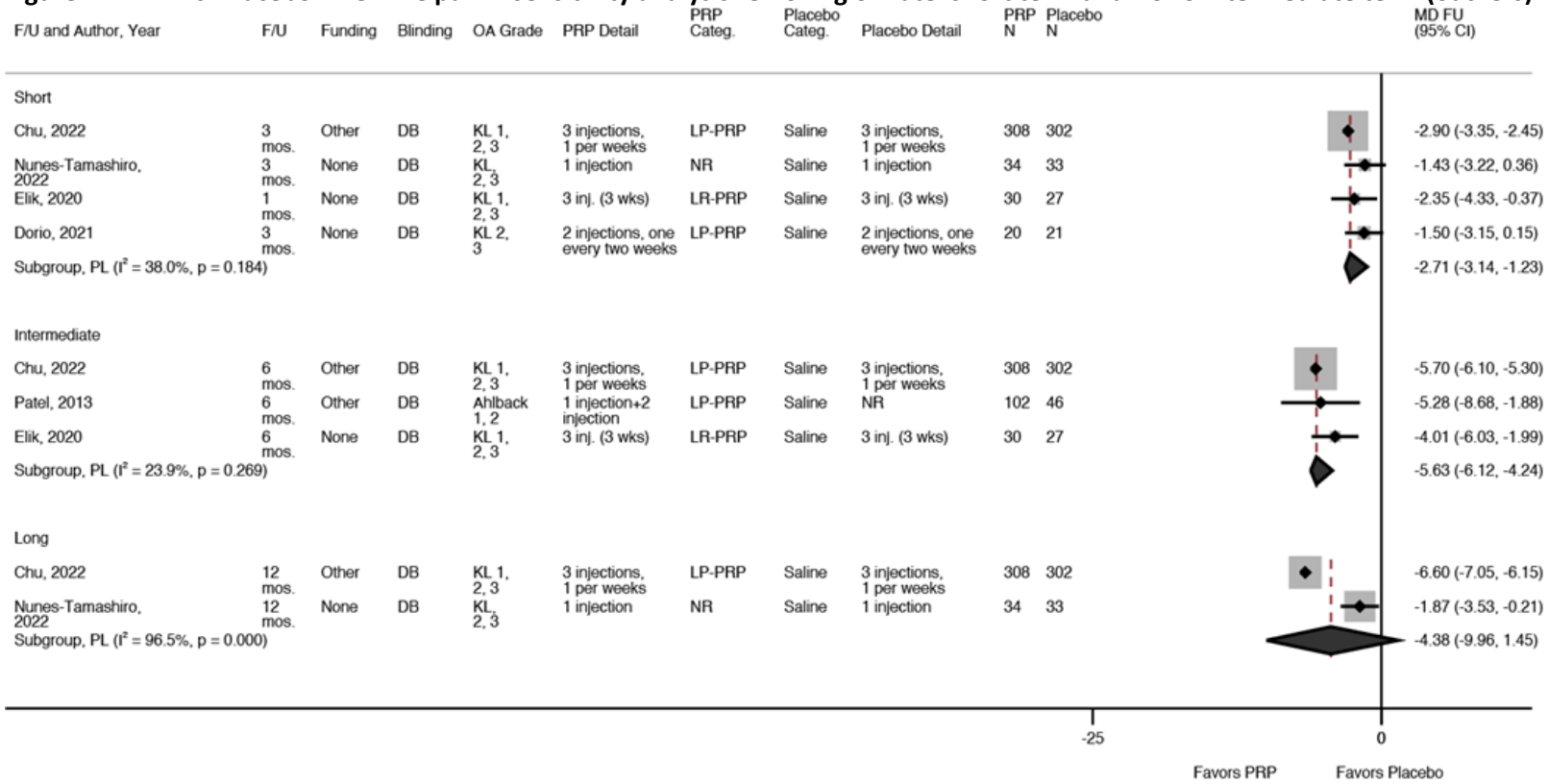
CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; KOOS ADL = Knee Injury and Osteoarthritis Outcome Score Activities of Daily Living subscale; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind.

Figure H6. PRP vs. Placebo: KOOS Sports and Recreation – sensitivity analysis removing of Yurtbay (outlier) intermediate and long term



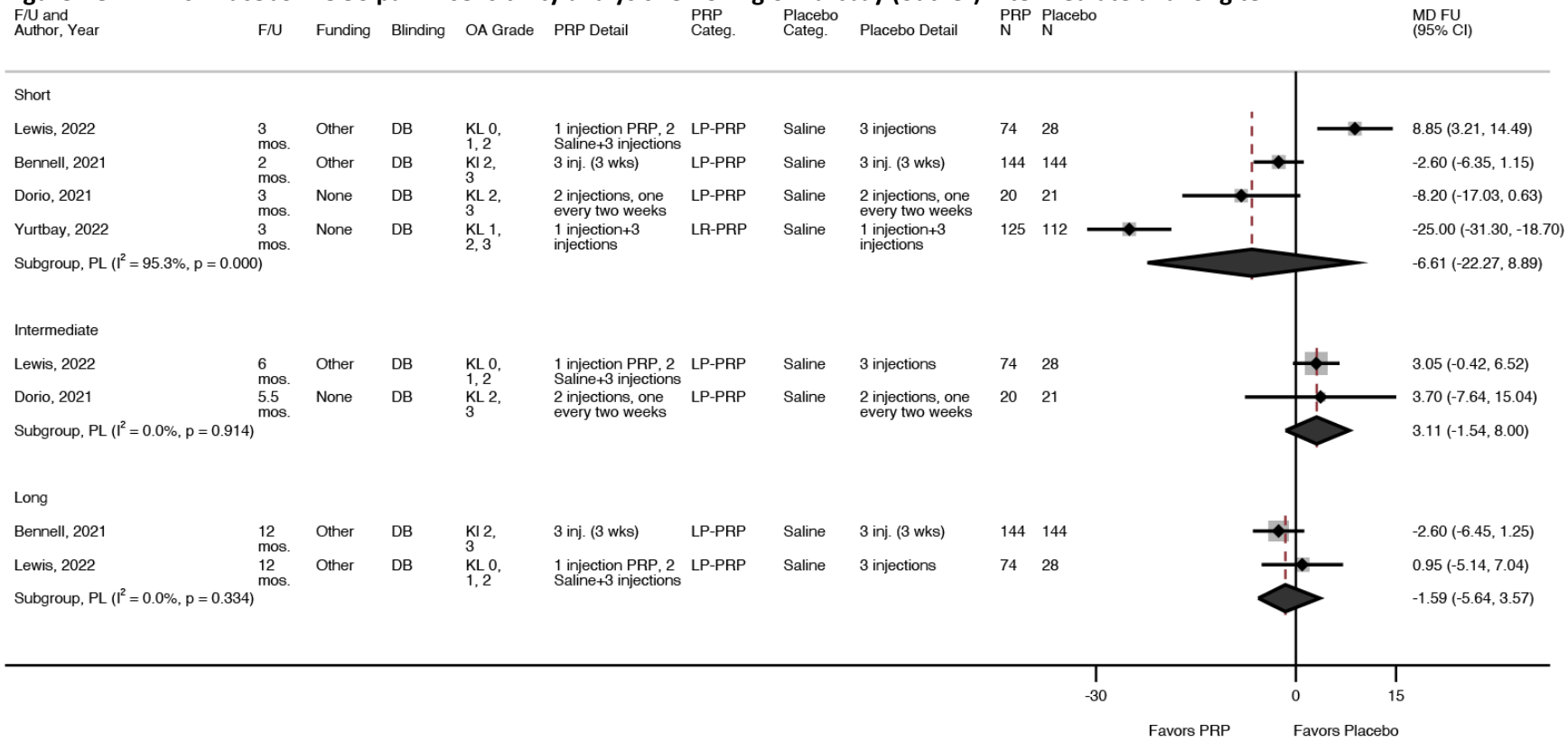
CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome Score; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind.

Figure H7. PRP vs. Placebo: WOMAC pain – sensitivity analysis removing of Patel short term and Dório intermediate term (outliers)



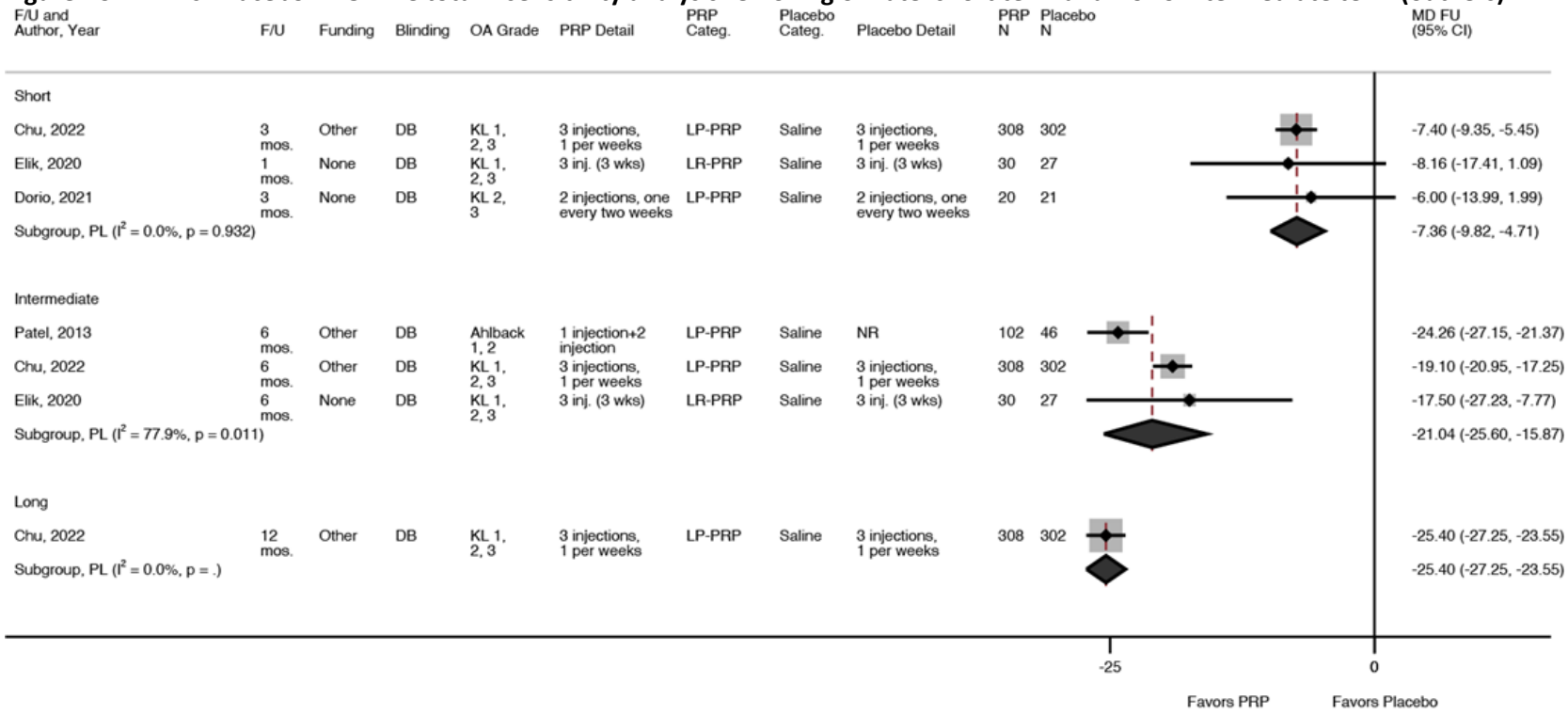
CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Figure H8. PRP vs. Placebo: KOOS pain – sensitivity analysis removing of Yurtbay (outlier) intermediate and long term



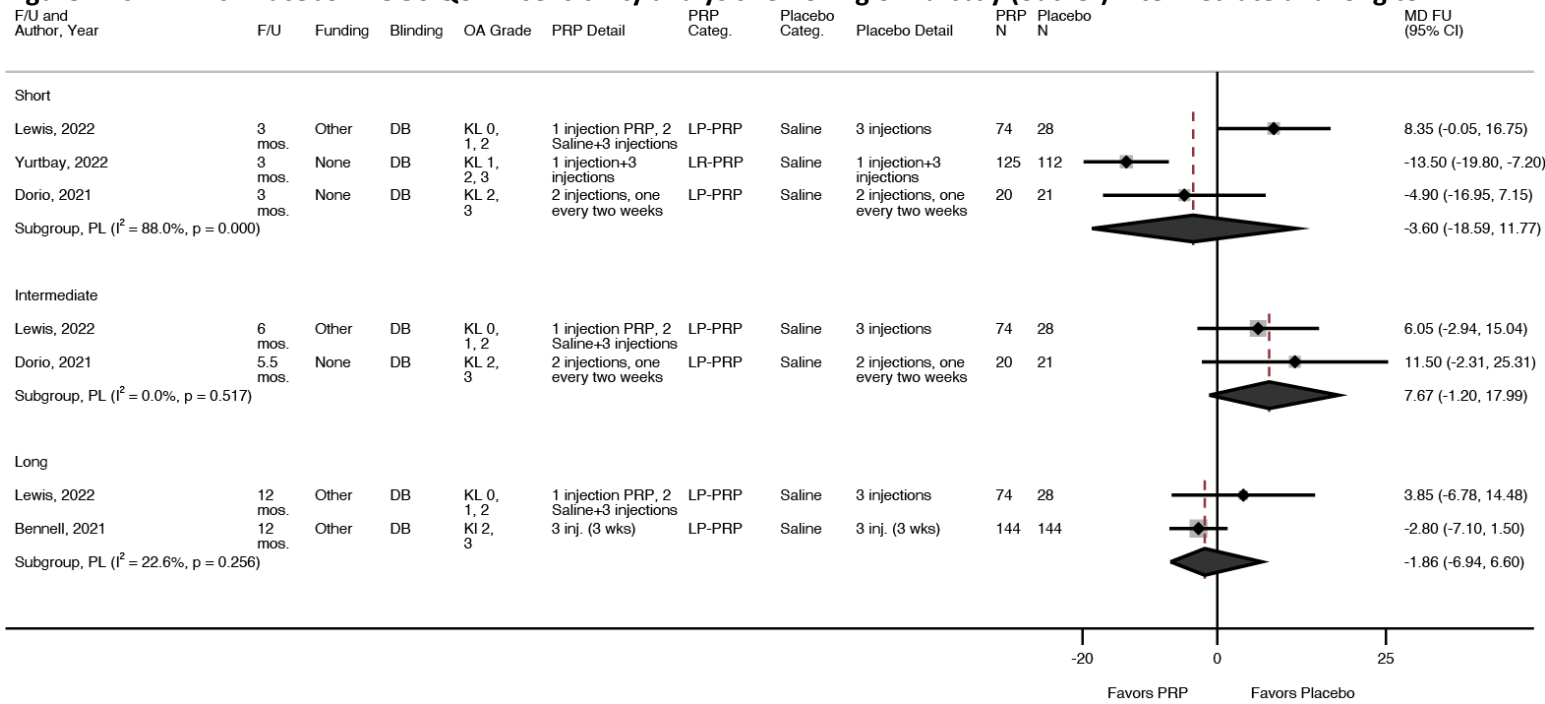
CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome Score; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind.

Figure H9. PRP vs. Placebo: WOMAC total – sensitivity analysis removing of Patel short term and Dório intermediate term (outliers)



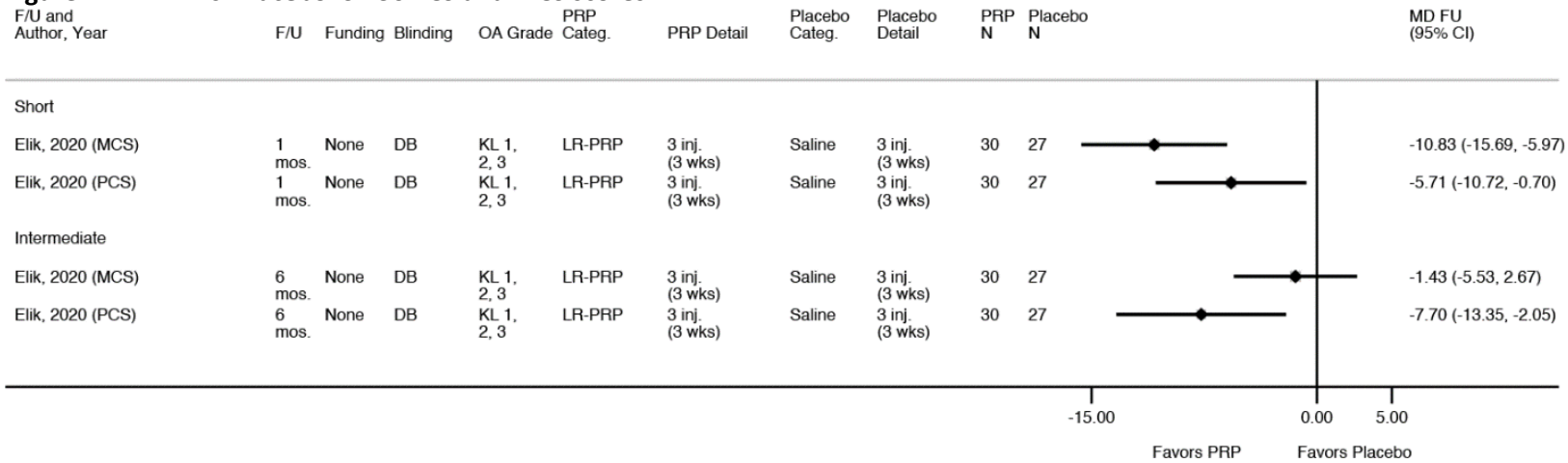
CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; SB = single blind; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Figure H10. PRP vs. Placebo: KOOS QoL – sensitivity analysis removing of Yurtbay (outlier) intermediate and long term



CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome Score; LP-PRP = leukocyte-poor platelet-rich plasma; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PRP = platelet-rich plasma; QoL = quality of life; SB = single blind.

Figure H11. PRP vs. Placebo: SF-36 PCS and MCS scores



CI = confidence interval; DB = double blind; F/U = Follow-up; KL = Kellgren-Lawrence; LP-PRP = leukocyte-poor platelet-rich plasma; MCS = mental component score; NR = not reported; LR-PRP = leukocyte-rich platelet-rich plasma; MD = mean difference; OA = Osteoarthritis; PCS = physical component score; PRP = platelet-rich plasma; SB = single blind; SF-36 = Short-form 36.

APPENDIX I. Economic Tables

Appendix Table I1. U.S. Cost-effectiveness study tables

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
Population	Patients with moderate to severe knee OA K&L grade 2 to 3 **N = 588 patients** from a randomized, placebo-controlled study, (with observational extension) non-responders or poor responders to prior conventional therapy. Male: 37%; Female: 63% Avg. age=61.7 Mean BMI=32.8 kg/m^2	Analysis of 5 RCT populations, N not reported. Population data not reported.	NR	NR
Intervention(s)	Bio-HA (1% Sodium hyaluronate 1%, Euflexxa)- two courses of 3-weekly intra-articular BioHA	VS (Synvisc® 3 injections, Durolane® 1 injection, Hyalgan® 3 injections, Supartz® 3 injections, Euflexxa® 3 injections)	HMW IA-HA (Euflexxa)	HA (Euflexxa) x3 injections
Comparator(s)	Continuation of baseline therapy (i.e., existing conventional OA care with NSAIDs, analgesics) - no assumption of disease progression model CC including escalating care costs due to disease progression	Conventional care (with NSAIDS, physiotherapy, ambulatory aids and acetaminophen, $321.5 per 6 months)	LMW IA-HA, PT and exercise, braces and orthoses, NSAIDs	PRP x3 injections
Country	United States	United States	United States	United States
Funding	Ferring Pharmaceuticals Inc.	Ferring Pharmaceutics Inc.	Ferring Pharmaceutics Inc.	NR

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
Study design	CUA	CUA	CUA	Decision tree model
Perspective	Payer	Payer	Payer	Societal
Time horizon	52 weeks	6 months	6 months	1 year (i.e., two 6-month cycles)
Analytic model	Decision Analytical Models (Monte Carlo simulation) **Model 1:** Bio-HA vs continuation of baseline treatment **Model 2:** Bio-HA vs conventional care including TKR	NR	Decision analysis model	Decision tree model (two 6-month cycles)
Effectiveness outcome	QALY	QALYs	QALYs	QALY
Effectiveness outcome components	Health utility not directly measured; Health Utilities Index Mark 3 (HUI-3) using Grootendorst model (WOMAC subscales, demographic variables, and duration of OA as inputs in a multiple regression model); Model 2 evaluated patients who did and did not respond to CC	Utility scores, QALYs, cost-utility ratio	Utility scores,QALYs;	Utility values based on published literature (SR performed by Meheux et al. (2016)) Conversion of WOMAC scores into health utilities
Source for effectiveness data	FLEXX Trial and extension study	Prior literature – SRs and RCTs (2002-2012 RCTs): (utility scores derived from WOMAC scores - (HUI-3) scores, Grootendorst modeling and from Hatoum (for, Euflexxa® and Raynauld for conventional care)	Prior literature; quality of prior literature used unclear; Sources varied by treatment;	Previous SR/studies
Costing year	2012	NR	NR	2019
Currency	USD	USD	USD	USD
Discounting	NR	NR (time horizon <1 year)	NR (time horizon <1 year)	Costs and health benefits at 3%
Components of cost data	**Model 1:**	Cost of initial visit, product, treatment visits, and	Cost of treatments (PT and exercise, braces and	Initial consultation fees Knee radiographs

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
	CC costs (Limited information states NSAIDs, analgesics based on Waddell including side effects) Costs due to disease progression Corticosteroid injections Surgery costs Bio-HA costs **Model 2:** Conventional treatment costs. Different source vs. Model 1; based on Locina; Unclear if NSAIDs only (analgesics, NSAIDs, corticosteroid injections, counseling, weight loss, joint rest, PT, arthroscopy, and total joint replacement); Bio-HA costs **Assumptions**: BioHA assumed to incur half the cost of NSAID/analgesics, conventional arm incurred full cost of conventional care	conventional care (including PT, NSAIDs, ambulatory aids, acetaminophen)	orthoses, medical including NSAIDs, one injection HA) Cost of complications (PT and exercise, braces and orthoses, medical including NSAIDs) Cost of HA complication (sepsis, synovitis and other serious AEs, skin flare) Cost of physician visit Cost of one knee injection	Injection procedure Cost of x3 HA injections (Euflexxa) Cost of x3 PRP injections and procedure + materials including PRP kit
Cost sources	Published literature. Model 1: Claims data for common conservative treatment (NSAIDs, analgesics) based on Waddell including side effects; Model 2: Data from Losina economic analysis of disease modifying drugs versus conventional care	Centres for Medicare and Medicaid Services Fees Schedule Wholesale supplier database Losina E, Daigle ME, Reichmann WM, et al. Disease-modifying drugs for knee osteoarthritis: can they be cost-effective? Osteoarthr Cartil.2014;21(5):655–67.	Peer-reviewed literature Assumptions based on expert opinion if evidence unavailable Non-peer reviewed/ unpublished literature	Centers for Medicare & Medicaid Services Physician Fee Schedule Current Procedural Terminology code 20610
Sensitivity analysis	For both models, one-way sensitivity analyses	One way sensitivity analysis only: changing costs and utilities ±20% (for Synvisc®,	One-way sensitivity analysis for HMW IA-HA vs.	Sensitivity analysis on costs of HA and PRP

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
		Durolane®, Hyalgan®, Supartz®, Euflexxa®, conventional care)	comparators +/-10% for cost and utilities;	
QHES	67/100	79/100	67/100	58/100
Results:				
Cost/QALY of intervention	**Model 1 Cost effectiveness ratio:** $21,281/QALY for Bio-HA **Model 2 Cost effectiveness ratio:** $8,816/QALY for Bio-HA	Synvisc® 3 injections • Cost: $1073.90 • Cost/QALY: $6,928.39 to $10,825.60 Durolane® 1 injection • Cost: $676.62 • Cost/QALY: $6,384.08 to $9,975.13 Hyalgan® 3 injections • Cost: $659.90 • Cost/QALY: $7,541.71 to $11,783.93 Supartz® 3 injections • Cost: $758.90 • Cost/QALY: $6,187.38 to $9,667.77 Euflexxa® 3 injections • Cost: $838.90 • Cost/QALY: $4,821.26 to $7,231.90 *Highest and lowest cost/QALY estimates from both sensitivity analyses used	**Early/Moderate Knee OA** HMW IA-HA Cost/QALY: $10,482.76	HA VS: $5,331.75/QALY (cost/QALY <$50k) More cost effective than PRP
Cost/QALY of comparator(s)	**Model 1:** CC dominated **Model 2:** $3,686/QALY for CC	Average cost of conventional care: $321.50	LMW IA-HA Cost/QALY: $23,896.55 PT and exercise Cost/QALY: $20,477.27	PRP: $8,635.23/QALY (cost/QALY <$50k) Higher utility value than HA at 1 year (i.e., 0.69 vs 0.58, p-value=0.0062)

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
			Braces and orthoses Cost/QALY: $200,000.00 NSAID/analgesic medication Cost/QALY: $10,562.50	
ICER	**Model 1:** No ICER calculated as Bio-HA was the dominant strategy compared to CC. **Model 1:** At week 52, estimated avg QALYs gained=0.163 (95% CI=-0.162 to 0.488) for the 214 patients who received 2 courses of x3 BioHA injections/week **Model 2:** ICER for Bio-HA, with CC as baseline = $38,741/QALY	Base Case: HA product vs. conventional care Euflexxa® 3 injections: $4499.13/QALY Supartz® 3 injections: $6420.80/QALY Synvisc® 3 injections: $8004.25/QALY Durolane® 1 injection: $6481.67/QALY Hyalgan® 3 injections: $7869.77/QALY	**Early-Stage Knee OA** • HMW IA-HA vs. LMW IA-HA, ICER: Dominated • HMW IA-HA vs. PT and exercise, ICER: Dominated • HMW IA-HA vs. Braces and orthoses, ICER: $7,157.89 • HMW IA-HA vs. NSAID/analgesic medication, ICER: $10,384.62	ICER=$12,628.15/QALY for PRP (vs HA)
One-way SA	ICER for BioHA most sensitive to treatment response rates (i.e., both BioHA and conventional treatment groups) BioHA ICER=$124,000 per QALY when BioHA response rate at lowest at 45% BioHA ICER=$77,500 per QAL when response rate for CC when set high at 48%	**HA vs. Conventional Care** Synvisc® 3 injections ICER/QALY: $5,719.36 to $10,872.83 Durolane® 1 injection ICER/QALY: $3,996.29 to $9,387.09 Hyalgan® 3 injections ICER/QALY: $4,800.46 to $10,939.07 Supartz® 3 injections	**Early Knee OA** HMW IA-HA remained dominant versus LMW IA-HA and PT and exercise and was cost effective versus braces and orthoses and NSAIDs/analgesics in sensitivity analyses varying costs ±10%: Range (low cost to high cost • HMW IA-HA vs. LMW IA-HA: Dominated • HMW vs. PT/exercise: Dominated	PRP cost-effectiveness at 1 year, ICER=$12,628.15/QALY vs HA

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
		ICER/QALY: $$4,200.29 to $9,018.95 Euflexxa® 3 injections ICER/QALY: $3,050.17 to $6,016.28 *Highest and lowest ICER vs. conventional care estimates from both sensitivity analyses used	• HMW vs. Braces/orthoses: $7508.77- $6897.02 • HMW vs. NSAIDs/analgesic: $11,684.62– $9084.62 **Late-Stage Knee OA;** HMW IA-HA vs. LMW IA-HA • ICER (50% responder rate): Dominated • ICER (10% responder rate): Dominated HMW IA-HA vs. PT and exercise • ICER (50% responder rate): $36,875 • ICER (10% responder rate): $8,027.03 HMW IA-HA vs. Braces and orthoses • ICER (50% responder rate): $11,600 • ICER (10% responder rate): $67,333.33 HMW IA-HA vs. NSAID/analgesic medication . • ICER (50% responder rate): $67,000 • ICER (10% responder rate): Dominating, • Medication was cheaper and more effective that HMW-HA	
Other SA	Monte Carlo Simulation Probabilistic model:	NR	NR	NR

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
	BioHA a cost-effective strategy for OA treatment in ~70% of simulations, when WTP level at $50,000/QALY Acceptability of BioHA=91% when WTP threshold=$100,000/QALY (vs 9% for CC)			
Author's Conclusion	**In Model 1:** BioHA dominant strategy (vs CC) **In Model 2:** BioHA more cost-effective (vs CC)	• IA-HA can be cost effective compared to conventional treatment and no treatment, with Euflexxa being particularly cost-effective compared to other formulations tested	• HMW IA-HA is considered cost-effective versus all comparator treatments in early and moderate knee OA, but cost-effectiveness is not as apparent in late-stage knee OA due to uncertainty in responder rates.	PRP cost-effectiveness at 1 year, ICER=$12,628.15/QALY vs HA
Limitations	• ICERs dependent on Method used to convert WOMAC scores to HUI-3 values to determine QALYs. Limitations of utility determination – models may overpredict utility values in severe disease • Limited information on disease progression w/ respect to CC • No collection of downstream healthcare resource utilization data in FLEXX Trial and Extension Study	• Grootendorst method limited potential RCTs to only those reporting all three WOMAC components on the Likert scale rather than the 100mm scale. • Various sources/studies used for utilities for different formulations and conservative care; possibly representing different patient populations and OA severity • Variation in year (older RCTs used) and location in RCTs may generate heterogeneity across studies and between	• Responder rates were an assumed range based on reduced effectiveness in sample population; sources for response rates for various treatments differed • Modeling of HA versus conservative care, particularly for late-stage knee OA, appears to rely on indirect assessment of findings for the treatment options informed by expert opinion; few head to head trials of HA with conventional/conservative	• No population details/information • No distinction made between "responder" and "nonresponder" in model (i.e., analysis was performed using avg patients improvement rate within their groups) • Cost of analgesics, PT, medical equipment, etc. not included in analysis • Utility values based on another study (SR performed by Meheux et al. (2016))

Type 1 Studies:	Hatoum 2014	Rosen 2016	Rosen 2020	Samuelson 2020
	• FLEXX trial did not include a conventional treatment comparison arm. • Different sources for costing data rationale used in models leading to different costs for conventional care; limited detail of what was included • Treatment response, response rate not defined, components not described.	study group; OA severity, and other factors across studies may add to heterogeneity. • Cost for components of conventional care not detailed • Conventional care assumed to be received in full capacity regardless of additional treatment, may artificially inflate costs for HA treatment • Cost of adverse effects and additional treatments not accounted for • Limited sensitivity analyses regarding model assumptions • Limited time horizon: unclear assumptions regarding progression of OA, need for/delay of joint replacement and other longer-term outcomes	care options modeled are available. • Assumptions are made regarding costs associated with complication rates as well as utility scores at different stages of knee OA • Model assumes conservative care is effective in those experiencing late-stage knee OA • Progression to joint replacement was not considered. • Limited sensitivity analyses described for assumptions and different sensitivity analyses were done by OA stage. It is unclear why changes in treatment response rates for early/moderate OA patients were reported. • Short time horizon	• Not factoring in molecular weight of HA (i.e., LMW vs HMW) • Not factoring in leukocytes (poor vs rich) and platelet concentrations in PRP • Not factoring in any AEs related to IA-HA VS or PRP

AE = adverse effects; Bio-HA = bioengineered hyaluronic acid; CC = Conventional care; CEA = cost-effectiveness analysis; CST = Conventional supportive therapy; CUA = cost-utility analysis; HA = hyaluronic acid; HMW = High molecular weight; IA-HA = intra-articular hyaluronic acid; ICER = incremental cost-effectiveness ratio; K&L = Kellgren & Lawrence; LMW = Low molecular weight; NR=not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; OA = osteoarthritis; PRP= Platelet-rich plasma; PSA = probabilistic sensitivity analysis; PT = physical therapy; QALY = quality-adjusted life years; RCT = randomized controlled trial; TKA = total knee arthroplasty; TKR = total knee replacement; VS = viscosupplementation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WTP = willingness to pay.

Appendix Table I2. Non-U.S. Cost-effectiveness study tables

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
Population	N=156 (intervention group=77; control group=79) Age: 18-65 Mean age (intervention group=53.6; control group=54.8) Female (intervention group=48%; control group=51%) BMI (intervention group=28.9 kg/m2; control group=29.2 kg/m2) Pain > 3months Pain severity > 2 on NRS, KL grade 1 to 3	Cohort of 1,000 patients Age: 50> age > 80 years old Largest group of patients aged between 70 and 79 years old (i.e., ~36% of patients) 59% male; 41% female WOMAC scores (pain, stiffness, physical function): scale from 0 to 96 ~70% patients placed in grades 2 and 3 severity scale Distribution of knee OA based on disease severity scale according to K-L grade 1 (22.4%), grade2 (37.4%), grade 3 (33.5%), grade 4 (6.7%).	Cohort of 1,000 patients including most relevant grades of OA (Kellgren & Lawrence grades 1–4) and stratified by age.	N=401 (intervention group=202; control group=199) 252 pharmacists Age: 40-75 Mean age (intervention group=65.6; control group=62.3) Men (intervention group=41%; control group=45%) WOMAC scores (pain, stiffness, physical function) K&L grade 2 (intervention group=54%; control group=52%) to 3 (intervention group=46%; control group=48%)
Intervention(s)	HMW HA (x3 weekly IA injections with Hylan G-F 20)	VS (Synvisc/Hylan G-F 20) x1 or x2 per year (one 6-ml injection per application)	**Knee OA** VS (Synvisc-One® – hylan G-F 20 1×6 mL) per year VS (Synvisc® – called hylan G-F 20 3×2 mL) per year **Hip OA:** VS (Synvisc® – called hylan G-F 20 1×2 mL) every 6 months	IA-HA VS (Arthrum H 2% i.e., 40mg HA per 2mL-syringe x3 injections weekly)
Comparator(s)	CC (i.e., NSAIDs, PT)	CST incl. NSAIDs and opioids, PT, IA corticosteroids, and arthroscopy for debridement and/or correction of associated injuries; physiotherapy; and recommendations of lifestyle changes (weight loss).	NSAIDs, acetaminophen, PPI, COX2, AE incidence, TKR/THR and knee/hip revision	NSAIDs, antalgics, PPI, corticosteroids
Country	Netherlands	Colombia	Italy	France

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
Funding	Dutch Ministry of Health, Welfare and Sport	Sanofi-Aventis de Colombia S.A.	Sanofi Italia	LCA Pharmaceutical
Study design	CUA	Discrete-event simulation over time using hypothetical cohort of 1,000 patients	CUA	CUA Benefit risk analysis
Perspective	Societal (medical and productivity costs)/Healthcare (medical costs)	Payer	Payer	Healthcare (medical costs)
Time horizon	52 weeks	Reference case was predefined as 20 years of follow-up. Treatment outcome simulated in the interval of 5 to 20 years.	5-year time horizon	6-month period preceding inclusion + 6-month follow-up
Analytic model	IPTW (to adjust for baseline differences in QALY and pain), logistic regression, OLS	Discrete-event simulation of clinical outcomes (disease progression, VS, symptom improvement, and frequency of TKR. Monte-Carlo simulation.	Kaplan-Meier survival curve to estimate delay in knee/hip surgery Markov model with states for stages 2, 3, and 4 on the Kellgren–Lawrence scale	Observational (non-randomized), prospective and multicenter study
Effectiveness outcome	EQ-5D	QALYs Avg WOMAC score	QALYs	OMAC sub-scores and the EQ-5D Quality of Life index
Effectiveness outcome components	Change in pain scores for patients receiving hylan G-F 20 + radiologic degree of OA + QALYs until the end of the stipulated time horizon	Annual change in WOMAC scores for patients receiving Hylan G-F 20 + and QALYs until end of time horizon	Stages 2 to 4 on the Kellgren–Lawrence (K-L) scale, TKR or THR, the after-replacement period, and death + utilities based on intervention used	Reduction for any WOMAC index (pain, stiffness, function), increase of EQ-5D, QALY
Source for effectiveness data	RCT concurrent with CUA; QALY through 3-level EuroQol questionnaire at baseline, 6, 13, 26, 38 and 52 weeks	RCTs WOMAC score variations from published studies (i.e., Raman et al. (2008))	Prior literature	CELTIPHARM French national health insurance database
Costing year	May 2009 – May 2010	NR	NR	May 2014 – November 2014

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
Currency	1 USD = 0.9249 euro (avg exchange rate in 2023)	1 USD = 4761 Colombian Pesos (avg exchange rate in 2023)	1 USD = 0.9267 euro (avg exchange rate in 2023)	1 USD = 0.9249 euro (avg exchange rate in 2023)
Discounting	NR	Outcomes and costs, 3%	Outcomes and costs, 3.5%	NR
Components of cost data	Productivity costs (i.e., knee related absence from work and knee related lost productivity while being present at work), medical costs (i.e., physician and paramedical therapist visits, braces, inlay soles, home care use, surgery), medication costs (prescription fees pharmacists receive per prescription).	Cost of two treatments, physical therapy costs, medication costs, administration, pretreatment evaluation, routine laboratory parameters, and diagnostic imaging	Direct costs of drugs (NSAIDs and acetaminophen) Average between the cost of originator and the cost of generic drugs treatment costs Ultrasound-guided IA injection costs	Direct costs of medical consultations, rheumatologists/specialists, paramedical consultations, hospitalizations, radiological examinations, drugs, devices, stays in healthcare centers, medical transportation), sick leave, global mean cost per patient, indirect costs in case of AEs
Cost sources	PRODuctivity and Disease Questionnaire (PRODISQ, patient reported) Dutch guideline tariffs Dutch Healthcare Authority	Sistema de Información de Precios de Medicamentos (SISMED) (Drug Information System of the Ministry of Social Protection),"Farmaprecios" database, Seguro Obligatorio de Accidentes de Tránsito (SOAT) tariff Manual 2012 and ISS 2001 tariffs	Italy's National Health Service Pharmaceutical company CODIFA Database Published literature for cardio AE treatment costs and NSAIDs GI AE	CELTIPHARM French national health insurance database
Sensitivity analysis	Non-parametric bootstrapping	Probabilistic SA, SA for costs and transition probabilities between degrees of knee OA Monte-Carlo simulations	One-way sensitivity analysis for hylan G-F 20 1×6 mL, hylan G-F 20 3×2 mL and hylan G-F 20 1×2 mL (vs NSAIDs and acetaminophen). PSA for knee and hip (cost-effectiveness planes and a cost-effectiveness acceptability curves (CEAC))	NR

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
QHES	78/100	76/100	59/100	77/100
Results:				
Cost/QALY of intervention	€7,745 (95% CI €5,426; €10,436) QALY = 0.779	Avg total cost/patient in a 20- year time horizon = US $27,541 for Hylan G-F 20 QALY = 15.43 VS with Hylan G-F 20 cost-effectiveness over time (i.e., during the first 10 years of simulation). Avg cost between VS and CST roughly similar in a 20-year follow-up simulation	**Knee OA** (Synvisc-One® – hylan G-F 20 1×6 mL) per year hylan G-F 20 1×6 mL vs Acetaminophen incremental cost: +1,109,868 euros hylan G-F 20 1×6 mL vs NSAIDs incremental cost: +641,704 euros (Synvisc® – called hylan G-F 20 3×2 mL) per year hylan G-F 20 3×2 mL vs Acetaminophen: +1,350,484 euros hylan G-F 20 3×2 mL vs NSAIDs: +882,319 euros **Hip OA:** Synvisc® – called hylan G-F 20 1×2 mL) every 6 months hylan G-F 20 1×2 mL vs Acetaminophen: +170,133 euros hylan G-F 20 1×2 mL vs NSAIDs: -252,447 euros over the 5-year horizon: - 55 and 36 AEs and 10 and 8 deaths simulated in the NSAIDs cohort for	€526 (M-6 to M0=€296.18; M1 to M3=€158.30; M4 to M6=€71.46) Gain over 3 months compared to NSAIDs: - M0-M3: QALY=0.010 year - M4-M6: QALY=0.032 year - M0-M6: QALY=0.042 year

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
			hylan G-F 20 1×6 mL and hylan G-F 20 3×2 mL for knee, respectively. - 26 serious AEs and 5 deaths simulated in the NSAIDs cohort for hip. - Reduction in NSAIDs-related AEs with hylan G-F 20 1×6 mL and hylan G-F 20 3×2 mL	
Cost/QALY of comparator(s)	€7,270, €95%CI €5,453; €9,262) QALY = 0.727	Avg total cost/patient in a 20- year time horizon = US $27,203 for CST QALY = 14.34		€528 (M-6 to M0=€307.42; M1 to M3=€107.37; M4 to M6=€113.36)
ICER	ICER=€9,061/QALY (societal perspective) ICER=€8,701/QALY (healthcare perspective) Based on Dutch maximum WTP for similar conditions to knee OA is considered, probability that HMW-HA is cost-effective is 64% (societal) and 86% (healthcare)	In 10-year follow-up simulation period, ICER for VS dominant: QALY of 8.12 for VS and 7.81 for CST (i.e., 0.31 in favor of Hylan G-F 20); treatment costs: US $14,128 and US $13,552 (i.e., US $576 decrease with Hylan G-F 20)	**Knee OA:** hylan G-F 20 1×6 mL: ICER = 3,161 euros / QALY and 7,440 euros / QALY hylan G-F 20 3×2 mL): ICER = 3,846 euros / QALY and 10,230 euros / QALY both interventions (vs acetaminophen and NSAIDs) well below €25,000 (cost-effectiveness threshold for Italy). **Hip OA:** hylan G-F 20 1×2 mL: ICER = 937 euros / QALY and dominated	ICER=€9,03/QALY (healthcare perspective) ICER=€9,03/0.042=€215 per QALY (healthcare perspective) WOMAC sub-scores and the EQ-5D Quality of Life index were significantly improved in the IA HA group (p<0.0001) at 3 and 6 months.

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
			intervention vs acetaminophen well below €25,000 and intervention vs NSAIDs dominant.	
One-way sensitivity analysis	Limited detail provided; costs associated with knee surgery were the main cost drivers for medical cost (healthcare perspective, 9 in HA group, 7 in control); productivity costs were largest drivers from societal perspective in both groups;	Annual disease progression, joint function, and QALY following Drummond's model (2003): - 87% of patients treated with Hylan G-F 20 show improvement versus 25% of patients treated with CST. - 6.4% of group 4 patients treated with Hylan G-F 20 underwent TKR (vs 12.8% of patients treated with CST). In patients with grade 4 OA treated with VS using Hylan G-F 20, TKR delayed by 3 years vs patients treated with CST	Results of hylan G-F 20 1×6 ml and hylan G-F 20 3×2 mL remained robust (maintaining ICER under €17,000) for any parameters within plausible ranges. Results for hylan G-F 20 1×2 mL remained robust (maintaining the ICER under €7,000) for any parameters within plausible ranges. VS with hylan G-F 20 1×6 mL/hylan G-F 20: decrease in medication consumption and drug-related AEs, and delay of prosthesization.	NR
Other sensitivity analysis	Non-parametric bootstrapping Probability that HMW-HA is cost-effective is 64% (societal) and 86% (healthcare) at WTP of €20,000/QALY (Dutch maximum); The probability that HA is dominant was 39% for societal perspective, 9% from healthcare perspective (unadjusted estimates)	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 VS (over CST)	Monte Carlo simulation for hip: hylan G-F 20 1×2 mL dominating the other interventions (i.e., acetaminophen and NSAIDs) Probabilistic sensitivity analysis for knee and hip (cost-effectiveness	NR

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
			planes and a cost-effectiveness acceptability curves (CEAC))	
Author's Conclusion	HMW HA added to CC for knee OA is cost-effective	VS with hylan G-F 20 vs CST improved disease symptoms, joint function, and quality of life, reduced direct treatment costs, delayed TKR by 3 years, and was cost-effective in Colombia.	**Knee OA:** Hylan G-F 20 1×6 mL and hylan G-F 20 3×2 mL (cost-effective treatment option vs acetaminophen and NSAIDs). **Hip OA:** Hylan G-F 20 1×2 mL vs NSAIDs dominant (cost-effective treatment option vs acetaminophen and NSAIDs).	Treatment with IA HA cost-effective + functional improvement of knee OA and QALY (gain of QALY equivalent to half a month, after 6-month follow-up) and decreased consumption of NSAIDs
Limitations	• Small sample size • Limited modeling of uncertainty/drivers of costs; not well documented • Modeling of harms not reported/no assumptions described • Limited information regarding assumptions and model inputs for some components • Exclusion of patients with KL grade IV, those with substantial varus/valgus deformation, and inflammatory arthritis;- uncertainty regarding impact of exclusions	• Most of the variables taken from literature using populations that may differ from Colombian population (i.e., possible difference in epidemiological data, disease management, and progression • Assumption of equal probabilities of disease progression with CST due to lack of data • Annual change in WOMAC scores for patients receiving Hylan G-F 20 based on RCTs • No discussion of potential biases	• Author provided expert opinion in the study. • Patient progression through the K-L states based on prior literature. • Costs and annual probability of gastrointestinal and cardiovascular AEs estimated. • Specialist visit costs have been excluded. • Lack of Kaplan–Meier curve for hylan G-F 20 1×6 mL, Waddell's study was used for	• Outcomes data from nonrandomized studies • Applicability to US healthcare system unclear • No discussion around potential biases • No sensitivity analysis

	Hermans 2018	Castro 2011	Migliore 2019	Thomas 2017
	• Applicability to US healthcare system unclear	• No reference or use of ICER metric and measurement of costs not clearly described	hylan G-F 20 1×6 mL too • variables taken from the literature based on non-Italian populations where disease management and progression can be different. Parameters based on retrospective cohort studies may not reflect current technology	

AE = adverse event; BMI = body mass index; CEA = cost-effectiveness analysis; CST = Conventional supportive therapy; CUA = cost-utility analysis; EQ-5D = European Quality of Life Five Dimension; GI = gastrointestinal; IA-HA = intra-articular hyaluronic acid; ICER = incremental cost-effectiveness ratio; IPTW = inverse probability-of-treatment weighting; KL = Kellgren-Lawrence; NR = not reported; NRS = numeric rating scale; NSAIDs = nonsteroidal anti-inflammatory drugs; OA = osteoarthritis; OLS = ordinary east squares; Proton pump inhibitors = PPI; PSA = probabilistic sensitivity analysis; PT = physical therapy; QALY = quality-adjusted life years; RCT = randomized controlled trial; VS = viscosupplementation; USD = United States dollar; WTP = willingness to pay.

APPENDIX J. Definitions for Magnitude of Effects

Table J1. Definitions for Magnitude of Effects, Based on Mean Between-Group Differences

Slight/Small	Moderate	Large/Substantial
Pain		
5–10 points on a 0-to 100-point VAS or the equivalent 0.5–1.0 points on a 0-to 10-point numerical rating scale or the equivalent	>10–20 points on a 0-to 100-point VAS or the equivalent >1–2 points on a 0-to 10-point numerical rating scale or the equivalent	>20 points on a 0-to 100-point VAS or the equivalent >2 points on a 0-to 10-point numerical rating scale or the equivalent
Function		
4.8–9.6 points on the WOMAC	>9.6–19.2 points on the WOMAC	>19.2 points on the WOMAC
3.4-6.8 points on the WOMAC PF	>6.8-13.6 points on the WOMAC PF	>13.6 points on the WOMAC PF
1-2 points on the WOMAC pain	2-4 points on the WOMAC pain	>4 points on the WOMAC pain
5–10 points on the KOOS	>10–20 points on the KOOS	>20 points on the KOOS
5-10 points on the KSS	>10–20 points on the KSS	>20 points on the KSS
5-10 points on the IKDC	>10–20 points on the IKDC	>20 points on the IKDC
1-2 points on Lequesne Index	>2-5 points on the Lequesne Index	5 points on the Lequesne Index
5-10 points on the SF-36	>10-20 on the SF-36	>20 points on the SF-36
5-10 points on the EQ-VAS	>10-20 on the EQ-VAS	>20 points on the EQ-VAS
Pain or function		
0.2–0.5 SMD	>0.5–0.8 SMD	>0.8 SMD

FIQ = Fibromyalgia Impact Questionnaire; IKDC = International Knee Documentation Committee; KOOS=Knee Injury and Osteoarthritis Outcome Score; KSS = Knee Society Score; PF = physical function; SF-36 = 36-item Short Form Survey; SMD = standardized mean difference; EQ-VAS = EuroQol visual analogue scale; WOMAC = Western Ontario and Mc Maters Universities Osteoarthritis index;

Table J2. Definitions of effect sizes

Effect Size	Definition
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.

APPENDIX K. FDA Approved HA Brands/Formulations

Table K1. FDA Approved HA Brands/Formulations

Proprietary Name	Composition	Source	Formulation	MW (kDa)	Dose and Treatment Schedule	Premarket Submission Number
Hyalgan	Sodium hyaluronate	Avian	Linear chain	500-730	10 mg/ml, 5 weekly injections (2 ml)	P950027
Triluron	Sodium hyaluronate	Avian	Linear chain	500-730	10 mg/ml, 3 weekly injections (2 ml)	P180040
Supartz/Supartz FX/Artz; VISCO-3	Sodium hyaluronate	Avian	Linear chain	620-1,170	10 mg/ml, 5 weekly injections (2.5 ml)	P980044
Orthovisc	Hyaluronan	Bacterial fermentation	Linear chain	1,000-2,900	15 mg/ml, 3-4 weekly injections (2 ml)	P030019
Monovisc*	Hyaluronan	Bacterial fermentation	Crosslinked	1,000-2,900	22 mg/ml, 1 injection (4 ml)	P090031
Durolane	Stabilized hyaluronic acid gel (NASHA)	Bacterial fermentation	Linear chain, 1% crosslinked	100,000	20 mg/ml, 1 injection (3 ml)	P170007
Euflexxa/Neflexxa	Sodium hyaluronate (BioHA)	Bacterial fermentation	Linear chain	2,400-3,600	10 mg/ml, 3 weekly injections (2 ml)	P010029
Gel-One	Sodium hyaluronate (Gel-200)	Avian	Crosslinked	Not reported as formulation is highly crosslinked	10 mg/ml, 1 injection (3 ml)	P080020
Sinoval/Gelsyn-3/Gel-Syn	Sodium hyaluronate	Bacterial fermentation	Linear chain	1,400-2,100	8.4 mg/ml, 3 weekly injections (2 ml)	P110005
GenVisc 850†	Sodium hyaluronate	Bacterial fermentation	Linear chain	620-1,170	10 mg/ml, 5 weekly injections (2.5 ml)	P140005
TriVisc	Sodium hyaluronate	Bacterial fermentation	Linear chain	620-1,170	10 mg/ml, 3 weekly injections (2.5 ml)	P160057
Hymovis	Hyaluronan (HYADD 4)	Bacterial fermentation	Linear chain	500-730	8 mg/ml, 2 weekly injections (3 ml)	P150010
SYNOJOYNT	Sodium hyaluronate	Bacterial fermentation	Linear chain	1,000	3 weekly injections	P170016
Synvisc	80 Hylan A:20 Hylan B (Hylan G-F 20)	Avian	Crosslinked	6,000	8 mg/ml, 3 weekly injections (2 ml)	P940015
Synvisc One	80 Hylan A:20 Hylan B (Hylan G-F 20)	Avian	Crosslinked	6,000	8 mg/ml, 1 injection (6 ml)	P940015

* Same grade and specification of HA that is used in Orthovisc.

† Generic drug equivalent of Supartz/Supartz FX.

APPENDIX L. Clinical Expert Peer Review

Andre Abadin, DO, CAQSM, RMSK
Acting Assistant Professor - Department of Family Medicine
Primary Care Sports Medicine
University of Washington

Erek W. Latzka, MD, RMSK
Orthopedics and Sports Medicine
Attending Physician and Assistant Professor, UW Sport Medicine Center
University of Washington

APPENDIX M. Public Comment

No public comments were received.

APPENDIX N. Appendix References

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