Washington State Health Care Authority

July 21, 2023 Meeting Materials
Health Technology Clinical Committee

Hyaluronic acid/platelet-rich plasma

Contents

- ☐ HTCC clinical expert information
- ☐ Agency Medical Director presentation
- ☐ Scheduled public comments presenters and presentations
- ☐ HA/PRP evidence presentation
- ☐ HTCC decision aid
- ☐ HA/PRP final key questions

Health Technology Clinical Committee Application for Membership

Washington State Health Care Authority

Clear form

1 Contact information

First name: Brian

Middle initial: C

Last name: Liem

Address:

Phone number:

Best method, time to reach you:

Email:

Today's date: 03/28/2023

2 Personal information (optional)

Gender:

✔ Male ☐ Female ☐ X/non-binary[1]

Pronouns (select all that apply)

☐ She/her ✔ He/him ☐ They/them ☐ Other (subj./obj.):

Race or Ethnicity

☐ American Indian or Alaska Native

✔ Asian or Pacific Islander American

☐ Black/ African American

☐ Latino, Hispanic, Spanish

☐ White/ Caucasian

☐ Other:

3 Professional training

Education (list degrees): BA, MD

Health care practitioner licenses: MD60467931

Professional affiliations: AAPMR, AMSSM, ACSM

Board certifications, formal training, or other designations: American Board of Physical Medicine and Rehabilitation (2013) and Sports Medicine (2013)

Current position (title and employer): Clinical Associate Professor, University of Washington

Current practice type and years in practice: Clinical Sports Medicine. 10 years

Total years as an active practitioner: 10 years

Location of practice (city):

1 *Non-binary (X) is an umbrella term used to describe those who do not identify as exclusively male or female. This includes but is not limited to people who identify as genderqueer, gender fluid, agender, or bigender.*

4 Experience

Provide a brief explanation (up to 150 words each) addressing the following:

1) Why you would like to serve on the clinical committee;

I have 10 years of experience with treating patients with a number of musculoskeletal and sports conditions and have always striven to provide patients with evidenced based treatments including those not well covered by insurance (e.g. PRP and Hyaluronic acid injections). I would like to provide my clinical experience with these treatments to hopefully develop sound guidelines for their use.

2) The value of informing health policy decisions with scientific evidence, including any examples incorporating new evidence into your practice;

Scientific evidence evolves and changes very rapidly. It is important to continually apprise the most up-to-date literature and modify current existing practice when the evidence suggests a better way to care for patients. How I practiced initially out of training has changed in may ways based on new data. This way I can provide the most clinically effective and cost efficient care.

3) How your training and experience will inform your role on the committee

I have board certifications in both Physical Medicine and Rehabilitation as well was Sports Medicine and have been in practice for 10 years. Specifically for knee osteoarthritis I treat at least 2-3 patients a day with this condition and provide hyaluronic acid and platelet rich plasma injections to these individuals when appropriate and after a robust discussion about risks, benefits, efficacy data, costs, and alternatives.

4) Treating populations that may be underrepresented in clinical trials: women, children, elderly, or people with diverse ethnic and racial backgrounds, including recipients of Medicaid or other social safety net programs?

I am faculty at the University of Washington Medical Center, a state institution that welcomes a diverse group of individuals regardless of race/gender/age/socio-economic standing. On a day-to-day basis I will serve 16-20 patients of all ages, ethic, racial and gender identity backgrounds and economic standing. The same level of care is provided to each patient.

5 Ability to serve

Are you able to participate in all-day meetings, an estimated six times per year? ☐ Yes ☐ No

Are you willing to commit to the responsibilities of a committee member, including:

- Attending meetings prepared for the topics of the day;
- Actively participating in discussions;
- Making decisions based on the evidence presented and the public interest[1]? ☑ Yes ☐ No

Could you, or any relative, benefit financially from the decisions made by the HTCC? ☑ Yes ☐ No

6 References

Provide three professional references:

1.

First name: Erek
Last name: Latzka
Relationship: Colleague
Title: Clinical Assistant Professor
Contact email:
Phone number:

2.

First name: Stephen
Last name: Johnson
Relationship: Colleague
Title: Clinical Associate Professor
Contact email:
Phone number:

3.

First name: Mark
Last name: Harrast
Relationship: Colleague
Title: Clinical Professor
Contact email:
Phone number:

Please return:

✓ Completed application ✓ curriculum vitae ✓ **conflict of interest disclosure**

Submit to send via email to: **shtap@hca.wa.gov**

OR mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

1 *Detailed in Washington Administrative Code (WAC) and committee bylaws*

Health Technology Clinical Committee Conflict of Interest Disclosure

Washington State Health Care Authority

As stewards of public funds, the practicing clinicians who serve (or apply to serve) on the Committee strive to uphold the highest standards of transparency and impartiality. Identifying financial, professional, and other interests contribute to the effective management of perceived, potential, and/or real conflicts of interest/bias that could affect Committee determinations. (WAC 182-55)

This Conflict of Interest form must be completed by an applicant for appointment to the State of Washington Health Technology Clinical Committee (HTCC) or appointment to any of its subcommittees or work groups.

A member of the HTCC or any of its subcommittees or work groups may not participate in discussions or deliberations of any class of drugs, health technology, or any agenda item for which a conflict of interest is identified and may not vote on any such matter.

If a conflict of interest is so great as to make it difficult for any member to participate meaningfully in the work of the HTCC, that member may be asked to resign.

1 Applicant information

First name: Brian

Middle initial: C

Last name: Liem

Phone number: [redacted]

Email: [redacted]

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

Indicate the source and date of the financial interest. For each chosen category, include date and if your activities are ongoing.

Indicate the recipient. Family: spouse, domestic partner, child, stepchild, parent, sibling (his/her spouse or domestic partner) currently living in your home.

Financial interest categories

Use these categories to indicate the nature of the financial interest:

A. Payment from parties with a financial or political interest in the outcome of work as part of your appointment or activity.

B. Employment including work as an independent contractor, consultant, whether written or unwritten.

C. Ownership or owning stock (stock, options, warrants) or holding debt or other significant proprietary interests or investments in any third party that could be affected.

D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.

E. Participating on a company's proprietary governing boards.

F. Participating in a speakers bureau.

G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topics(s):

No

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topics(s):

No

Could a coverage determination based on a Committee decision conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying committee staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership.

To sign this request, do not use the "Fill & Sign" function; instead, simply click in the signature field to add your signature.

[redacted]

Date 8/28/2023

Submit

or return form to **shtap @hca.wa.gov**

Or mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Date Last revised 2.17.23

BRIAN C. LIEM, MD, RMSK, CAQ Sports Medicine, FAAPMR
Curriculum Vitae

CURRENT OFFICE ADDRESS:

EDUCATION:

Undergraduate

9/2000-6/2004 Bachelor of Arts, Business Administration, Foster School of Business, University of Washington Seattle, WA

Graduate

6/2004-62008 Doctor of Medicine, New York University (NYU) School of Medicine, New York, NY

Post Graduate Training

6/2008-6/2009 **Internship:** Internal Medicine, Virginia Mason Medical Center, Department of Internal Medicine, Seattle, WA

6/2009-6/2012 **Residency:** Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Department of Physical Medicine and Rehabilitation, Chicago, IL

7/2012-7/2013 **Fellowship:** Sports Medicine, University of Washington, Department of Rehabilitation Medicine, Seattle, WA

FACULTY POSITIONS HELD:

7/2021-PRESENT Clinical **Associate** Professor, University of Washington, Department of Rehabilitation Medicine, Seattle, WA

10/2014-6/2021 Clinical **Assistant** Professor, University of Washington, Department of Rehabilitation Medicine, Seattle, WA

HOSPITAL POSITOINS HELD:

7/2013-7/2014 Attending Physician, Houston Methodist Willobrook Hospital, Houston, TX

7/2013-7/2014 Attending Physician, Houston Methodist Sugar Land Hospital, Sugar Land, TX

7/2013-7/2014 Attending Physician, Oak Bend Medical Center, Richmond, TX

7/2013-7/2014 Attending Physician, Houston Hospital for Specialized Surgery, Houston, TX

HONORS/AWARDS:

2004	Washington Scholar (Full Academic Scholarship), University of Washington, Seattle WA
2004	Cum Laude, University of Washington, Seattle WA
2004	Business School Honors with Distinction, University of Washington, Seattle, WA
2011	Excellence in Teaching Award, Northwestern University Feinberg School of Medicine, Chicago, IL
2011	Sewell Resident Award—Achievements in Academics and Research, Rehabilitation Institute of Chicago, Chicago, IL
2012	First Prize for Illinois State PM&R Annual Research Quest, Chicago, IL
2012	American Pain Society Scholarship Recipient, Chicago, IL
2012	Helen Cooper Outstanding Resident Teaching Award, Rehabilitation Institute of Chicago, Chicago, IL
2015	Fellow, American Academy of Physical Medicine and Rehabilitation
2018	Top Doctor, Seattle Met Magazine
2018	Teacher of the Year, UW Department of Rehabilitation Medicine
2019	Top Doctor, Seattle Met Magazine
2020	Top Doctor, Castle Connolly
2020	Top Doctor, Seattle *Met* Magazine
2021	Top Doctor, Castle Connolly
2021	Top Doctor, Seattle *Met* Magazine
2022	Top Doctor, Castle Connolly
2022	Top Doctor, Seattle Magazine

BOARD CERTIFICATIONS:

9/2013-12/2023	Physical Medicine and Rehabilitation, American Board of Physical Medicine and Rehabilitation
9/2013-12/2023	Subspecialty in Sports Medicine, American Board of Physical Medicine and Rehabilitation

OTHER CERTIFICATIONS

1/2022 Registered in Musculoskeletal Ultrasound (RMSK), Alliance for Physician Certification and Advancement (APCA)

MEDICAL LICENSES:

2013-2015 Physician, State of Texas
P6017

2014-PRESENT Physician, State of Washington
MD 60467931

PROFESSIONAL MEMBERSHIPS:

2007-PRESENT American Academy of Physical Medicine and Rehabilitation

2010-PRESENT North American Spine Society

2010-PRESENT American College of Sports Medicine

2012-PRESENT American Medical Society for Sports Medicine

TEACHING RESPONSIBILITIES:

2014-PRESENT UW PMR Residency Mentorship

2014-PRESENT Resident and Fellow Clinical Teaching, UW Medicine
Teaching and Mentoring Rehabilitation and Family Medicine Fellows and Residents

2014-PRESENT Medical Student Clinical Teaching and Mentorship, UW School of Medicine
Teaching and Mentoring medical students in clinic

2014- PRESENT Co-Course Director, Clinical Musculoskeletal Course, UW PM&R Residency Program
Direct teaching of musculoskeletal physical examination, Presentation of lectures, Recruitment of faculty speakers

2015- PRESENT Course Director, PM&R Residency and Sports Fellows Musculoskeletal Ultrasound Course, UW PM&R Residency Program

2015- PRESENT Course Director, 2nd through 4th year Annual Musculoskeletal Ultrasound Intensive Workshop, UW PM&R Residency Program

2015- PRESENT Faculty, Family Medicine Sports Medicine Fellowship

2019-PRESENT Session Director, Transition to Residency Capstone Course, UW School of Medicine

COMMITTEES

2014-PRESENT: PM&R Sports Medicine Fellowship Clinical Competency Committee

2016-PRESENT: UWP Physician Champion and Compliance

2016-PRESENT: UW PM&R Residency Clinical Competency Committee (CCC)

2016-2019: UW PM&R Residency Committee for Resident Education, Evaluation and Development (CREED)

2018 UW Medicine Spine Steering Committee

2018-2020 Faculty Search Committee, Sports and Spine, UW Department of Rehabilitation Medicine

2018-2021 Destination One Clinical Transformation Committee, UW Medicine

NATIONAL RESPONSIBILITIES

2016-PRESENT Section Editor, Current Physical Medicine and Rehabilitation Reports

2016-PRESENT Reviewer, National Examination, AMSSM

2016-PRESENT Journal Reviewer, PM R Journal

2017-PRESENT Musculoskeletal Module Chair, UW PM&R Board Review Course

2017-PRESENT In Training Examination Committee, AMSSM

2019-PRESENT Examiner Ultrasound STEP program, AAPMR

2019-PRESENT Co-Chair, Medical Student Program, AAPMR Annual Assembly

2021-PRESENT Member, Investments Committee, AAPMR

SPECIAL LOCAL RESPONSIBILITIES

2014-2015 Assistant Team Physician, Seattle University Athletics

2014-PRESENT Assistant Team Physician, Ballard High School Athletics

2018-PRESENT Associate Program Director, UW PM&R Sports Medicine Fellowship

OTHER VOLUNTEER WORK

2015-PRESENT Medical Volunteer, Seattle Slam Quad Rugby

2015-PRESENT Medical Volunteer, Seattle Adaptive Sports

2014-PRESENT Medical Volunteer, Seattle Marathon

2015-PRESENT Medical Volunteer, Seattle Rock and Roll Marathon

BIBLIOGRAPHY:

Manuscripts in Referred Journals:

1. Schulman R, Liem B, Moroz A. Treatment of carpal tunnel with medical acupuncture. *Medical Acupuncture*. 2008; 20(3): 163-167.

2. Press J, Liem B, Walega D, et al. Survey of inspection and palpation rates among spine providers: The evaluation of physician performance of the physical examination for patients with low back pain. *Spine.* 2013; 38(20): 1779-84.

3. Liem B, Truswell H, Harrast M. Rehabilitation and return to running after lower limb stress fractures. *Curr Sports Med Rep*. 2013; 12(3):200-7.

4. Liem B, Loveless M, Apple E, Krabak B. Case report: Non-operative management of acetabular labral tear in a skeletally immature figure skater. *PMR*. 2014;6(10): 951-5

5. McCormick, Z, Lynch M, Liem, B et al. Feasibility for developing cardiovascular exercise recommendations for persons with motor-complete paraplegia based on manual wheelchair propulsion; a protocol and preliminary data. *J Spinal Cord Med 2015.*

6. Porrino J, Liem, B. Calcaneal osseous avulsion of the extensor digitorum brevis with radiographic and magnetic resonance imaging correlation. *PM R.* 201515:1-3.

7. Lynch M, McCormick, Z, Liem, B. et al Energy cost of lower body dressing, pop-over transfers, and manual wheelchair propulsion in people with paraplegia due to motor-complete spinal cord injury *Top Spinal Cord Inj Rehabil.* 2015. 21(2):140-8.

8. Liem B, Olafsen N, Harrast M, Herring S. Final Comment: Return to play decision making: Does level of competition make a difference. PM R. Supplement 2016.

9. Liem B, Olafsen N. Pectoralis major injuries: Return to play potential. Current Physical Medicine and Rehabilitation Reports: Sports Section, June 2017.

10. Matsuwaka S, Liem B. The role of exercise in treatment of lumbar spinal stenosis symptoms. Current Physical Medicine and Rehabilitation Reports: Musculoskeletal Section, Feb 2018.

11. McMullen C, Liem B. Efficacy of ultrasound percutaeneous tenotomy (Tenex). Current Physical Medicine and Rehabilitation Reports: Sports Section: June 2018.

12. Sedeberg M, Latzka E, Liem, B. Brief Ultrasound-Aided Teaching to Improve the Accuracy and Confidence of Resident Musculoskeletal Palpation. PMR. 2019

13. Cervario, Brian, Liem, B. Approach to Periscapular Pain in the Athlete. Current PMR Reports: Sports Section. July 2022.

Book Chapters:

Liem B, Hunt T, Herring S. Chapter 3: Head Injuries: Concussions. In: Limpisvasti O, Krabak BJ, Albohm MJ. *The Sports Medicine Field Manual*. Rosemont, IL: AAOS Publications; 2015.

Concannon C, Liem, B, Herring C. Chapter 24: Definitions of Sports Concussion, Initial Diagnosis and On field Evaluation. In: Spine Injuries in Athletes. Rosemont, IL: AAOS Publications; 2015

Liem, B, Loveless, M, Krabak, B. Sports Medicine Cases. In Physical Medicine and Rehabilitation Oral Board Review: Interactive Case Discussions. 2017

Impastato D, Harrast M, Liem B. Wrist and Hand Tendinopathy. In *Tendinopathy: From Basic Science to Clinical Management.* 2018

Liem, B, Loveless, M, Krabak, B. Wise, A. Sports Cases. In Physical Medicine and Rehabilitation Oral Board Review: Interactive Case Discussions 2nd edition. 2020

Book Chapters in Submission:

Manuscripts In Submission:

Lim, Sara, Liem, B. First MTP Joint Injuries in Athletes. Current Sports Medicine Reports—Pending 2023

Manuscripts in Press:

Other Publications:

1. Liem B. Class Act: Is there evidence to support chiropractic care of low back pain?. NYU Langone Internal Medicine Clinical Correlations. July 2007. *http://www.clinicalcorrelations.org/?p=327*.

2. Liem B, Stanos S. Complex Regional Pain Syndrome (Type 1)—Treatment with the Biopsychosocial Interdisciplinary Approach . AAPM&R Case of the Month, Pain Case #15. January 2012*, http://me.e-aapmr.org/CaseStudies.aspx.*

3. Liem B. Is fellowship for you? The decision to pursue post-residency training. The PM&R Resident. April 2012. *http://www.aapmr.org/members/residents/newsletter/Pages/Resident-Newsletter-April-2012-Issue.aspx.*

4. Liem B, Harrast M. Cramping in Marathon Running. Seattle Marathon Running Tips. September 2012. *http://www.seattlemarathon.org/marathon/runningtips.php.*

5. Giacomazzi C, Liem B. Abrasions. AMSSM Tip Sheet 2021

6. Giacomazzi C, Liem B. Hyperhdrosis. AMSSM Tip Sheet 2021

OTHER:

International Presentations

2017 Liem B. Buttock Pain. Lecture presented at Pre-Conference Workshop *Increasing Your Odds of Effective Pain Management*. Canadian Association of Physical Medicine and Rehabilitation Annual Meeting. Niagra Falls, Ontario, Canada. May 25, 2017.

National Presentations:

2011 Liem B, Roth E, Rydberg L et al. Determining the metabolic energy requirements of common activities of daily living and mobility skills in patients with paraplegia. Scientific poster presented at the Association of Academic Physiatrists Annual Meeting. Las Vegas, NV. March 1, 2011.

2011 Liem B., Casey E. Hip pain in a marathon runner—Intertrochanteric stress fracture and the female athlete triad. Clinical case presented at the American College of Sports Medicine Annual Meeting, Denver, CO. June 1, 2011.

2011 Liem B. Patient with paraneoplastic limbic encephalitis transitions from palliative care to rehabilitation: a case report. Scientific poster presented at the American Academy of Physical Medicine and Rehabilitation Annual Meeting, Orlando, FL. Nov 17, 2011.

2012. Liem B, Casey E. Forearm pain in softball player. Clinical case presented at the American College of Sports Medicine Annual Meeting, San Francisco, CA. May 30, 2012.

2013. Liem B, Jacobs G, McCormick Z, et al. Energy cost of wheelchair propulsion, lower extremity dressing, and pop-over transfers in paraplegics. Scientific oral paper presentation at the Association of Academic Physiatrists Annual Meeting. New Orleans, LA. March 8, 2013.

2013. Liem B, Jacobs G, McCormick Z, et al. Energy cost of wheelchair propulsion, lower extremity dressing, and pop-over transfers in paraplegics. Scientific oral paper presentation at the Association of Academic Physiatrists Annual Meeting. New Orleans, LA. March 8, 2013.

2013 Liem B, Harrast M. Thigh Pain in a Biathlete. Clinical case presented at the American College of Sports Medicine Annual Meeting, Indianapolis, IN. May 30, 2013.

2013 Liem B, Kaufman M, Kennedy D. A Pain in the Butt: Evaluation and management of gluteal region pain—Soft Tissues. Lecture presented at the National Athletic Trainers Association Annual Meeting. Las Vegas, NV. June 10, 2013.

2017 Liem B. Upper Extremity Review. University of Washington Physical Medicine and Rehabilitation Board Review Course. March 8,2017.

2017 Patel S, Liem B. Ischial-pubic ramus stress fracture in a marathon runner. Clinical case presented at the American Medical Society for Sports Medicine Annual Scientific Meeting, San Diego, CA. May 10, 2017.

2018 Matsuwaka, Liem B. Low back pain in recreational soccer player. Clinical case presented at the American College of Sports Medicine Annual Meeting, Minneapolis, MN. May 31, 2018

2018 Liem, B. Bhatti, O. Cervical Spine Injuries--Cases. Lecture presented at the National Athletic Trainers Association Annual Meeting. New Orleans, LA. June, 29,2018

2018 Liem B. MRI Interpretation Shoulder and Knee with Ultrasound Correlations, Session Director, Skills Lab, American Academy Physical Medicine and Rehabilitation Annual Meeting, Orlando, FL. October 26, 2018.

2019 Liem B. MRI Interpretation Ankle and Knee with Ultrasound Correlations, Session Director, Skills Lab, American Academy Physical Medicine and Rehabilitation Annual Meeting, San Antonio, TX.November 15, 2019.

2020 LaCourse M., Liem B. Hip and Thigh Pain in a Runner. Clinical case accepted fro presentation at the American College of Sports Medicine Annual Meeting, San Francisco, CA. May 27, 2020

2021 Liem, B. Approach to Posterior Shoulder and Upper Back Pain: Cased Based. Session Director. American Academy of Physical Medicine and Rehabilitation Annual Meeting, Hybrid Virtual Format Nashville, TN November, 13, 2021

2021 Liem, B, Meron, A. Medical Student Program: Solidifying your career path in PM&R. Session Director. American Academy of Physical Medicine and Rehabilitation Annual Meeting, Hybrid Virtual Format Nashville, TN November, 13, 2021

2022 Liem, B, Meron, A. Medical Student Program Introduction to PM&R. Session

Director. American Academy of Physical Medicine. Virtual. August 18, 2022

Local Presentations:

2012 Liem B, Pelto H. Common Medical Conditions in Marathon Runners: How to prevent them and what to look out for. Seattle Marathon Exposition, Seattle, WA. November 23, 2012.

2012 Liem B, Murphy L. Stretching your way to the finish line: key stretches to keep you running, Seattle Marathon Exposition, Seattle, WA. November 23, 2012.

2012 Liem B. Becoming a Sports Medicine Physician, Mt Si High School Sports Medicine class, Career Speaker Series, Snoqualmie, WA. May 6th, 2012.

2012 Liem B. Injuries in Golfers, PM&R Musculoskeletal and Sports Medicine Conference, University of Washington, Seattle, WA. November 10, 2012.

2012 Liem B. Cervical pain after concussion: Diagnosis and Treatment, Sports Academic Conference, University of Washington, Seattle, WA. April 5th, 2012.

2015 Liem B, O'Connor E. Sitting Disease, Whole U Lecture Series, University of Washington, UW HUB, Seattle, WA. February 3rd, 2015

2015 Liem B, O'Connor E. Sitting Disease, Roosevelt Grand Rounds , University of Washington, Seattle, WA, April 7th, 2015.

2015 Liem B. Upper Extremity Review. University of Washington Physical Medicine and Rehabilitation Board Review Course. March 18,2015.

2016 Liem B. Complementary and Alternative Treatments in MSK and Sports Medicine, MSK Grand Rounds, Department of Rehabilitation Medicine, University of Washington. Jan 5, 2016.

2016 Liem B. Spondylolysis and Spondylolisthesis. Clinical Musculoskeletal Course, UW PM&R Residency Program. Februrary 2, 2016

2016 Liem B. Upper Extremity Review. University of Washington Physical Medicine and Rehabilitation Board Review Course. March 19,2016.

2016 Liem B. Efficacy of Ultrasound Guided Steroid Injections. MSK Grand Rounds, Department of Rehabilitation Medicine, University of Washington. Dec 6, 2016.

2017 Liem B. Joint Ultrasound and Injection of the Shoulder and Knee. Pacific Northwest 40th Annual National Conference: Advanced Practice in Primary and Acute Care. Washington State Convention Center. Oct 28, 2017.

2018 Liem B, O'Connor, E. Sitting Disease—2018 Update. Google Recharge Week. Google Seattle Corporate Campus, Jan 10, 2018

2019 Liem B. Ultrasound Injection of the Shoulder and Knee. Pacific Northwest 42th Annual National Conference: Advanced Practice in Primary and Acute Care. Washington State Convention Center. Oct 26, 2019

Washington State Health Care Authority

Washington State Agency Medical Directors' Group Comments

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

Azadeh Farokhi, MD, MPH
Associate Medical Director
Department of Labor and Industries

July 21 , 2023

Osteoarthritis

- One of the most common disabilities affecting people in US
  - Currently affecting 32.5 million
  - By 2032, estimates as high as 29.5% of US adults over the age of 45
- Most commonly occurs in the knee and hip
  - Knee OA affecting 40% of men and 47% women
  - Hip OA affecting 18.5% of men and 28.6% of women
- Progressive disease that may often lead to joint failure
  - Causing pain, fatigue, disability, and general limitations to daily life activities
  - No cure, treatment can become considerably expensive long-term
    - Healthcare costs in the US estimated at $45.4 billion/year
    - Reduced ability to work resulting in additional wage loss

Treatment Management of OA

- Conservative management commonly includes
  - Exercise and physical therapy
    - Benefit both pain relief and maintenance of functionality
    - May be difficult to begin for overweight or obese individuals
  - Use of NSAIDs or acetaminophen
    - Easy to access and low cost, but long-term use increases risk of potentially serious adverse events
  - Supportive devices
- Intra-articular corticosteroid injections
  - Effective at reducing pain in short- and medium-term
  - Risk of adverse events such as pain flare and rapid destructive osteoarthritis of the joint as well as increased risk of post-operative surgical infection
- Joint replacement surgery
  - Invasive, surgical complications

Hyaluronic Acid

- Occurs naturally in connective tissue, joints, and other places where extracellular matrix is present
- Increase joint cushioning and fluid retention
- Theoretically carries no risk of immune response when injected
- Thought to:
  - Inhibit inflammatory mechanisms and nociceptor firing within the joint
  - Temporarily restore a portion of the joint's natural hyaluronan-producing mechanisms
- Requires clearance from the FDA
  - Currently 12 FDA-approved HA products available in US

Platelet Rich Plasma (PRP)

- Derived from a patient's own blood by separating the plasma, platelets, and other cells and compounds including leukocytes and growth factors from RBCs in a centrifuge or via filtration, and injecting the resulting compound into the intra-articular space
- Not regulated as a pharmaceutical product due to its autologous nature, therefore lacks standardization
- Thought to:
  - Lubricate the joint, suppress several inflammatory mechanisms, and increase cartilage production
  - May be capable of repairing damage within osteoarthritic joint

2013 HTCC Review - Hyaluronic Acid/ Viscosupplementation

- Hyaluronic Acid/ Viscosupplementation
  - Hyaluronic Acid/ Viscosupplementation is a covered benefit with conditions for the treatment of knee OA.
  - https://www.hca.wa.gov/assets/program/ha_final_findings_decision_082010_superceded%5B1%5D.pdf
  - https://www.hca.wa.gov/assets/ha-final-findings-decision-20140321.pdf

Number and Coverage Topic:

20131114A – Hyaluronic Acid/ Viscosupplementation

HTCC Coverage Determination:

Hyaluronic Acid/ Viscosupplementation is a **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination.

HTCC Reimbursement Determination:

Limitations of Coverage

Hyaluronic Acid/Viscosupplementation is a **covered benefit for the treatment of pain associated with osteoarthritis of the knee (OA), when all of the following conditions are met:**

- Restricted to patients who have a documented medical contraindication to other forms of non-surgical care including all of the following: NSAIDS, corticosteroid injections, and physical therapy/exercise;
- Is limited to two courses per year with at least four months between courses; and
- Documented evidence of clinical benefit in terms of pain and function from the prior course of treatment is required for subsequent treatment courses.

Non-Covered Indicators

2016 HTCC Review - Autologous Blood/ Platelet-rich Plasma Injections

- Autologous Blood/ Platelet-rich Plasma Injections
  - Autologous Blood/ Platelet-rich Plasma Injections are not covered for any condition or indication.
  - https://www.hca.wa.gov/assets/program/prp_final_findings_decision.pdf

Number and Coverage Topic:

20160520B – Autologous Blood/ Platelet-rich Plasma Injections

HTCC Coverage Determination:

Autologous blood/ platelet-rich plasma injections are **not a covered benefit.**

HTCC Reimbursement Determination:

Limitations of Coverage: NA

Non-Covered Indicators: NA

Washington State Health Care Authority

2023 HTCC re-reviews

- Why PRP and HA are selected for re-review
  - There is a growing evidence base on PRP: only 5 RCTs in the 2016 HTA report for various MSK disorders, but 34 RCTs in the 2023 HTA report for knee and hip OA alone
    - e.g., PRP vs. Placebo for knee OA
      - 2016 HTA report: 2 fair-quality RCTs (N=78, 136)
      - 2023 HTA report: 9 RCTs (2 good and 7 fair quality; total N=1,683, N range 33 to 644) and 3 NRSIs (fair quality; 20 knees in 40 patients [2 NRSIs], 58 knees [patients unclear, 1 NRSI])
  - Stakeholders' requests on HA
    - Challenge in implementing coverage decision
    - Stakeholder request letter????

Agency Medical Director Concerns

Hyaluronic acid/viscosupplementation | Washington State Health Care Authority

Safety = Medium

Efficacy = Medium

Cost = Medium

Autologous blood or platelet-rich plasma injections | Washington State Health Care Authority

Safety = Medium

Efficacy = Medium/High

Cost = Medium

Washington State Health Care Authority

Current State Agency Policies - HA

- HA for the treatment of knee OA:

Agency	Policy
ERB*/UNIFORM MEDICAL PLAN (UMP)	Covered with conditions per HTCC determination
MEDICAID	Covered with conditions per HTCC determination
LABOR AND INDUSTRIES	Covered with conditions per HTCC determination

*Employee and Retiree Benefits (ERB), the HCA program encompassing the Public Employees Benefits Board (PEBB) and School Employees Benefits Board (SEBB)

Current State Agency Policies - PRP

- PRP for any condition or indication:

Agency	Policy
ERB*/UNIFORM MEDICAL PLAN (UMP)	Not covered per HTCC determination
MEDICAID	Not covered per HTCC determination
LABOR AND INDUSTRIES	Not covered per HTCC determination

*Employee and Retiree Benefits (ERB), the HCA program encompassing the Public Employees Benefits Board (PEBB) and School Employees Benefits Board (SEBB)

Combined Utilization: Costs of HA Injections and Related Procedures and Encounters

	2019	2020	2021	2022	Total (unique)
Washington State – Combined Medicaid, PEBB/SEBB UMP, L&I					
Individuals with at least one HA-related procedure/service	1,728	1,463	1,685	1,795	**6,671**
Female, count	1,184	1,005	1,120	1,228	**4,537**
Male, count	541	458	560	560	**2,119**
Number of encounters with HA	4,572	3,828	4,609	4,790	**17,799**
Amount paid, HA	$690,297	$547,793	$526,562	$553,669	**$2,318,321**
Amount paid, HA and related procedures	$2,513,854	$2,147,306	$2,325,811	$2,374,955	**$9,361,926**

Average Amount Paid for HA Injections and Related Procedures per Individual

	Ave encounters per individual	Amount paid for injections per individual	Ave total payments per individual*
Medicaid (MC)	3	$725	$1,459
PEBB/SEBB UMP	3	$211**	$728**
LNI	2	$517	$9,995

*These values include payments for HA injections and other related procedures, such as arthrocentesis.

** The values do not reflect patient cost share.

Combined Utilization: PRP Costs and Encounters

	2019	2020	2021	2022	Total (unique)
Washington State – Combined Medicaid, PEBB/SEBB UMP, L&I					
Individuals with at least one PRP-related procedure/service	25	29	54	57	**165**
Female, count	14	11	25	31	**81**
Male, count	11	18	29	26	**84**
Number of encounters with PRP	27	53	86	77	**243**
Amount paid, PRP	$0	$1,009	$600	$77	**$1,686**
Amount paid, PRP and related procedures	$0	$1,009	$600	$77	**$1,686**

Washington State Health Care Authority

Efficacy: HA for Knee OA

Summary of evidence for HA vs. Placebo (saline) for treatment of knee OA

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

Efficacy: PRP for Knee OA

Summary of evidence for PRP vs. Placebo (saline) for treatment of knee OA

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

Efficacy: HA vs. PRP for Knee OA

Summary of evidence for HA vs. PRP for treatment of knee OA

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success	No difference (SOE: Low); 4 RCTs	HA – lower likelihood (SOE: Low),1 RCT	HA – lower likelihood (SOE: Low),1 RCT
WOMAC PF Scores	No difference (SOE: Low); 4 RCTs	Small (PRP Favored) (SOE: Low); 4 RCTs	Small (PRP Favored) (SOE: Low);4 RCTs
Other functional Measures	No difference (SOE: Low); 4 RCTs	No difference (SOE: Low); 4 RCTs	No difference (SOE: Low); 4 RCTs
WOMAC pain Success	No difference (SOE: Low); 4 RCTs	Small (PRP Favored) (SOE: Low); 1 RCT	No evidence
WOMAC Pain	No difference (SOE: Low); 6 RCTs	Small (PRP Favored) (SOE: Low); 4 RCTs	Small (PRP Favored) (SOE: Low); 5 RCTs
VAS pain	Small (PRP Favored) (SOE: Low); 5 RCTs	Small (PRP Favored) (SOE: Low); 6 RCTs	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

Evidence Considerations: Knee OA

- Hyaluronic acid
  - No difference
    - Placebo (moderate evidence)
    - Steroid (low to moderate evidence)
    - NSAIDs (low evidence)
    - Small improvement favoring PT (low evidence)
  - Most studies were industry funded
- Platelet-rich plasma
  - Moderate improvement in function and pain compared to placebo (moderate)
  - Small improvement in pain but not function when compared to steroid (low)
  - Improvement in function and pain when compared to analgesics (low)
  - No difference between PRP and exercise (low)

Efficacy: HA for Hip OA

Summary of evidence for HA vs. Placebo (saline) for treatment of hip OA

	Short	Intermediate	Long
WOMAC PF or Lequesne	No difference (SOE: low); 2 RCTs	No difference (SOE: low); 1 RCT	No evidence
WOMAC pain Success	No difference (SOE: low); 1 RCT	No difference (SOE: low); 1 RCT	No evidence
WOMAC Pain VAS pain	No difference (SOE: low); 2 RCTs	No difference (SOE: low); 1 RCT	No evidence
WOMAC Total	INSUFFICIENT	INSUFFICIENT	No evidence
OMERACT	INSUFFICIENT	INSUFFICIENT	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	No evidence
Serious AEs	INSUFFICIENT	INSUFFICIENT	No evidence
Tx-Related* AEs	Any time; No difference (SOE: low); 1 RCT		No evidence
Withdrawal due to AE	Any time; No difference (SOE: low); 1 RCT		No evidence

Efficacy: PRP for Hip OA

Summary of evidence for HA vs. PRP for treatment of hip OA

	Short	Intermediate	Long
WOMAC PF	No difference (SOE: low); 1 RCT	No evidence	No difference (SOE: low); 1 RCT
WOMAC Pain VAS pain	No difference (SOE: low); 1RCT	No evidence	No difference (SOE: low); 1 RCT
WOMAC Total	No difference (SOE: low); 1 RCT	No evidence	No difference (SOE: low); 1RCT
Harris Hip	No difference (SOE: low); 1 RCT	No evidence	No difference (SOE: low); 1 RCT
OMERACT	No difference (SOE: low); 1 RCT	No difference (SOE: low); 1 RCT	No difference (SOE: low); 1 RCT
Arthroplasty	Any time: No difference (SOE: low); 1 RCT		
Serious AEs	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

Evidence Considerations: Hip OA

- Hyaluronic Acid
  - No difference between HA and Placebo or Steroid use
- Platelet-rich Plasma
  - No difference between HA and PRP on measures of function or pain

Safety – Hyaluronic Acid

- Knee OA
  - Substantial heterogeneity regarding how adverse events were categorized, reported, and described
  - Serious AEs uncommon following HA injection
  - Treatment-related AEs (variably defined, not specified as serious)
    - More common
    - No difference between HA and comparator groups
- Hip OA
  - One serious treatment-related AE (arthralgia in the saline group)

Safety – Platelet-rich Plasma

- Substantial heterogeneity regarding how AEs were categorized, reported and described (if described at all)
- Evidence on safety/harms was considered insufficient due to generally poor reporting of SAEs and small sample sizes
- Two studies reported SAE as defined by authors
  - Three LR-PRP cases experienced swelling and mild fever → one requiring arthroscopic debridement
  - One LP-PRP case experienced severe inflammation with swelling and stiffness
- Hip OA - Insufficient evidence to draw conclusions

Cost-effectiveness

- Three US-based studies comparing HA with various forms of conservative care
  - HA was cost-effective at a willingness to pay of $50,000/QALY
- One poor-quality US-based study compared HA with PRP
  - PRP injections were not more cost-effective than HA
- Four economic studies conducted outside of US
- Studies in the US were mostly industry funded with high risk of bias
- Conclusion regarding cost-effectiveness of HA were difficult

Selected Other Payers' Policies -Intra-articular Hyaluronan Injections for Knee and Hip OA

Payer	Policy	Note
CMS	Centers for Medicare Services does not have an NCD on HA injection for knee and hip OA.	
WPS Insurance Corporation	Viscosupplementation therapy for the knee via intra-articular injections of hyaluronic preparations will be considered medically reasonable and necessary when all the conditions are met.	Local Coverage Determination (LCD) (L39529)2023
Cigna	Medically necessary when conditions are met.	2023-2024. Intraarticular Hyaluronic Acid Derivatives (IP0322)
United Healthcare	Medically necessary when conditions are met for knee osteoarthritis; not for other indication	2022. Sodium Hyaluronate (2022D0081G)
Aetna	Medically necessary for the treatment of knee OA when the conditions are met	2023-2024. Viscosupplementation (0179)
Premera Blue Cross	**Not** medically necessary for the knee; **Investigational** for all other joints.	2022. Intra-Articular Hyaluronan Injections for Osteoarthritis (2.01.534)

Selected Other Payers' Policies -Platelet Rich Plasma Injections for Knee and Hip OA

Payer	Policy	Note
CMS	Centers for Medicare Services does not have an NCD on PRP injection for knee and hip OA.	
Noridian Healthcare Solutions, LLC	A NON-coverage policy for all Platelet Rich Plasma Injections and/or applications as a means of managing musculoskeletal injuries and/or joint conditions.	Local Coverage Determination (LCD) (L39060) 2022
Cigna	Experimental, investigational or unproven for any condition or indication	2022-2023. Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP]) (0507)
United Healthcare	Unproven and not medically necessary for any condition or indication	2022. Prolotherapy and Platelet Rich Plasma Therapies (2022T0498V)
Aetna	Experimental and investigational for all indications	2023. Blood and Adipose Product Injections for Selected Indications (0784)
Premera	Investigational for all orthopedic indications.	2022. Orthopedic Applications of Platelet-Rich Plasma (2.01.98)

Guidelines on the Use of HA for knee or/and hip OA

Clinical guidelines	Recommendations
American Academy of Orthopaedic Surgeons (2022)	Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition: Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee
American College of Rheumatology (ACR) (2020)	Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee: ACR Conditionally recommends against IAHA use in the knee and strongly recommends against its use in the hip.
Veterans Affairs/Department of Defense (2020)	Clinical practice guideline for the non-surgical management of hip & knee osteoarthritis: VA/DOD suggests offering intraarticular viscosupplementation injection(s) (HA) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions but suggests against its use in the hip.
Phillips et al., (2021)	A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis: Of the 27 included clinical guidelines, 20 were in favor of use of IAHA for knee OA.

Guidelines on the Use of PRP for knee or/and hip OA

Clinical guidelines	Recommendations
American Academy of Orthopaedic Surgeons (2022)	*Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition*: Platelet-rich plasma may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.
American College of Rheumatology (ACR) (2020)	Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee: ACR strongly recommends against PRP use in both the knee and hip.
Veterans Affairs/Department of Defense (2020)	Clinical practice guideline for the non-surgical management of hip & knee osteoarthritis: VA/DOD does not have sufficient evidence to recommend for or against PRP injections in the knee or hip.
Phillips et al., (2021)	A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis: Of the 27 included clinical guidelines, 9 indicated uncertainty or inability to make a recommendation for or against the use of PRP.

Agency Medical Directors Recommendation

- Hyaluronic acid injection is not a covered benefit for the treatment of knee osteoarthritis

- Hyaluronic acid injection is not a covered benefit for the treatment of hip osteoarthritis

Agency Medical Directors Recommendation (cont.)

- Platelet-rich plasma injection is a covered benefit with conditions for the treatment of knee osteoarthritis
  - Adults > 18 yo
  - Symptomatic knee OA
  - Treatment after failure of conservative treatments
  - Repeat injection covered or not? Overall no difference between single vs. multiple injections
  - Concerns for lack of standardization and heterogeneity (No FDA guidance)

- Platelet-rich plasma injection is not a covered benefit for the treatment of hip osteoarthritis

Questions?

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Washington State Health Care Authority

Washington State Health Care Authority

Hyaluronic acid/platelet-rich plasma

Order of scheduled presentations:

No scheduled comments

Day of comments:

	Name
1	
2	
3	
4	
5	
6	

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

Presentation to

Washington State Health Care Authority
Health Technology Clinical Committee

Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS

July 21, 2023

Report prepared by:
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Previous Reports

2013 Report – HA/Viscosupplementation

- **19 included studies; 14 (6 SRs, 4 RCTs, 4 case series) focused on efficacy (primarily) and safety outcomes, one narrative review focused on pseudosepsis risk, 4 economic analyses**
- Most evidence for placebo (saline): 4 SRs (81 generally placebo-controlled trials and >10,000 patients) and 3 additional placebo-controlled RCTs; 1 SR compared HA with corticosteroid injections; 1 SR and 1 RCT compared different formulations of HA.
- **Conclusions**
  - **Effectiveness:**
    - Moderate-quality evidence of some benefit in pain and function vs. placebo, no effect QoL
    - Clinically relevant difference vs. placebo: None, MDs generally smaller than MCID
    - Comparable efficacy to NSAIDs, inferior efficacy to IA corticosteroids
    - Cross-linked HA may provide increased benefit, no difference between high and low molecular weight
  - **Safety:**
    - High quality evidence of short-term safety, no evidence on long-term safety

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Previous Reports, cont.

2016 Report – Autologous blood or PRP

- **26 relevant included studies; 16 (12 RCTs, 4 NRSIs) on efficacy, 9 (7 RCTs, 2 NRSIs) on safety**
- **Various musculoskeletal conditions to include OA (10 RCTs knee OA, 1 RCT hip OA); interventions out of scope for this re-review (e.g., ACS, PRFG-Endorcet)**
- **Conclusions**
  - **Effectiveness:**
    - Short- and intermediate-term improvement in pain and function versus saline
    - For PRP vs. HA, no difference in pain or function short-term, slightly improved pain with PRP intermediate-term, improved long-term pain and function outcomes with PRP
    - Comparable efficacy to exercise with or without TENS, slightly superior efficacy to IA corticosteroids in intermediate-term
    - Many results based on low quality or insufficient evidence
  - **Safety:**
    - PRP had significantly more adverse events than saline, but was comparable with other treatments

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Re-Review Rationale

- **New evidence on effectiveness, safety, comparisons to more treatment options**
  - 64 RCTs (67 publications), 8 formal cost-effectiveness analyses
  - Wealth of new data available since previous reports
- **New review is specific to OA of the knee and hip**
  - Previous reports included other OA locations and/or musculoskeletal conditions
- **HA and PRP are the primary forms of treatment or concurrent with other primary therapies**

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Background

Osteoarthritis (OA)

- **Progressive disease that causes deterioration of joints in the body**
  - Not reversible
  - Incurable, may eventually lead to need for total joint replacement surgery
  - Knee and hip are first and third most affected joints
    - 40% of men and 47% of women at risk of developing knee OA
    - 18.5% of men and 28.6% of women at risk of developing hip OA
- **Approx. 32.5 million Americans currently affected by OA**
  - May affect as much as 29.5% of US adults over 45 by 2032
- **$45.4 billion/year in healthcare costs**
  - Affected individuals lose an additional $2,982 in additional healthcare costs and lost wages

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Osteoarthritis Classification

- **Severity classified radiographically via validated scales**
  - **Kellgren-Lawrence (KL) scale is most common**
    - Grade 1: Possible osteophytic lipping and lack of joint space narrowing
    - Grade 2: Clear osteophytes and likely joint space narrowing
    - Grade 3: Moderate osteophytes, clear joint space narrowing and sclerosis, possible bone-end deformity
    - Grade 4: Large osteophytes, severe joint space narrowing, sclerosis, clear bone-end deformity
  - **Ählback scale also used by several studies**
    - Grade 0: Absence of disease
    - Grade 1: Joint space narrowing less than three millimeters/50% of the joint space
    - Grade 2: Obliteration of joint space
    - Grade 3: Bone defect or loss less than five millimeters
    - Grade 4: Bone defect or loss of five to ten millimeters
  - **Shahriaree scale used by one included study (MRI-based)**

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Management of Osteoarthritis

- **Exercise and physical therapy**
  - Front-line treatments, provide functional benefit, pain relief
  - Considerable time and financial commitment
  - May be difficult for overweight or obese individuals
- **NSAIDs, acetaminophen, other analgesics**
  - Low cost, accessible pain relief options
  - Long term use associated with risk of stomach, kidney, liver, cardiovascular complication
- **Intra-articular corticosteroids**
  - May provide short- and intermediate-term pain relief
  - Carry larger risk profile (pain flare, rapid joint deterioration, infection, hypertension, increased blood glucose, reduced immune response)
- **Joint replacement surgery (e.g., total knee replacement)**
  - Alleviates symptoms via installation of a new joint and /or joint surface
  - Invasive, carries risk of infection, material rejection, surgical complications, need for additional surgery

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Hyaluronic Acid (HA)

- **Supplemental form of naturally occurring extracellular substance**
  - Pharmaceutical version made with rooster combs or bacterial fermentation
  - Administered via intra-articular route
  - Not specific to any tissue → Low/no risk of immune response to supplementation
- **Thought to provide anti-inflammatory, analgesic, chondroprotective effects**
  - Reduces nociceptor firing and within-joint inflammation, resulting in reduced pain and slowed OA progression
  - Temporarily restores joint's hyaluronan-producing capabilities, resulting in benefit beyond half-life of supplement
- **FDA approved for use in knee OA**
  - 12 products currently approved (Appendix K)
  - Can be particulate manufactured (particle size → longevity) or non-particulate manufactured (cross-linkage density → longevity)
  - Different particulate formulations self-describe as high or low molecular weight, but there is no standardized range for either designation
  - Treatment regimens (dose, # of injections, injection frequency) not standardized

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Platelet-Rich Plasma (PRP)

- **Autologous injection of naturally-occurring blood product**
  - Patients own blood is drawn and centrifuged once or (most often) twice to separate plasma and other components (e.g., platelets, leukocytes, etc.) from whole blood; PRP may be activated (e.g., calcium chloride) and injected into target joint
- **Mechanism of action not entirely clear, but current evidence supports lubricating, anti-inflammatory effect within joint**
  - May suppress inflammatory mechanisms within joint, reducing pain and stimulating healing
  - Increases cartilage production within joint, slowing and potentially reversing OA progression
- **Not FDA regulated as pharmaceutical product (autologous); "off-label" use**
  - Wide range of devices used to process PRP (i.e., centrifuge machines, PRP kits) cleared by the FDA (510(k))
  - Currently lacks standardization required to generate consistent enough products to determine broad efficacy
    - Treatment regimens (number of platelets, leukocyte concentration, dose/volume, # of injections, injection frequency) also not standardized

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HA, PRP – Indications, Contraindications, Possible AEs

- **Indications**
  - Pain relief for patients not responding to other front-line/preferred treatments
- **Contraindications**
  - Hypersensitivity/allergy to any injection components
  - Infection at injection site or in joint
- **Common adverse events (non-serious (mild), local, transient)**
  - **HA:** Injection site pain, joint swelling/effusion/stiffness, arthralgia
  - **PRP:** Pain and/or swelling at injection site, arthralgia
- **Serious adverse events**
  - **HA:** Pseudo-septic reaction
  - **PRP:** Severe swelling, serious infection, sepsis

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Questions and Scope

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Key Questions

1. In adults with symptoms related to knee or hip osteoarthritis considered for treatment with **HA:**

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

   b. What is the evidence regarding short- and longer-term **harms and complications** vs. comparators

   c. Is there evidence of **differential effectiveness or safety** of HA versus comparators

   d. What is the evidence of **cost-effectiveness** of HA versus comparators

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Key Questions, cont.

2. In adults with symptoms related to knee or hip osteoarthritis considered for treatment with **PRP**:

a. What is the **effectiveness** of PRP compared with placebo/sham, common conservative treatments, treatments other than HA, or no treatment in the short and longer-term?
b. What is the evidence regarding short- and longer-term **harms and complications** vs. comparators
c. Is there evidence of **differential effectiveness or safety** of HA versus comparators
d. What is the evidence of **cost-effectiveness** of HA versus comparators

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PICO Scope: Inclusion Criteria

- **Population**
  - Adults with symptomatic knee/hip OA
  - Subpopulations: patient characteristics, primary/secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options
- **Intervention**
  - PRP or HA (FDA approved) injection(s) used as the primary intervention or in conjunction with common conservative care options
- **Comparator**
  - Common conservative treatment(s) (e.g., NSAIDs, analgesics, exercise, PT, weight loss), arthroscopic lavage/debridement, prolotherapy, corticosteroid injection, placebo or sham (including saline), no treatment
- **Outcome**
  - Primary: Function, pain, need for invasive procedures (e.g., surgery), AEs or harms (***SOE only on these***)
  - Secondary: Symptom recurrence resulting in need for additional HA or PRP (within 2 months), quality of life, medication use, return to activities (e.g., sports, work, activity level)
  - Economic: Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome)

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PICO Scope: Inclusion Criteria

- **Timing**
  - Review will focus on persistence of relief ≥ 1-month post-treatment
- **Study Design**
  - Focus will be on studies with the least potential for bias
  - Key Questions 1 and 2 parts a and b: RCTs, high quality NRSIs will be considered in the absence of RCTs with a focus on comparative prospective studies
  - Key Question 1b and 2b: KQ2: In the absence of RCTs, NRSIs designed specifically to evaluate harms/adverse events that are rare or occur long-term
  - Key Question 1c and 2c: RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest and test for interaction
  - Key Question 1d and 2d: Formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies)
- **Publication**
  - Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)

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Methods

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Strength of Evidence (SoE)

SoE for overall body of evidence for primary outcomes was assessed based on:

- **Risk of bias**: the extent to which the individual included studies protect against bias
  - Appropriate randomization
  - Allocation concealment
  - Intention to treat analysis
  - Blind assessment of outcomes
  - Adequate follow-up (≥80%) and <10% follow-up difference between groups
  - Controlling for confounding
- **Consistency**: degree to which estimates are similar in terms of range and variability.
- **Directness**: whether the evidence is directly related to patient health outcomes.
  NOTE: None were considered indirect.
- **Precision**: level of certainty surrounding the effect estimates.
- **Publication/report bias**: selective reporting or publishing.

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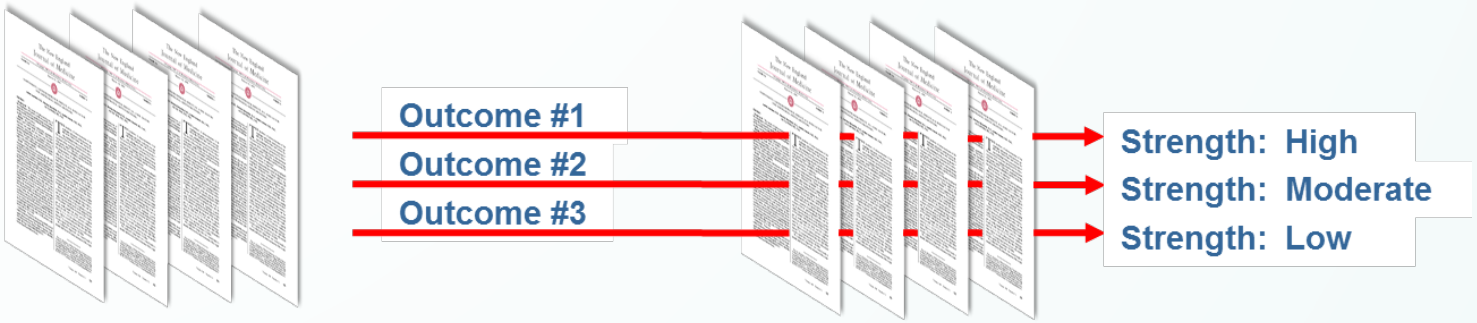
Systematic Review Process

Studies meeting eligibility criteria
- Efficacy: RCTs
- Harms: RCTs, observational studies
- Economic studies

Risk of Bias Appraisal (Study)
Good, Fair, or Poor
Synthesis/analysis

Overall Strength of Evidence Determination (GRADE/AHRQ)



Strength of Evidence Ratings	
High	Very confident that effect is true.
Moderate	Moderately confident.
Low	Limited confidence.
Insufficient	No evidence or no confidence in effect.

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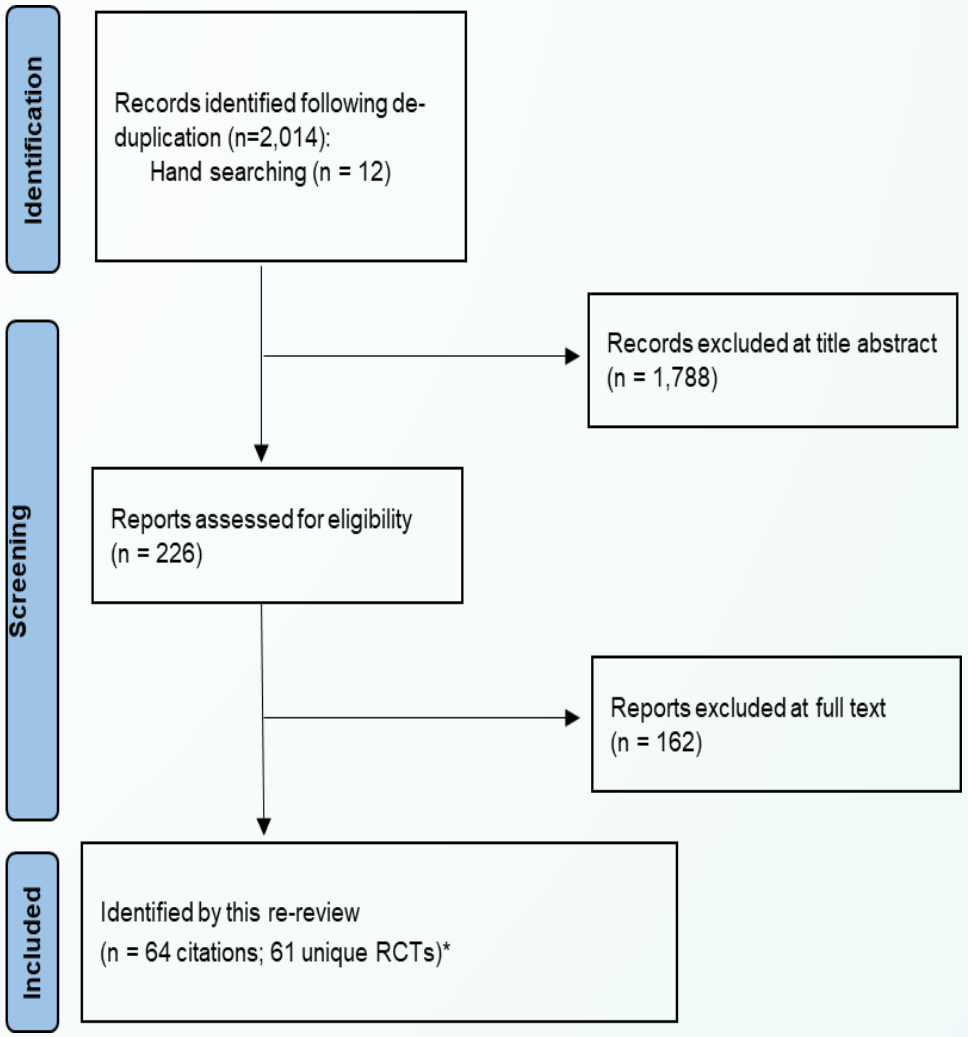
Results

Included Literature

- **Literature search**
  - PubMed, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews searched Jan 1, 2013 through Dec 31, 2022
  - Dual abstract review
  - Dual full text review
  - Conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations excluded



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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	>10–20 points on a 0-to 100-point VAS or the equivalent	>20 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	>1–2 points on a 0-to 10-point numerical rating scale or the equivalent	>2 points on a 0-to 10-point numerical rating scale or the equivalent
1-2 points on 0-20 scale	2-4 points on 0-20 scale	>4 points on 0-20 scale
Function		
5–10 points on the ODI	>10–20 points on the ODI	>20 points on the ODI
1–2 points on the RDQ	>2–5 points on the RDQ	>5 points on the RDQ
1-2 points on Lequesne Index	>2-5 points on the Lequesne Index	5 points on the Lequesne Index
5–10 points on the WOMAC-T	>10–20 points on the WOMAT	>20 points on the WOMAC-T
3.4-6.8 points on WOMAC PF	6.8-13.8 points on WOMAC- PF	>13.6 points on WOMAC PF
5–10 points on the KOOS	>10–20 points on the KOOS	>20 points on the KOOS
5-10 points on the IKDC	>10–20 points on the IKDC	>20 points on the IKDC
5-10 points on the Lysholm	>10–20 points on the Lysholm	>20 points on the Lysholm
Pain or function		
0.2–0.5 SMD	>0.5–0.8 SMD	>0.8 SMD
1.2 to 2.4 RR/OR	1.5 to 1.9 RR/OR	≥2.0 RR/OR

ODI = Oswestry Disability Index; RDQ = Roland Morris Disability Questionnaire; SMD = standardized mean difference; VAS = visual analogue scale. WOMAC = Western Ontario and Mc Maters Universities Osteoarthritis index with T=total and PF= physical function; IKDC=International Knee Documentation Committee knee scoring system KOOS=Knee Injury and Osteoarthritis Outcome Score

Presentation Organization and Notes

- Focus on primary outcomes of function, pain, invasive procedures and adverse events
- HA vs. comparators (KQ 1)
- PRP vs. comparators (KQ 2)
- Full SOE tables are in Section 7
- Key appendices
  - Appendix G: Patient and treatment characteristics
  - Appendix H: Additional figures

Aggregate Analytics

Key Question (KQ) 1: HA

Aggregate Analytics

HA information: Appendix K

- 15 FDA-approved brand names or generic
- Various compositions, sources, formulations
- Molecular weight vary across products (500 kDa to 100,000 kDa); no standard definition of high vs. low molecular weight
- Dose and treatment schedules vary
  - Dose range: 10 mg/ml to 22 mg/ml
  - Schedules: single; from 3 to 5 weekly injections

Aggregate Analytics

KQ 1: HA for Knee OA results

Comparisons	RCTs (publications)	Funding : No. RCTs (Publications)			
		Industry	Other*	None	NR
KNEE OA					
HA/Viscosupplementation					
HA vs. Placebo (Saline)	9 (12)	7 (10)	1	1	---
HA vs. PRP	11	2	4	5	---
HA vs. Corticosteroid	6	1	2	3	---
HA vs. NSAIDs	2	---	---	2	---
HA vs. Usual Care	1	---	1	---	---
HA vs. Exercise	1	---	---	---	1
HA vs. PT	1	---	---	1	---
HA vs. Prolotherapy	1	---	---	1	---
HA (HMW) vs. HA (LMW)	1	1	---	---	---
TOTAL: HA†	**30 (33)**	**11 (14)**	**8**	**10**	**1**

†8 RCTs contributed to more than one comparison

KQ 1a: Effectiveness of HA (Knee OA)

Patient and Intervention Characteristics:
HA vs. Placebo (saline) – Knee OA

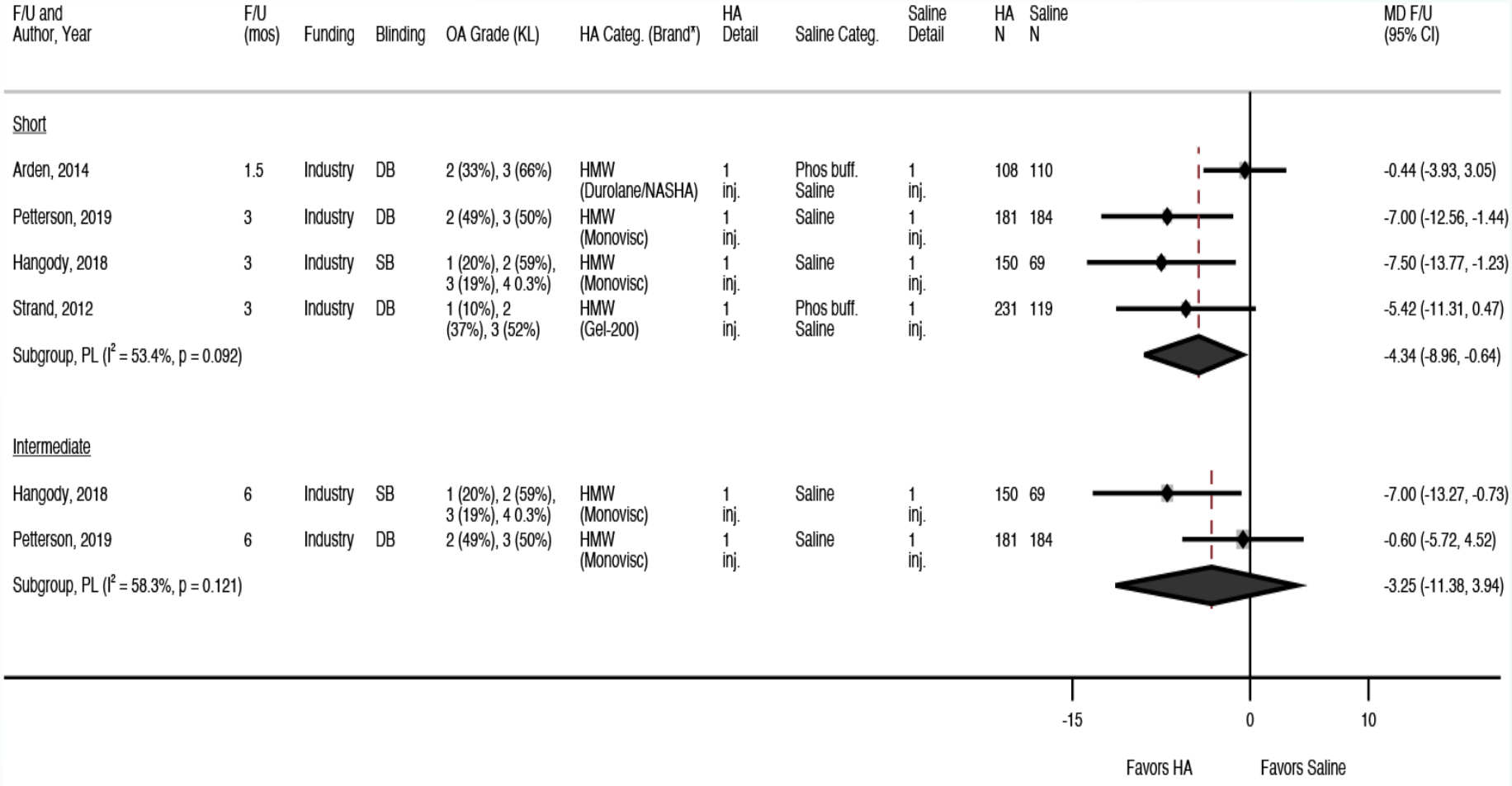
(See Appendix G – Tables G6a-G6c)

9 RCTs (7 industry funded), 12 publications, N=2696

- Mean age 59.8 years (53.1 to 62.0),
- Female: 60.3% (45.0% to 77.8%)
- Kellgren-Lawrence Grade :
  - Grade 1, 13.6% (0% to 27.7%)
  - Grade 2, 45.3% (35.8% to 62.1%) and
  - Grade 3, 40.8 % (18.7% to 58.4%)
- Mean symptom duration 2.7 years
- HA Injections
  - Injections: Single (7 RCTs), 3 (1 RCT), 5 (1 RCT); weekly if multiple
  - High MW (8 RCTs; 1000 kDa to 90,000 kDa), not reported (1 RCT)
  - Doses ranged 30 mg to 80 mg per injection
- Placebo (saline) injections: single (8 RCTs), 3 injections (weekly, 1RCT)

KQ 1a: HA vs. Placebo (saline) – FUNCTION – Knee OA

WOMAC Physical Function (0-68 scale)



F/U and Author, Year	F/U (mos)	Funding	Blinding	OA Grade (KL)	HA Categ. (Brand™)	HA Detail	Saline Categ.	Saline Detail	HA N	Saline N	MD F/U (95% CI)
Short											
Arden, 2014	1.5	Industry	DB	2 (33%), 3 (66%)	HMW (Durolane/NASHA)	1 inj.	Phos buff. Saline	1 inj.	108	110	-0.44 (-3.93, 3.05)
Petterson, 2019	3	Industry	DB	2 (49%), 3 (50%)	HMW (Monovisc)	1 inj.	Saline	1 inj.	181	184	-7.00 (-12.56, -1.44)
Hangody, 2018	3	Industry	SB	1 (20%), 2 (59%), 3 (19%), 4 0.3%)	HMW (Monovisc)	1 inj.	Saline	1 inj.	150	69	-7.50 (-13.77, -1.23)
Strand, 2012	3	Industry	DB	1 (10%), 2 (37%), 3 (52%)	HMW (Gel-200)	1 inj.	Phos buff. Saline	1 inj.	231	119	-5.42 (-11.31, 0.47)
Subgroup, PL (I^2 = 53.4%, p = 0.092)											-4.34 (-8.96, -0.64)
Intermediate											
Hangody, 2018	6	Industry	SB	1 (20%), 2 (59%), 3 (19%), 4 0.3%)	HMW (Monovisc)	1 inj.	Saline	1 inj.	150	69	-7.00 (-13.27, -0.73)
Petterson, 2019	6	Industry	DB	2 (49%), 3 (50%)	HMW (Monovisc)	1 inj.	Saline	1 inj.	181	184	-0.60 (-5.72, 4.52)
Subgroup, PL (I^2 = 58.3%, p = 0.121)											-3.25 (-11.38, 3.94)

Short-term: Small improvement with HA (SOE: MODERATE)

Intermediate term: No difference (SOE: MODERATE)

Aggregate Analytics

KQ 1a: HA vs. Placebo (saline) – PAIN – Knee OA
WOMAC Pain Success

		Scale	Threshold	HA	Saline	RR (95% CI)
Short	Arden, 2014	WOMAC Pain (0-68)	40% reduction w/ absolute improvement ≥5 points	30.6% (33/108)	26.4% (29/110)	**1.16 (0.76 to 1.77)**
	Petterson 2019	WOMAC Pain (0-68)	>50% improvement and >20 mm absolute improvement	52.5% (95/181)	52.7% (97/184)	**1.00 (0.82 to 1.21)**
Intermediate	Ke, 2021	WOMAC A1 Pain (0-4)	>2-pt improvement WOMAC A1 NRS	67.0% (146/218)	68.2% (150/220)	**0.98 (0.86 to 1.12)**
	Petterson 2019	WOMAC Pain (0-68)	>50% improvement and >20 mm absolute improvement	51.4% (93/181)	48.9% (90/184)	**1.04 (0.85 to 1.28)**

Short-term: No difference (SOE MODERATE)

Intermediate term: No difference (SOE MODERATE)

Aggregate Analytics

KQ 1a: HA vs. Placebo (saline) – WOMAC Pain (0-20 scale) and VAS Pain (0-10) – Knee OA

Outcome*	Time	Studies	HA vs. Placebo (saline) Effect	Quality (SoE)
Pain Scores **WOMAC (0-20)** **VAS (0-10 scale)**	3 mos.	**WOMAC Pain** 4 RCTs (N=827) **VAS Pain†** 3 RCTs (N=604)	**WOMAC Pain (0-20)** All RCTS: MD -1.15, 95% CI -1.80 to -0.26, I^2=60.8% **3 low ROB RCTs:** MD -0.90, 95% CI -1.75 to 0.11, I^2=65.2% **VAS Pain (0-10)†** ALL RCTS (3 RCTs): MD – 0.23, 95%CI -1.37 to 0.94, I^2=89.3% **1 low ROB RCT** (Ke, N=438); MD 0.03, 95% CI -1.37 to 0.94 **Conclusion: No based on highest quality trials**	⊕⊕⊕◯ MODERATE (imprecision)
	Intermediate (6 mos.)	**WOMAC Pain** 1 RCT (N= 219) **VAS Pain** 2 RCTs (N= 1247)	**WOMAC (0-20)** MD -0.88 95% CI -1.50 to -0.26 **VAS Pain (0-10)** MD -0.03, 95%CI -0.20 to 0.09, I^2=0%) [excludes 1 small poor-quality trial, Farr 2019] **Conclusion: No difference; WOMAC Pain scores effect estimate are below threshold for small effect; no difference in VAS**	⊕⊕⊕◯ MODERATE (Imprecision)
	Long	**VAS Pain** 1 RCT (N=32)	**VAS Pain** MD 0.12, 95% CI -1.24 to 1.48 **Conclusion: No difference**	⊕◯◯◯ INSUFFICIENT (ROB, consistency, imprecision

KQ 1a: HA vs. Placebo (saline) – OMERACT-OARSI Responder Knee OA

Outcome*	Time	Studies	HA vs. Placebo (saline) Effect estimate (95% CI) Conclusion	Quality (SoE)
OMERACT-OARSI Responder	3 mos.	1 RCT (N=375) Strand, 2012	RR 1.12, 95% CI 0.92 to 1.38 61 % vs. 54.6% <u>Conclusion</u>: No difference	⊕⊕◯◯ LOW (imprecision, consistency unknown)
	6 mos.	1 RCT (N=33) Farr, 2019	RR 0.92, 95% CI 0.40 to 2.09 <u>Conclusion</u>: No difference	⊕◯◯◯ INSUFFICIENT (ROB -2, consistency, imprecision)
	12 mos.	1 RCT (N=29) Gomoll, 2019	RR 0.84, 95% CI 0.34 to 2.09 <u>Conclusion</u>: No difference	

Aggregate Analytics

HA vs. PRP: Knee OA

- Eleven RCTs (11 publications), N=1160
- Funding:
  - Industry (2 RCTs); other (4 RCTs)
  - Funding not reported (5 RCTs)
- Only 1 RCT conducted in the U.S.

Aggregate Analytics

Patient and Intervention Characteristics: HA vs. PRP – Knee OA

(See Appendix G – Tables)

11 RCTs, (N= 1160)

- Mean age: 58.3 years (53.6 to 65.1); Female 69.8% (37.5% to 83.6%)
- **OA severity (various measures)**
  - Kellgren-Lawrence Grade:
    - (8 RCTs) Grade 2, 46% (0% to 100%) Grade 3, 43.8 %(0% to 100%)
    - 3 RCTs included Grade 1 (2.9% to 55.4%); 2 RCTs, Grade 4 (1.1% to 13.8%)
  - Ähl back: (1 RCT, grade 2, 36.3%, grade 3, 63.7%);
- Mean symptom duration x 5.5 years (2RCTs)
- **HA Injections**
  - Injections: Single (2 RCTs), 3 (9 RCTs; intervals ranged from weekly to monthly)
  - High MW (6 RCTs, 620 kDa to 100,000 kDa), Low MW (5 RCTs, 500 to 730 kDa)
  - Doses ranged 16mg to 60mg per injection
- **PRP injections:**
  - Injections: Single (4 RCTs), 2 (3 RCTs), 3 (6RCTs); weekly to monthly
  - LR-PRP (5 RCTs); LP-PRP (5 RCTs); not reported (1 RCT)
  - Platelet counts varied; most reported 2-5 times normal blood platelet count
  - Activating agents (calcium chloride, calcium gluconate, serum)

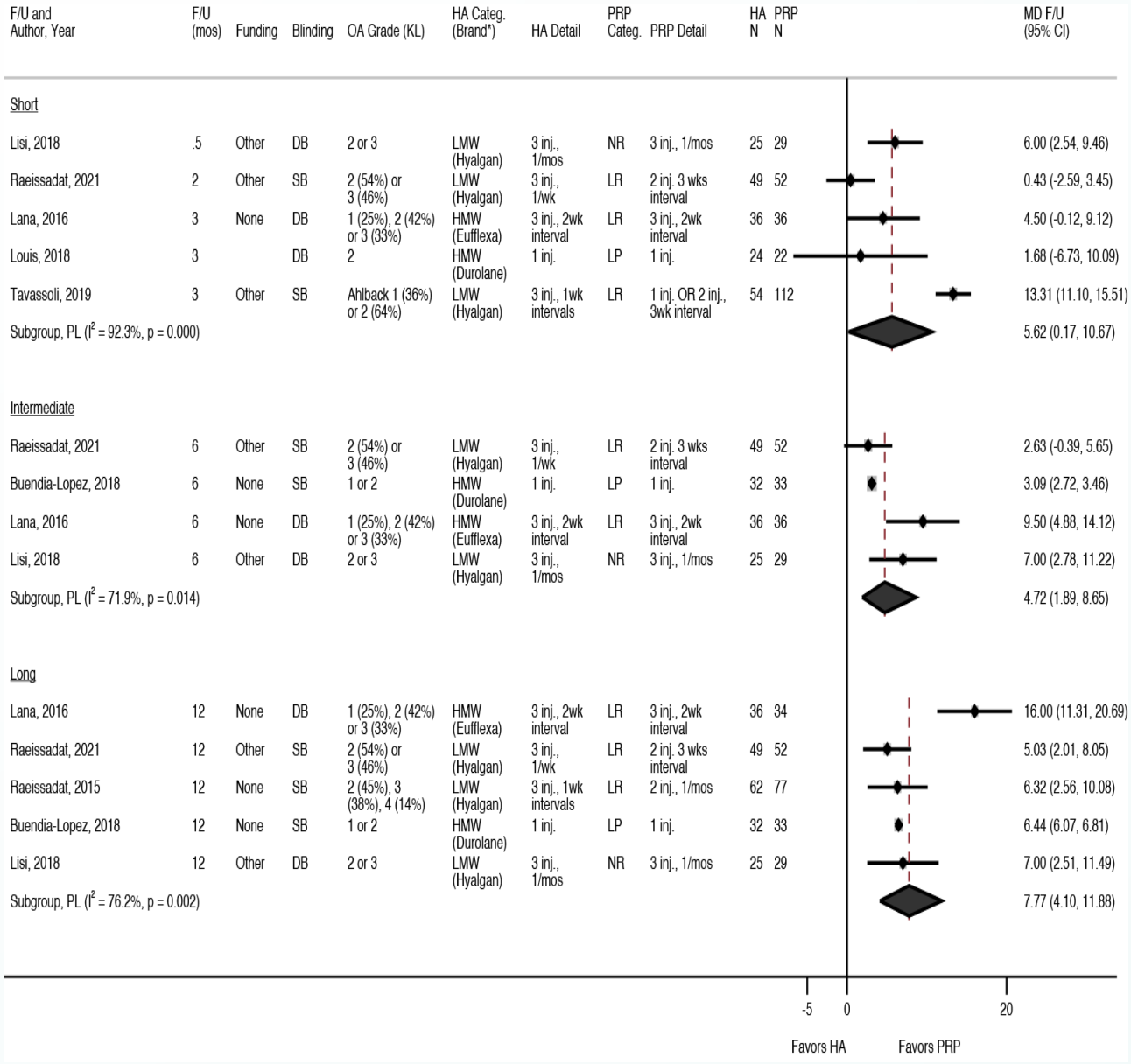
KQ 1a: HA vs. PRP – FUNCTION – Knee OA
WOMAC Physical Function (0-68 scale) - Success

Outcome*	Time	Studies	HA vs. PRP Effect estimate (95% CI)	Quality (SoE)
Function Response (success) WOMAC Physical Function	Short term	1 RCT (N= 83) Tavassoli, 2019	**30% decrease in score** 0% vs. 62.5% **50% decrease in score** 0% vs. 10.7% **Conclusion:** No HA recipient met thresholds for response threshold	⊕◯◯◯ INSUFFICIENT (ROB -2, unknown consistency, precision)
	Intermediate term	1 RCT (N= 65) Buendia-Lopez, 2018	**20% decrease in score** 14.2% vs. 45% RR 0.34, 95% CI 0.14 to 0.84 **Conclusion:** HA associated with *lower likelihood* of treatment response versus PRP	⊕⊕◯◯ LOW (ROB, Precision)
	Long term	1 RCT (N=65) Buendia-Lopez, 2018	**20% decrease in score** 0% vs. 24% **Conclusion:** HA associated with *lower likelihood* of treatment response versus PRP	

Aggregate Analytics

KQ 1a: HA vs. PRP – FUNCTION – Knee OA

WOMAC Physical Function (0-68 scale) - Scores



Short term

No difference (LOW)

4 RCTs, N=287

MD 3.24, 95% CI -0.18 to 6.72 I^2=51.3% (excluding outlier reporting knees)

Intermediate

Small improvement with PRP (LOW)

4 RCTs, N=292

MD 4.72, 95% CI 1.89 to 8.65, I^2=71.9%)

Long Term

Small improvement with PRP (LOW)

4 RCTs, N=359

MD 6.42, 95% CI 5.68 to 6.95, I^2=0%) excludes outlier trial

KQ 1a: HA vs. PRP – FUNCTION – Knee OA
Other measures

Outcome	Time	Studies	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
Other functional measures **IKDC (0-100)** **Lysholm (0-100)**	Short term	**IKDC** 2 RCTs (N=288) **Lysholm** 2 RCTs (N=155)	**IKDC** MD 2.24, MD -8.39 to 14.51, I^2= 69.5% **Lysholm** MD 0.09, 95% CI -0.71 to 1.07, I^2=0% **Conclusion**: No difference	⊕⊕◯◯ LOW ROB, Imprecision
	Intermediate term	**IKDC** 3 RCTs (N=410) **Lysholm** 2 RCTs (N=155)	**IKDC** MD 6.47, 95% CI 3.67 to 9.21, I^2= 0% **Lysholm** MD 2.07, 95% CI 0.59 to 3.93 I^2=71.4% **Conclusion**: **IKDC: small improvement with PRP vs. HA** Lysholm: Insufficient	⊕⊕◯◯ LOW IKDC ⊕◯◯◯ INSUFFICIENT Lysholm ROB, inconsistency, precision)
	Long term	**IKDC** 2 RCTs (N=288) **Lysholm** 2 RCTs (N=155)	**IKDC** MD 9.75, 95% CI 3.05 to 16.81, I^2=0%) **Lysholm** MD 1.11, 95%CI 0.18 to 2.57, I^2=43.3%) **Conclusion**: **IKDC: small improvement with PRP vs. HA** Lysholm: Insufficient	

Lysholm effect size estimates are below threshold for small effect

Same studies reporting Lysholm are represented in WOMAC PF

KQ 1a: HA vs. PRP – PAIN – Knee OA
WOMAC Pain, VAS Pain Success

Outcome	Time	Studies	HA vs. PRP Effect estimate (95% CI) Conclusion	Quality (SoE)
Pain "success" (responders) WOMAC Pain (0-20) **VAS Pain (0-10)**	Short term	1 RCT (N=83) Tavassoli, 2019	**WOMAC Pain –** 30% decrease: 0% vs. 92.8% 50% decrease: 0% vs. 39.3% **VAS Pain:** 50% decrease 0% vs. 33.9% **Conclusion:** No HA recipient met thresholds for treatment response: more PRP recipients met thresholds	⊕◯◯◯ INSUFFICIENT ROB- 2, unknown consistency, imprecision
	Intermediate term	1 RCT (N=65) Buendia-Lopez, 2018	**WOMAC Pain** 20% decrease 21.9% vs. 48.5% RR 0.45, 95% CI 0.21 to 0.95 **VAS Pain** 20% decrease 25% vs. 48.5% RR 0.52, 95% CI 0.26 to 1.03) **Conclusion:** Substantially more PRP recipients achieved 20% decrease in pain scores than HA recipients	⊕⊕◯◯ LOW unknown consistency, imprecision

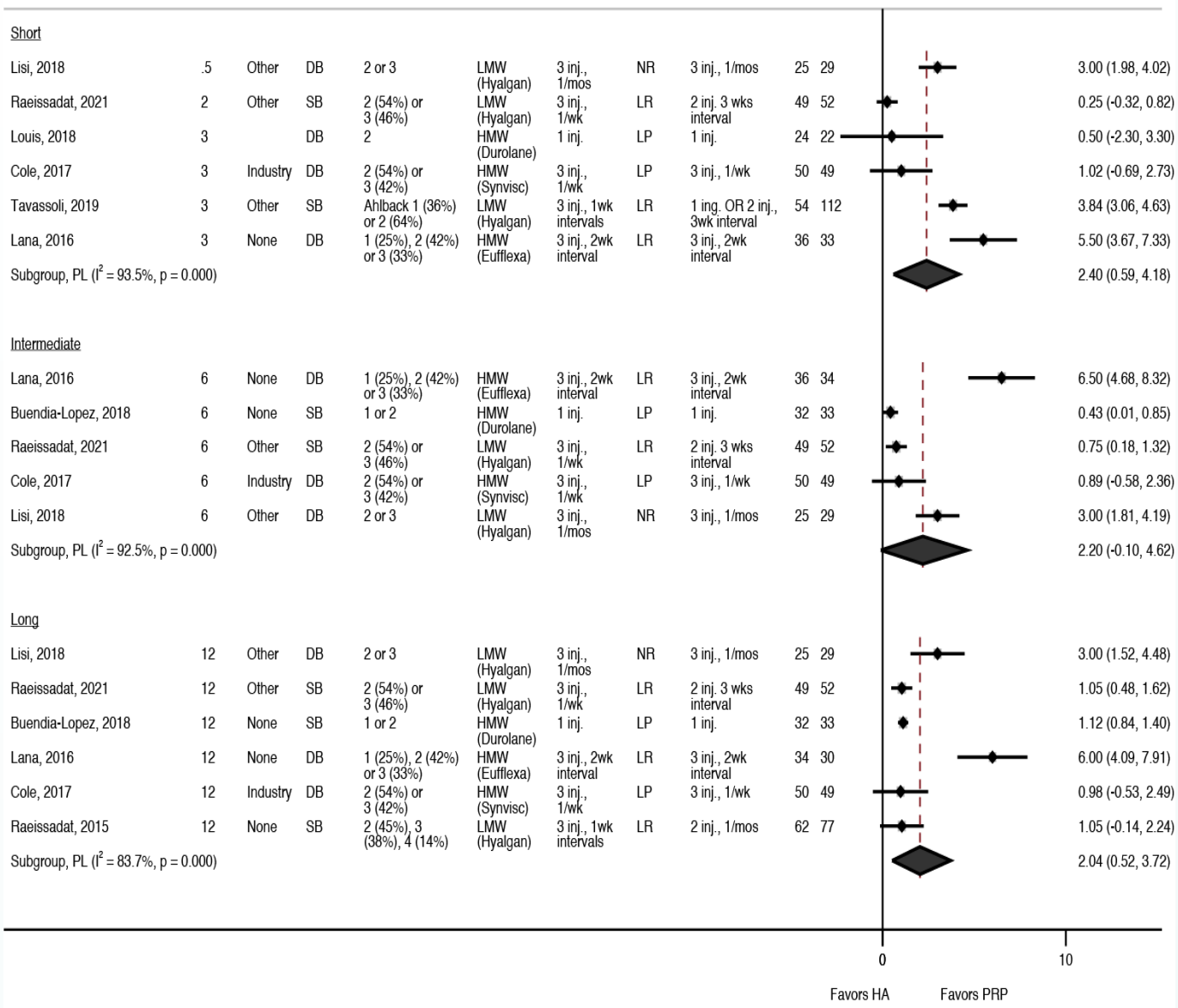
Pain success (response) was more common with PRP vs. HA

Aggregate Analytics

KQ 1a: HA vs. PRP – PAIN – Knee OA

WOMAC Pain (0-20 scale) - Scores

F/U and Author, Year	F/U (mos	Funding	Blinding	OA Grade (KL)	HA Categ. (Brand*)	HA Detail	PRP Categ.	PRP Detail	HA N	PRP N	MD F/U (95% CI)
Short											
Lisi, 2018	.5	Other	DB	2 or 3	LMW (Hyalgan)	3 inj., 1/mos	NR	3 inj., 1/mos	25	29	3.00 (1.98, 4.02)
Raeissadat, 2021	2	Other	SB	2 (54%) or 3 (46%)	LMW (Hyalgan)	3 inj., 1/wk	LR	2 inj. 3 wks interval	49	52	0.25 (-0.32, 0.82)
Louis, 2018	3		DB	2	HMW (Durolane)	1 inj.	LP	1 inj.	24	22	0.50 (-2.30, 3.30)
Cole, 2017	3	Industry	DB	2 (54%) or 3 (42%)	HMW (Synvisc)	3 inj., 1/wk	LP	3 inj., 1/wk	50	49	1.02 (-0.69, 2.73)
Tavassoli, 2019	3	Other	SB	Ahlback 1 (36%) or 2 (64%)	LMW (Hyalgan)	3 inj., 1wk intervals	LR	1 inj. OR 2 inj., 3wk interval	54	112	3.84 (3.06, 4.63)
Lana, 2016	3	None	DB	1 (25%), 2 (42%) or 3 (33%)	HMW (Eufflexa)	3 inj., 2wk interval	LR	3 inj., 2wk interval	36	33	5.50 (3.67, 7.33)
Subgroup, PL (I^2 = 93.5%, p = 0.000)											2.40 (0.59, 4.18)
Intermediate											
Lana, 2016	6	None	DB	1 (25%), 2 (42%) or 3 (33%)	HMW (Eufflexa)	3 inj., 2wk interval	LR	3 inj., 2wk interval	36	34	6.50 (4.68, 8.32)
Buendia-Lopez, 2018	6	None	SB	1 or 2	HMW (Durolane)	1 inj.	LP	1 inj.	32	33	0.43 (0.01, 0.85)
Raeissadat, 2021	6	Other	SB	2 (54%) or 3 (46%)	LMW (Hyalgan)	3 inj., 1/wk	LR	2 inj. 3 wks interval	49	52	0.75 (0.18, 1.32)
Cole, 2017	6	Industry	DB	2 (54%) or 3 (42%)	HMW (Synvisc)	3 inj., 1/wk	LP	3 inj., 1/wk	50	49	0.89 (-0.58, 2.36)
Lisi, 2018	6	Other	DB	2 or 3	LMW (Hyalgan)	3 inj., 1/mos	NR	3 inj., 1/mos	25	29	3.00 (1.81, 4.19)
Subgroup, PL (I^2 = 92.5%, p = 0.000)											2.20 (-0.10, 4.62)
Long											
Lisi, 2018	12	Other	DB	2 or 3	LMW (Hyalgan)	3 inj., 1/mos	NR	3 inj., 1/mos	25	29	3.00 (1.52, 4.48)
Raeissadat, 2021	12	Other	SB	2 (54%) or 3 (46%)	LMW (Hyalgan)	3 inj., 1/wk	LR	2 inj. 3 wks interval	49	52	1.05 (0.48, 1.62)
Buendia-Lopez, 2018	12	None	SB	1 or 2	HMW (Durolane)	1 inj.	LP	1 inj.	32	33	1.12 (0.84, 1.40)
Lana, 2016	12	None	DB	1 (25%), 2 (42%) or 3 (33%)	HMW (Eufflexa)	3 inj., 2wk interval	LR	3 inj., 2wk interval	34	30	6.00 (4.09, 7.91)
Cole, 2017	12	Industry	DB	2 (54%) or 3 (42%)	HMW (Synvisc)	3 inj., 1/wk	LP	3 inj., 1/wk	50	49	0.98 (-0.53, 2.49)
Raeissadat, 2015	12	None	SB	2 (45%), 3 (38%), 4 (14%)	LMW (Hyalgan)	3 inj., 1wk intervals	LR	2 inj., 1/mos	62	77	1.05 (-0.14, 2.24)
Subgroup, PL (I^2 = 83.7%, p = 0.000)											2.04 (0.52, 3.72)



Short term

No difference (LOW)

5 RCTs, N=480

MD 1.87 95% CI 0.16 to 3.45, I^2=93.4%) (excluding outlier)

Intermediate

Small improvement with PRP (LOW)

4 RCTs, N=319

MD 1.16, 95% CI -0.01 to 2.47, I^2= 81.3 [excludes extreme outlier

Long Term

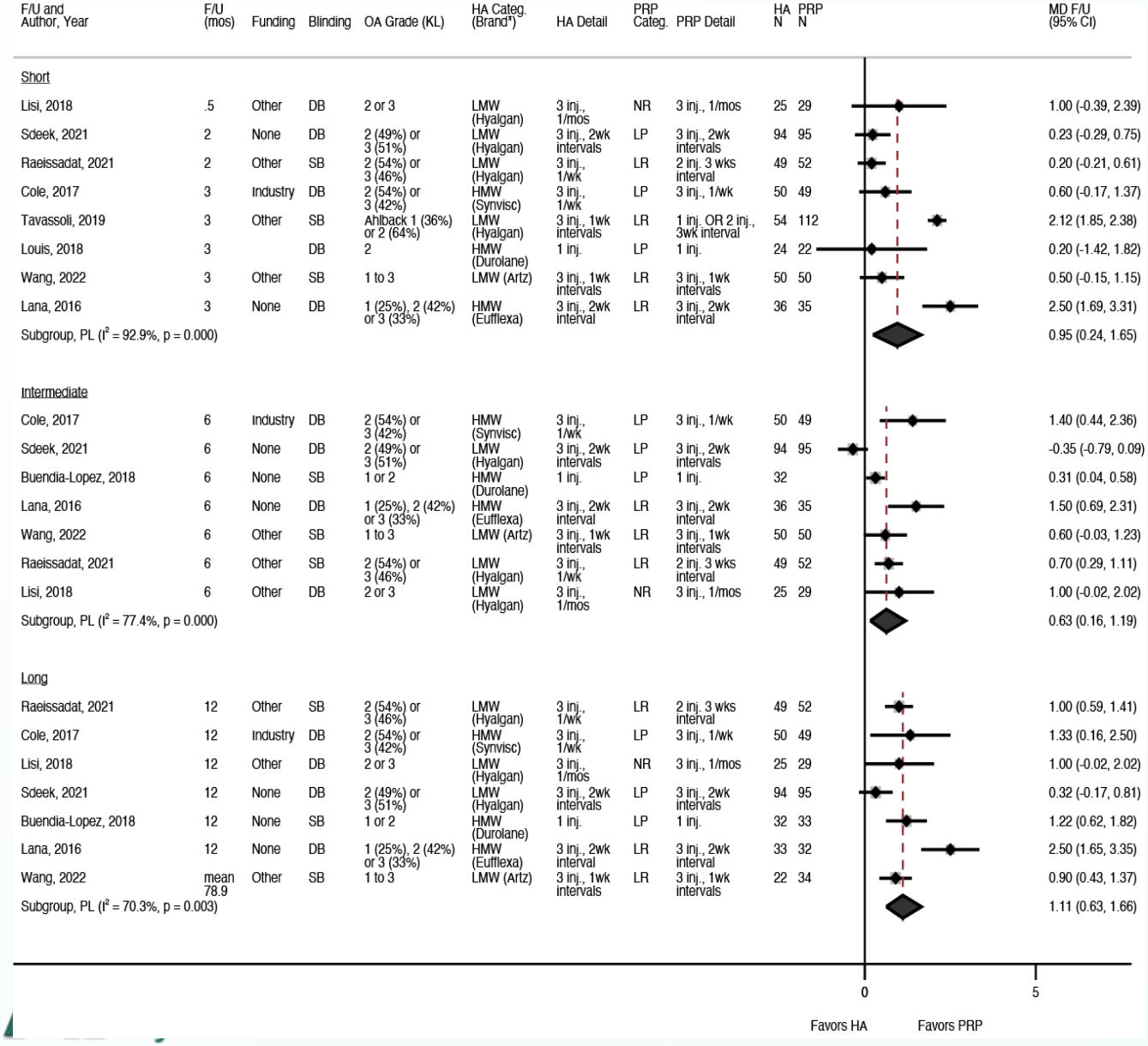
Small improvement with PRP (LOW)

5 RCTs, N=458

MD 1.15, 95% CI 0.90 to 1.57, I^2=36.2%) excludes outlier

KQ 1a: HA vs. PRP – PAIN – Knee OA

VAS Pain (0-10 scale) - Scores



Short term

No difference (LOW)

6 RCTs, N=589

MD 0.33, 95% CI 0.07 to 0.63,

I^2= 0% (excluding 2 outlier)

Intermediate

Small improvement with PRP (LOW)

6 RCTs, N=608

MD 0.49, 95 % CI 0.04 to 1.04 [excludes Lana]

Long Term

Small improvement with PRP (LOW)

6 RCTs, N=564

0.88, 95% CI 0.57 to 1.24

I^2=29.9%) excludes outlier

Patient, Intervention Characteristics: HA vs. Steroids – Knee OA

(See Appendix G – Tables)

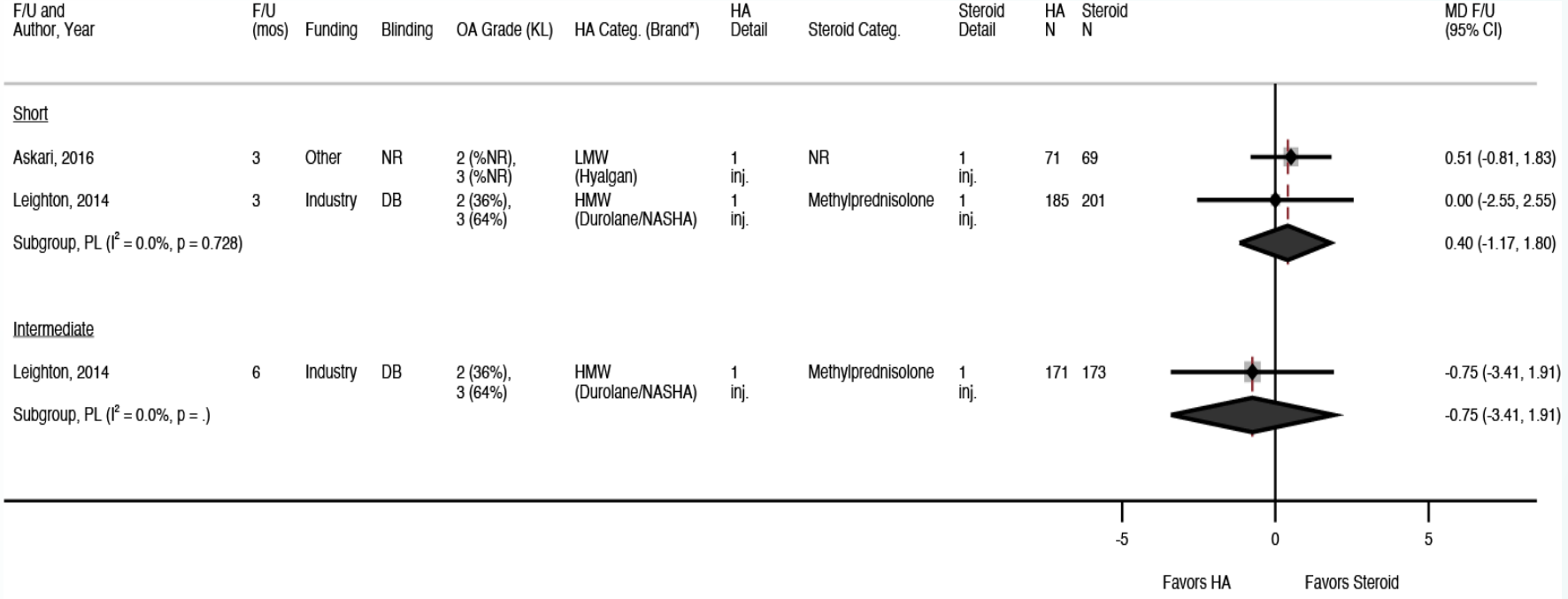
6 RCTs, (N= 1044); Industry funded (N=1), NR (N=3), non-industry (N=2)

- Mean age: 62.5 years (57.8 to 70); Female 64% (49% to 85%)
- **OA severity (various measures)**
  - Kellgren-Lawrence Grade:
    - 3 RCTs: Grade 2, 35% (22 to 49%); Grade 3, 55.8 %(41.4 % to 64%)
    - 1 RCT: Grade 2 or 3; 1 RCT not reported
    - 1 RCT: Grade 1 (22%) and Grade 4 (14%)
- Mean symptom duration 4.8 years (1 RCT); inclusion symptoms >3 months (1 RCT)
- **HA Injections**
  - Injections: Single (5 RCTs), 2 injections (1 RCT) with week interval between
  - High MW (4 RCTs, 6000 to 90,000 kDa), Low MW (2 RCTs, 500 to 730 kDa)
  - Doses ranged 48mg to 60mg per injection
- **Steroid injections:**
  - Injections: Single (5 RCTs), 2 injections (1 RCT) with week interval between
  - Methylprednisolone (1 RCT), triamcinolone acetonide (2 RCTs), triamcinolone hexa-acetate (1 RCT), not reported (1 RCT)
  - Doses: 20mg to 40mg per injection

KQ 1a: HA vs. Steroid – FUNCTION – Knee OA

Outcome	Time	Studies	HA vs. Steroid Effect estimate (95% CI)	Quality (SoE)
Function: WOMAC physical function scores and KOOS ADL and KSS function	Short term (3 mos.)	**WOMAC, KOOS** 1 RCT (N= 140) **KSS function** 2 RCTs N-160)	**WOMAC Physical Function** MD 0.25 (-3.69 to 4.19) **KOOS ADL** MD 0.37 (-5.42 to 6.61) **KSS** Pooled MD-2.63 (-17.4 to 12.40), I^2=61.6% **Conclusion**: No difference between HA and steroid based on the good quality RCT (WOMAC, KOOS), pooled KSS analyses across 2 poor quality RCTs	⊕⊕◯◯ LOW ROB, unknown consistency imprecision
KSS Function	Intermediate (6 months)	**KSS function** 2 RCTs N-160)	Pooled MD -6.63 (-22.6 to 9.73), I^2=67.1% Conclusion: No difference between HA and steroid	⊕◯◯◯ INSUFFICIENT ROB -2 unknown consistency imprecision

KQ 1a: HA vs. PRP – Knee OA
WOMAC Pain scores (0-20 scale)



F/U and Author, Year	F/U (mos)	Funding	Blinding	OA Grade (KL)	HA Categ. (Brand*)	HA Detail	Steroid Categ.	Steroid Detail	HA N	Steroid N	MD F/U (95% CI)
Short											
Askari, 2016	3	Other	NR	2 (%NR), 3 (%NR)	LMW (Hyalgan)	1 inj.	NR	1 inj.	71	69	0.51 (-0.81, 1.83)
Leighton, 2014	3	Industry	DB	2 (36%), 3 (64%)	HMW (Durolane/NASHA)	1 inj.	Methylprednisolone	1 inj.	185	201	0.00 (-2.55, 2.55)
Subgroup, PL (I^2 = 0.0%, p = 0.728)											0.40 (-1.17, 1.80)
Intermediate											
Leighton, 2014	6	Industry	DB	2 (36%), 3 (64%)	HMW (Durolane/NASHA)	1 inj.	Methylprednisolone	1 inj.	171	173	-0.75 (-3.41, 1.91)
Subgroup, PL (I^2 = 0.0%, p = .)											-0.75 (-3.41, 1.91)

Short-term: No difference (SOE MODERATE)

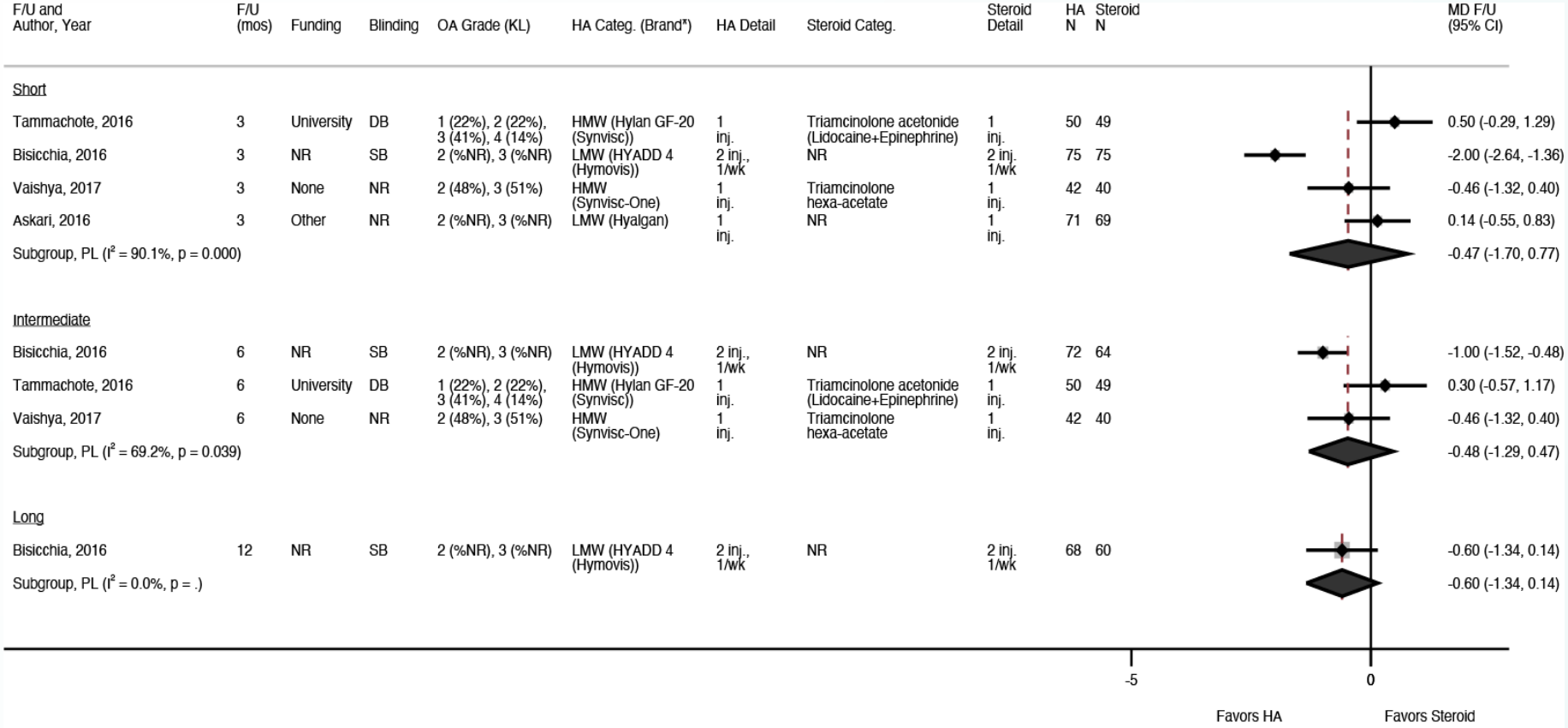
Intermediate term: No difference (SOE MODERATE)

Aggregate Analytics

KQ 1a: HA vs. Steroid – Knee OA

VAS Pain scores (0-10 scale)

F/U and Author, Year	F/U (mos)	Funding	Blinding	OA Grade (KL)	HA Categ. (Brand*)	HA Detail	Steroid Categ.	Steroid Detail	HA N	Steroid N	MD F/U (95% CI)
Short											
Tammachote, 2016	3	University	DB	1 (22%), 2 (22%), 3 (41%), 4 (14%)	HMW (Hylan GF-20 (Synvisc))	1 inj.	Triamcinolone acetonide (Lidocaine+Epinephrine)	1 inj.	50	49	0.50 (-0.29, 1.29)
Bisicchia, 2016	3	NR	SB	2 (%NR), 3 (%NR)	LMW (HYADD 4 (Hymovis))	2 inj., 1/wk	NR	2 inj. 1/wk	75	75	-2.00 (-2.64, -1.36)
Vaishya, 2017	3	None	NR	2 (48%), 3 (51%)	HMW (Synvisc-One)	1 inj.	Triamcinolone hexa-acetate	1 inj.	42	40	-0.46 (-1.32, 0.40)
Askari, 2016	3	Other	NR	2 (%NR), 3 (%NR)	LMW (Hyalgan)	1 inj.	NR	1 inj.	71	69	0.14 (-0.55, 0.83)
Subgroup, PL (I^2 = 90.1%, p = 0.000)											-0.47 (-1.70, 0.77)
Intermediate											
Bisicchia, 2016	6	NR	SB	2 (%NR), 3 (%NR)	LMW (HYADD 4 (Hymovis))	2 inj., 1/wk	NR	2 inj. 1/wk	72	64	-1.00 (-1.52, -0.48)
Tammachote, 2016	6	University	DB	1 (22%), 2 (22%), 3 (41%), 4 (14%)	HMW (Hylan GF-20 (Synvisc))	1 inj.	Triamcinolone acetonide (Lidocaine+Epinephrine)	1 inj.	50	49	0.30 (-0.57, 1.17)
Vaishya, 2017	6	None	NR	2 (48%), 3 (51%)	HMW (Synvisc-One)	1 inj.	Triamcinolone hexa-acetate	1 inj.	42	40	-0.46 (-1.32, 0.40)
Subgroup, PL (I^2 = 69.2%, p = 0.039)											-0.48 (-1.29, 0.47)
Long											
Bisicchia, 2016	12	NR	SB	2 (%NR), 3 (%NR)	LMW (HYADD 4 (Hymovis))	2 inj., 1/wk	NR	2 inj. 1/wk	68	60	-0.60 (-1.34, 0.14)
Subgroup, PL (I^2 = 0.0%, p = .)											-0.60 (-1.34, 0.14)



Short-term: No difference (SOE MODERATE)

Intermediate-term: No difference (SOE MODERATE)

Long-term: INSUFFICIENT

Aggregate Analytics

Patient and Intervention Characteristics: HA vs. NSAIDs – Knee OA

(See Appendix G – Tables)

2 RCTs, N=131, funding NR, both fair quality

- Mean age: 59.3 years old (57 to 61.9); Female: 68.5% (52.3% to 86.4%)

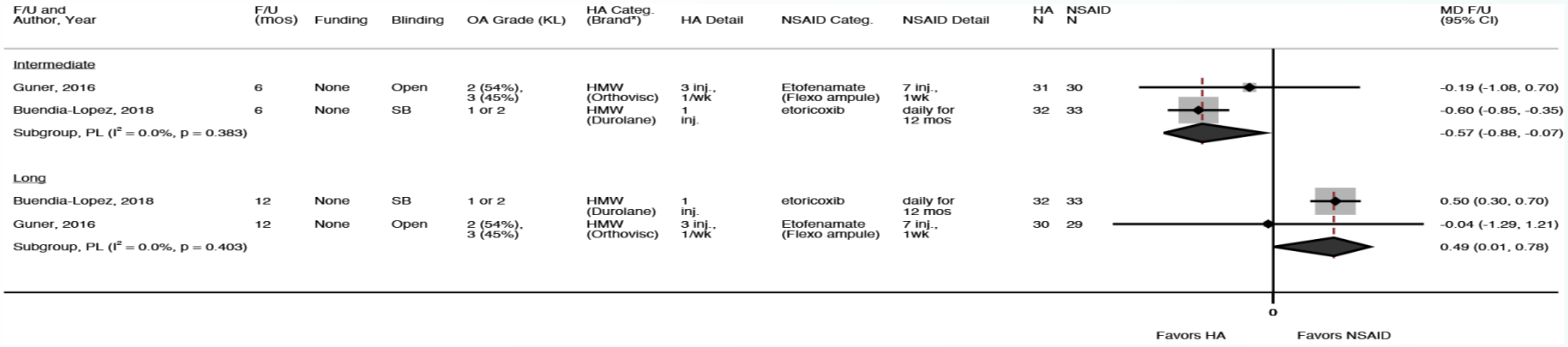
- Interventions differed substantially
  - 1 RCT (N=65): Kellgren-Lawrence Grades 1 (54%) and 2(46%) only
    - HA: single injection (60 mg, 2ml), high MW (100,000kDa)
    - NSAID: Oral etoricoxib (60 mg daily for 52 weeks)

  - 1 RCT (N=59): Kellgren-Lawrence Grade 2 (54%) and Grade 3 (46%)
    - HA: 3 injections high MW (1,000-2,900kDa), 1/week for 3 weeks
    - NSAID: IM etofenamate (100mg/2mL); 7 injections over 7 days

KQ 1a: HA vs. Oral NSAID – Knee OA

Function				
WOMAC PF success; ≥20% decrease in score	6 months 12 Months	1 RCT (N=66) HA vs. oral NSAID	**6 months** 15.7% vs. 12.2% RR 1.29 (0.38, 4.37) **12 months 0% vs. 0 %** **Conclusion**: No difference at either time	⊕⊕◯◯ LOW
WOMAC Physical Function Scores (0=68)	6 months 12 Months		**6 months** MD -4.07 (-4.48, -3.66) **Conclusion: Small improvement with HA versus oral NSAID** **12 months** MD -0.13 (-0.48, 0.22) **Conclusion:** No difference	⊕⊕◯◯ LOW
Pain				
Pain Success ≥20% decrease in score **WOMAC** **VAS**	6 months	1 RCT (N=65) HA vs. oral NSAID	**WOMAC** 21.5% vs.15.2%; RR 1.44 (0.51, 4.08) **VAS** 25% vs. 18.2%; RR 1.38 (0.54, 3.52) **Conclusion**: No difference	⊕⊕◯◯ LOW
	12 Months		**WOMAC** 0% vs. 0 % **VAS** 0% vs.6% RR 0.26 (0.01, 5.50) **Conclusion** No difference	⊕⊕◯◯ LOW
WOMAC Pain scores (0-20)	6 months	1 RCT (N=65) HA vs. oral NSAID	MD -4.07, 95% CI -4.48 to -3.66 **Conclusion**: **Moderate pain improvement with HA vs**. NSAID	⊕⊕◯◯ LOW
	12 Months		MD -0.13 (-0.48, 0.22) **Conclusion**: No difference	⊕⊕◯◯ LOW

KQ 1a: HA vs. Oral NSAID or IM NSAID – VAS Pain – Knee OA



Time	HA vs. NSAID, Effect estimate (95% CI); Conclusion	Quality (SoE)
6 months	**Pooled MD** -0.57, 95% CI -0.88 to -0.07, I^2=0% **Guner,** IM etofenamate: MD -0.19, 95%CI -1.08 to 0.07 **Buendia-Lopez,** Oral etroicoxib: MD -0.60, 95% CI -0.85 to -0.35) **Conclusion**: Small improvement in pain **favoring HA vs. oral NSAID** in pooled analysis and for RCT of HA vs. oral NSAID No difference in RCT of HA vs. IM etofenamate	⊕⊕◯◯ LOW
12 Months	**Pooled** MD 0.49, 95% CI 0.01 to 0.78 **Guner**: MD -0.04 (95% CI -1.29 to 1.21 **Buendia-Lopez**: 0.50 (95% CI 0.30 to 0.70) **Conclusion:** Small improvement in pain **favoring oral NSAID** vs. HA No difference between HA vs. IM etofenamate in the other RCT or in pooled analysis	⊕⊕◯◯ LOW

Patient, Intervention Characteristics: HA vs. other comparators and HA with at least Low SOE – Knee OA

(See Appendix – data abstraction tables)

1 fair-quality RCT, no funding, 3 arms relevant treatment arms

- Patients were 65 to 70 years, mostly female, pain duration 70-75 months
- HA vs. PT (N=55)
  - HA: Hyalgan (500-730 kDa), 2 ml, three injections, 1 week apart
  - PT: 20 minutes superficial heat pack; TENS and pulsed ultrasound
- HA vs. dextrose prolotherapy
  - HA: Hyalgan (500-730 kDa), 2 ml, three injections, 1 week apart
  - Prolotherapy: 8 ml, 20% dextrose plus 2 ml 2% lidocaine, 3 injections total, one month apart.

1 fair-quality RCT, industry funding

- Patients: 60 years, 77% female, mild to moderate knee OA
- Animal-derived HA (Artz®; molecular weight 620-1,170 kDa); 4 doses
- Nonanimal HA (Durolane®; molecular weight 100,00 kDa); 1 dose, 3 sham

KQ 1a: HA vs. PT – knee OA

Outcome	Studies	HA vs. PT Effect estimate, Conclusion	Quality (SoE)
Function			
KOOS ADL (0-100)	1 RCT (N=55) Rezasoltani, 2020	Means (SD were NR): 36.5 vs. 42.7; MD 6.2 (-0.81, 13.21) **Conclusion**: No difference	⊕⊕◯◯ LOW
KOOS Sport & Recreation (0-100)		Means (SD were NR) 12.0 vs. 17.3 MD 5.3 (4.32, 6.28) **Conclusion**: A small improvement in this measure favoring PT over HA	⊕⊕◯◯ LOW
Pain			
VAS Pain scores (0-10)	1 RCT (N=55) Rezasoltani, 2020	Means (SD were NR) 5.75 vs. 3.9 MD 1.85 (1.36, 2.34) **Conclusion**: A moderate pain improvement with PT vs HA	⊕⊕◯◯ LOW
KOOS Pain (0-100 (best))		Means (SD were NR) 22.3 vs. 30.5 MD 8.2 (5.10, 11.30) **Conclusion:** A small pain improvement with PT vs HA	⊕⊕◯◯ LOW

- Effect depends on which measure is used
- Short term (3 months) data only

Aggregate Analytics

KQ 1a: HA vs. Prolotherapy – knee OA

Outcome	Studies	HA vs. Prolotherapy Effect estimate (95% CI); Conclusion	Quality (SoE)
Function			
KOOS ADL (0-100 scale)	1 RCT (N=55) Rezasoltani, 2020	Means (SD were NR) 35.6 vs. 61.8 MD 25.3 (17.98, 32.62) **Conclusion**: Large **improvement favoring prolotherapy** over HA	⊕◯◯◯ INSUFFICIENT
KOOS Sport and Recreation (0-100 scale)		Means (SD were NR) 12.0 vs. 17.7 MD 5.7 (4.67 to 6.73) **Conclusion**: Small **improvement favoring prolotherapy** over HA	⊕⊕◯◯ LOW
Pain			
KOOS Pain (0-100 (best))	1 RCT (N=55) Rezasoltani, 2020	Means (SD were NR) 22.3 vs. 33.1 MD 10.8 (4.67, 6.73) **Conclusion:** Small improvement **favoring prolotherapy over HA**	⊕⊕◯◯ LOW
VAS Pain scores (0-10)		Means (SD were NR) 5.75 vs. 2.5 MD 3.25 (2.70, 3.80) **Conclusion**: A large improvement favoring **prolotherapy over HA**	⊕⊕◯◯ LOW

- Prolotherapy improved pain and function over HA
- Effect size depends on measure is used
- Short term (3 months) data only

KQ 1a: HA (animal) vs. HA (non-animal) – knee OA
Per-protocol, repeated measures analyses

Outcome	Studies	HA (Artz) vs. HA (Durolane) Effect estimate (95% CI)	Quality (SoE)
WOMAC Physical Function (0-68) Scores	1 RCT (N=319) Zhang, 2015	**Difference in change scores** MD −0.58 (−1.69 to 0.53) **Conclusion**: No difference	⊕⊕◯◯ LOW
WOMAC Pain Success (NOS) **Scores** (0-20)		**Pain success:** 81.6% (129/158) 78.9% (127/161) OR 0.96 (0.65 to 1.41) **Difference in change scores** MD −0.10 (−0.56 to 0.37) **Conclusion**: No difference between HA products	⊕⊕◯◯ LOW
OMERACT-OARSI Responder		93.7% (148/158) vs. 93.8% (151/161) OR 1.12 (0.63 to 2.05) **Conclusion**: No difference between HA products	⊕⊕◯◯ LOW

- No differences in pain, function, OMERACT-OARSI response,(SOE Low)
- Intermediate term (6 months) data only; no ITT analyses

Key Question 1b: Safety of HA (Knee OA)

Aggregate Analytics

Safety of HA vs. Comparators – Knee OA

- Table 20: summarizes reported events for trials of HA versus various comparators and HA vs. HA
- Specific harms and AEs were poorly described across trials
- Heterogeneity in classification and descriptions
- AE reports included events that may not be treatment related
- It is unclear whether patients could have >1 event
- Serious and serious treatment related AEs appear to be rare in HA recipients; many studies likely to be underpowered
- SOE: Insufficient for serious AEs (HA vs. all comparators) and for serious treatment-related (HA vs. saline), pain and swelling (HA vs. steroid)
- SOE: Low for reported treatment-related, "other" AEs and swelling
- SOE Low: HA vs. HA: No differences in serious, treatment-related AEs

Aggregate Analytics

KQ 1b: Safety of HA vs. Saline – Knee OA

Adverse event	Study	Descriptions reported	HA % (n/N)	Control % (n/N)	RR (95% CI)
Serious Related AEs or Withdrawal INSUFFICIENT	Farr, Gomoll, 2021†	Knee stiffness and pain (pseudo-septic reaction)	1.55% (1/64)	0% (0/68)	-
	Gormeli, 2017	Unable to tolerate tx after first injection	4.3% (2/46)	4.4% (0/45)	
	Hangody Arden, Ke, Bao	NR; report serious related AE Ns range 40-438	0%	0%	
Serious AEs INSUFFICIENT	Hangody, 2018	Arthralgia, peripheral edema, rash	1.5% (2/135)	3.2% (2/63)	0.47 (0.07, 3.24)
	Strand 2012		3.2% (8/249)	0% (0/128)	
	Petterson, 2019	NR	4.3% (8/184)	2.7% (5/185)	1.61 (0.54, 4.83)
	GEL 200, SSED	NR	1.7% (7/404)	1.5% (6/410)	1.18 (0.40, 3.49)
	Bao, Ke, Gormeli	NR; report serious AE Ns range 40-438	0%	0%	-
Treatment-Related AEs (general, not serious) **LOW**	Arden, 2014	NR	**15.7% (17/108)**	**5.5% (6/110)**	**2.89 (1.18, 7.04)**
	Strand, 2012	NR	**26.9% (67/249)**	**25.8% (33/128)**	**1.04 (0.73, 1.49)**
	Strand, 2016*	NR	**12.0% (15/125)**	**13.2% (14/106)**	**0.91 (0.46, 1.79)**
	Hangody, 2018	NR	2.2% (3/135)	0% (0/63)	-
	Petterson, 2019	NR	7.1% (13/184)	5.4% (10/185)	1.31 (0.59, 2.91)
	Ke, 2021	NR	7.3% (16/218)	7.3% (16/220)	1.01 (0.52, 1.97)
	Farr, Gomoll, 2021	Knee stiffness and pain (pseudo-septic reaction	1.6% (1/64)	0% (0/68)	-
	GEL 200, SSED	Includes arthralgia, joint swelling, joint effusion	6.2% (25/404)	6.6% (27/410)	0.94 (0.56, 1.59)
	Gormeli, Bao	NR, Ns 91, 40	0%	0%	-

KQ 1b: Safety of HA vs. Saline – Knee OA

Adverse event	Study	Descriptions reported	HA % (n/N)	Control % (n/N)	RR (95% CI)
Other AEs **LOW**	Petterson, 2019	Includes joint stiffness	**49.5% (91/184)**	**54.1% (100/185)**	**0.91 (0.75, 1.11)**
	Ke, 2021	Pyrexia, axillary pain, chest discomfort, peripheral edema, chills, malaise, thirst	**41.7% (91/218)**	**48.6% (107/220)**	**0.86 (0.70, 1.06)**
	Arden, 2014	NR	**40.7% (44/108)**	**40% (44/110)**	**1.02 (0.74, 1.41)**
	GEL 200 SSED	Includes arthralgia, joint swelling, joint effusion	**37.9% (153/404)**	**40.0% (164/410)**	**0.95 (0.80, 1.12)**
	Strand, 2012	Includes joint stiffness	19.7% (49/249)	16.4% (21/128)	1.20 (0.75, 1.91)
	Strand, 2016*	Includes joint effusion, upper respiratory infection	17.6% (22/125)	21.7% (23/106)	0.81 (0.48, 1.37)
	Farr, Gomoll,	NR	1.6% (1/64)	0% (0/68)	-
Swelling **LOW**	Petterson, 2019	Includes arthralgia, joint swelling, joint stiffness; Others NR	1.1% (2/184)	0.5% (1/185)	2.01 (0.18, 21.99)
	Strand, 2012	NR	**14.1% (35/249)**	**11.7% (15/128)**	**1.20 (0.68, 2.11)**
	Strand, 2016	NR	**17.6% (22/125)**	**12.3% (13/106)**	**1.44 (0.76, 2.71)**
	Ke, 2021	NR	3.7% (8/218)	0.9% (2/220)	4.04 (0.87, 18.79)
Mild pain	Petterson, 2019	Arthralgia, joint swelling, joint stiffness; Others NR	3.8% (7/184)	3.8% (7/185)	1.01 (0.36, 2.81)
	Strand, 2012	NR	7.3% (19/249)	9.4% (12/128)	0.81 (0.41, 1.62)
	Strand, 2016	NR	7.2% (9/125)	9.4% (10/106)	0.76 (0.32, 1.81)
	Ke, 2021	NR	8.7% (19/218)	7.7% (17/220)	1.13 (0.60, 2.11)

KQ 1b: Safety of HA vs. Other Comparators – Knee OA

Adverse event	Study	Descriptions reported	Comparison	HA % (n/N)	Control % (n/N)	RR (95% CI)
Serious AEs (any) **INSUFFICIENT**	Leighton, 2014	NR	HA vs. Steroid	4.1% (9/221)	2.7% (6/221)	1.50 (0.54, 4.14)
	Vaishya, Tammachote Campos	NR. No events Ns, 99 & 82, 103 knees	HA vs. Steroid	0%	0%	-
	Guner, 2016	NR, N=59	HA vs. NSAID	0%	0%	-
Treatment-Related AEs LOW	Leighton, 2014	NR	**HA vs. Steroid**	**21.7% (48/221)**	**6.8% (15/221)**	**3.20 (1.85, 5.54)**
	Hermans, 2019	Knee flare, GI, other	**HA vs. UC**	**45.0% (35/77)**	**18% (14/79)**	**2.56 (1.50, 4.38)**
Other AEs **LOW (steroid, UC)** **INSUFFICIENT (NSAID)**	Leighton, 2014	NR	HA vs. Steroid	54.3% (120/221)	64.3% (142/221)	0.85 (0.72, 0.99)
	Bissichia, 2016	heaviness, pruritus	HA vs. Steroid	6.6% (5/75)	5.3% (4/75)	1.25 (0.35, 4.47)
	Vaishya, 2018	NR	HA vs. Steroid	2.4% (1/42)	2.5% (1/40)	0.95 (0.06, 14.72)
	Hermans, 2019	Various, not tx related	HA vs. Usual care	9.1% (7/77)	7.6% (6/79)	1.20 (0.42, 3.40)
	Guner, 2016	NR	HA vs. NSAID	0% (0/30)	0% (0/29)	-
Swelling, Pain INSUFFICIENT	Leighton, 2014	NR (swelling)	HA vs. Steroid	2.3% (5/221)	0.5% (1/221)	
	Tammachote, 2016	knee pain & swelling	HA vs. Steroid	2.0% (1/50)	0% (0/49)	-
Mild pain	Leighton, 2014	NR	HA vs. Steroid	17.2% (38/221)	3.2% (7/221)	5.43 (2.48, 11.89)
	Bissichia, 2016	Injection site discomfort, erythema, or pain; arthralgia, sensation of heaviness, pruritus	HA vs. Steroid	2.7% (2/75)	2.7% (2/75)	1.00 (0.14, 6.91)

KQ 1b: Safety of HA vs. Other Comparators – Knee OA

Adverse event	Study	Descriptions reported	HA % (n/N)	Control % (n/N)	RR (95% CI)
HA vs. PRP					
Withdrawal **INSUFFICIENT**	Gormeli, 2017	Unable to tolerate treatment after first injection	4.3% (2/46)	4.3% (2/46)	1.00 (0.15, 6.80)
	Buendia-Lopez, 2019	Withdrawal: Pain and swelling	6.3% (2/32)	0% (0/33)	-
Serious Related AE **INSUFFICIENT**	Tavasoli, Sdeek	No descriptions. No events N range 58-189	0%	0%	-
Serious AEs	Louis, 2018	HA and PRP (1 each): Post-traumatic knee sprain, HA: amygdalotomy	8.3% (2/24)	4.2% (1/24)	2.0 (0.19 to 20.6)
Other AEs	Wang 2022 (poor)	Infection, poor healing, or neurological lesion	0% (0/43)	0% (042)	-
HA (animal derived) vs. HA (non-animal derived)			**Per protocol analyses**		
Serious AEs **LOW**	Zhang, 2015	Severe AEs (NR, tx related unclear)	4.6% (8/174)	3.4% (6/175)	1.34 (0.48, 3.78)
		Serious AEs (NR, none treatment related)	3.4% (6/174)	1.7% (3/175)	2.01 (0.51, 7.9)
Treatment-Related AEs **LOW**		NR Any treatment related, may include severe/serious AEs	**9.8% (17/174)**	**13.1% (23/175)**	**0.74 (0.41, 1.34)**
Other AEs **LOW**		Pts with ≥1 treatment-emergent AE, (NOS)	**42.5% (74/174)**	**47.4% (83/175)**	**0.90 (0.71, 1.13)**

Key Questions 1a and 1b: Effectiveness and Safety of HA (Hip OA)

Aggregate Analytics

KQ 1: HA for *Hip* OA

Comparisons	RCTs (publications)	Funding : No. RCTs (Publications)			
		Industry	Other*	None	NR
HIP OA					
HA/Viscosupplementation					
HA vs. Placebo (Saline)	2[23,102]	1[23]	1[102]	---	---
HA vs. PRP	1[145]	---	1[145]	---	---
HA vs. Corticosteroid	1[102]	---	1[102]	---	---
TOTAL: HIP OA	3[23,102,145]	1[23]	2[102,145]	---	---

Aggregate Analytics

Intervention Characteristics: Hip OA – HA vs. Placebo, Steroid and PRP

(See Appendix G– data abstraction tables)

3 fair-quality RCTs, non-industry funding

- HA vs. Placebo(saline), 2 RCTs (N= 426)
  - HA: Single, 6ml injection (1 RCT); 3, 2 ml injections (1 RCT)
  - Placebo (saline): Single, 6ml injection (1 RCT); 3 injections (1 RCT);
- HA vs. Steroid (1 RCT which also compared HA vs. saline)
  - HA: 3, 2 ml injections
  - Depomedrol: single, 1 ml injection
- HA vs. PRP (1 RCT, N=74)
  - HA: Single, 6ml injection
  - PRP: Single injection; platelet count $58{,}6216 \pm 15{,}3208 \times 10^3$

KQ 1a: HA vs. Placebo (saline) – Hip OA

Outcome	Time	Studies	HA vs. Placebo Effect estimate (95% CI); Conclusion	Quality (SoE)
Function: **WOMAC physical function (PF) scores** (0-68) **or** **Lequesne** (1-24 scale)	3 mos	**WOMAC PF** 1 RCT (N=357) **Lequesne** 1 RCT (N=69)	**WOMAC PF,** MD (change scores) -0.34 (-0.17 to 0.85) **Lequesne,** MD -0.2 (-1.73 to 1.33) **Conclusion:** No difference	⊕⊕◯◯ LOW
	6 mos.	**WOMAC** 1 RCT (N=357)	**WOMAC,** MD (change scores) 0.05 (-0.53 to 0.63) **Conclusion**: No difference	⊕⊕◯◯ LOW
WOMAC Pain (walking) ≥2 point decrease in 0-10 NRS)	3 mos.	**WOMAC** 1 RCT (N=357)	46.7% vs. 50.29%; OR 0.78 (0.49 to 1.23) **Conclusion**: No difference	⊕⊕◯◯ LOW
	6 mos.		40.7% vs. 42.49%, OR 0.81 (0.49 to 1.33) **Conclusion**: No difference	⊕⊕◯◯ LOW
Pain Scores **WOMAC (0-10 NRS)** **VAS (0-100 scale), walking**	3 mos.	**WOMAC Pain** 1 RCT (N=357) **VAS Pain** 1 RCT (N=69)	**WOMAC Pain (0-10 NRS)** MD (change scores) 0.32 (-0.19 to 0.83) **VAS Pain (0-100)** MD (graph estimate): -2.0 (-13.43 to 9.43) SMD (author report): 0.4 (-0.1 to 0.9) **Conclusion**: No difference between	⊕⊕◯◯ LOW
	6 mos.	**WOMAC Pain** 1 RCT (N=357)	**WOMAC (0-10 NRS)** MD (change scores): 0.06 (-0.52 to 0.65) **Conclusion**: No difference between HA and placebo	⊕⊕◯◯ LOW

No differences in function or pain (Low SOE)

Arthroplasty reported in 0% (0/38) vs. 2.8% (1/36) of patients (INSUFFICIENT)

KQ 1b: HA vs. Placebo (saline) – Hip OA
Adverse events – any time

Outcome	Studies	HA vs. Placebo Effect estimate (95% CI); Conclusion	Quality (SoE)
Serious adverse events (SAE) (Not defined)	1 RCT (N=357)	5.6% (10/182) vs. 8.7% (15/172) RR 0.63, 95% CI 0.29 to 1.3 **Conclusion**: No difference One event considered (arthralgia in the saline group) treatment-related; poorly reported	⊕◯◯◯ INSUFFICIENT
Treatment-related AEs at target hip		12.8% vs. 8.7% RR 1.47, 95% CI 0.79 to 2.7 **Conclusion:** No difference	⊕⊕◯◯ LOW
Withdrawal due to an AE		5.5% vs. 5.7 **Conclusion:** No difference	⊕⊕◯◯ LOW

No differences in adverse events

KQ 1a and b: HA vs. Steroid – Hip OA

Outcome 3 months	Studies	HA vs. Steroids Effect estimate (95% CI)	Quality (SoE)
Function			
Lequesne (1-24 scale)	1 RCT (N= 68)	Mean (SD) graph estimates 8.9 (NR) vs. 8.9 (NR) Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
Pain, Procedures			
Pain Scores VAS (0-100 scale), walking	1 RCT (N= 68)	Mean (SD) graph estimates 36 (NR)vs. 36 (NR) Conclusion: No difference	⊕◯◯◯ INSUFFICIENT
Invasive procedures (arthroplasty)		0% vs. 3.1% Conclusion: No firm conclusions can be drawn; this appears to be a rare event.	⊕◯◯◯ INSUFFICIENT
Safety			
Serious treatment related adverse events		Authors state that no serious AEs occurred Report pain flare occurred in 3 patients but don't say for which treatment. Conclusion: No conclusions can be drawn;	⊕◯◯◯ INSUFFICIENT

Insufficient for all outcomes

Aggregate Analytics

KQ 1a and 1b: HA vs. PRP – Hip OA

Outcome	Time	Studies	HA vs. PRP Medians [Interquartile range]	Quality (SoE)
Function				
Function: WOMAC physical function scores (0-68 lower score)	1 month	1 RCT (N= 74)	21.5 [14.2-45.8] vs. 21 [16.7-36], p=0.480 Conclusion: No difference between HA and PRP	⊕⊕◯◯ LOW
	12 mos		28 [20.2-48.7] vs. 23.5 [13.7-58], p=0.260 Conclusion: No difference	⊕⊕◯◯ LOW
Pain				
Pain Scores **WOMAC (0-20)** **VAS (0-100 scale)**	1 month	1 RCT (N= 74)	**WOMAC:** 6 [2-10] vs. 5 [2-7.2], 0.470 **VAS:** 4.5 [2-7] vs. 4 [2-6], 0.570 Conclusion: No difference	⊕⊕◯◯ LOW
	12 mos		**WOMAC** 9.5 [3.75-15] vs. 7 [1.75-11], 0.190 **VAS** 6 [2.7-8] vs. 5 [1.7-7.3], 0.150 Conclusion: No difference	⊕⊕◯◯ LOW
Safety				
Serious treatment related AE	Anytime	1 RCT (N= 74)	Study only reports that no adverse events occurred.	⊕◯◯◯ INSUFFICIENT

Aggregate Analytics

No Difference in function or pain (SOE Low)

Evidence on safety is insufficient

KQ 1c: Differential effectiveness of HA

KQ 1c: Differential Effects of HA - *Knee* OA

- 1 fair-quality RCT **HA vs. PRP and vs. saline** from prior report
- OA stage *may* modify treatment (PRP patients with early OA better function, QOL than those with advanced OA); 6 months
  - MDs differ for the early and advanced OA groups; there is little or no overlap in the confidence intervals; No test for interaction reported
- Evidence is insufficient

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

KQ 1c: Differential Effects of HA – *Hip* OA

1 fair-quality RCT (N=101): **HA vs. saline placebo and steroid**

- No modification by Kellgren-Lawrence grade (1 or 2 vs. 3 or 4) or presence of intra-articular effusion for change in pain while walking
- All test for interaction were not significant; limited data provided
- Evidence is insufficient; study was likely underpowered

Aggregate Analytics

KQ 1d: Cost-effectiveness of HA (Knee and Hip OA)

KQ 1d: Cost effectiveness

- **4 US-based studies, 4 non-US studies (6 industry funded, 1 government (Dutch), 1 did not report funding**
  - 7 studies evaluated HA in Knee OA
  - 1 Study also evaluated HA in Hip OA
  - 1 Study compared HA with PRP
- Poor to fair(moderate) quality
- **SR compared HA with UC, placebo, NSAIDS (no funding)**
  - 9 studies, including 4 older studies described in 2013 review, 5 newer studies
  - ICERs ranged between €240 and €53,225 per QALY gained
  - States that conclusions regarding the cost-effectiveness of HA were difficult to assert given the substantial heterogeneity across studies
  - Notes that industry sponsored analyses found HA to be more favorable than academic studies.

Aggregate Analytics

KQ 1d: Cost effectiveness

4 US-based studies

- 3 poor to moderate quality studies: HA vs. conventional care – knee OA; Industry funded
  - Base Case ICER ranged from $4499/QALY to 38,471/QALY
  - Range from sensitivity analyses: $77,500/QALY to $124,000/QALY
  - All authors concluded that HA was cost-effective at WTP of $50,000/QALY
- 1 poor quality study: series of HA vs. PRP injections – knee OA
  - Base case ICER $12,628.15/QALY for PRP versus HA
  - Authors conclusion: PRP is not more cost-effective than HA, but PRP is more effective at 1 year
  - No detail of sensitivity analyses reported; funding source NR

4 Non-US-based studies; 1 government funded; 3 industry funded

- 4 poor to moderate quality studies: HA vs. conventional care
  - All concluded that HA was cost effective vs. conventional care for **knee** OA
  - One study concluded HA was cost effective vs. conventional care for **hip** OA
  - Applicability of these studies to US unclear

Aggregate Analytics

Key Question 2: PRP (Knee OA)

Aggregate Analytics

Key Question 2: PRP – Knee OA Results

Comparisons	No. RCTs	No. NRSI*	Funding : No. RCTs			
			Industry	Other*	None	NR
PRP vs. Placebo (Saline)	9	3	---	4	4	1
PRP vs. Corticosteroid	9	---	---	2	3	4
PRP vs. Analgesics	3	---	---	1	1	1
PRP vs. Exercise	3	1	---	1	---	2
PRP vs. Prolotherapy	2	---	---	---	1	1
PRP vs. PT	1	---	---	---	1	0
PRP (1 injection) vs. PRP (>1 injection)	6	---	---	3	2	1
PRP (LP) vs. PRP (LR)	2	---	---	2	---	---
TOTAL: PRP†	**34**	---	---	**13**	**10**	**11**

*Randomization was done to two knees within same patient; considered observational cohorts for purposes of this report

†Some RCTs contributed to more than one comparison

- **Hip OA: No trials identified evaluating PRP**

Aggregate Analytics

Key Question 2a: Effectiveness of PRP (Knee OA)

Aggregate Analytics

KQ 2a: PRP vs. Saline (Knee OA)

Patient and Intervention Characteristics

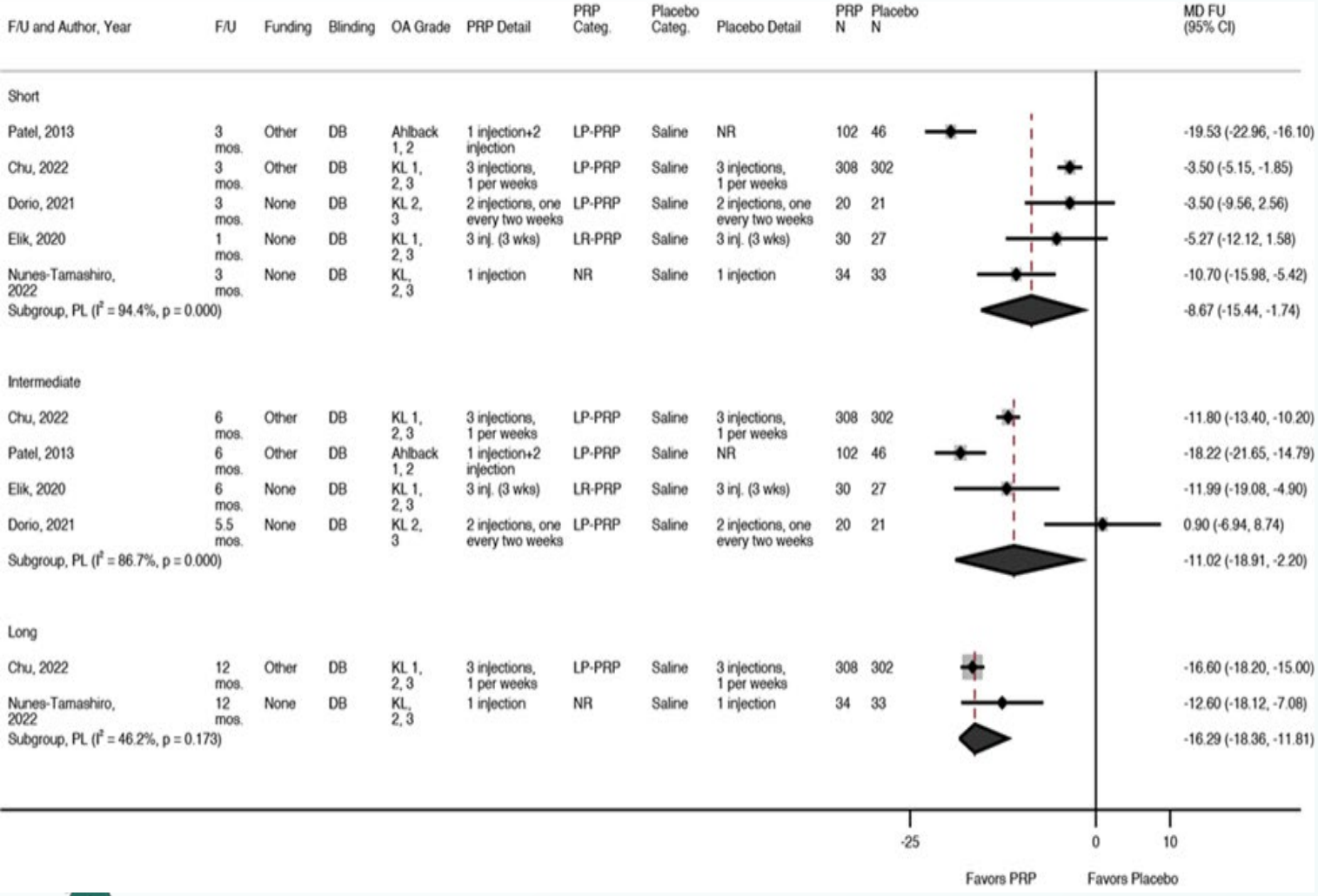
(See Appendix G – Tables G9a-G9e)

9 RCTs, N=1683 (range 33 to 644)

- Mean age: 57 years (52 to 68)
- Female: 58% (29% to 97%)
- OA Grade
  - Kellgren-Lawrence Grade 2-3 primarily (6 RCTs); Grade 1-2 (1 RCT), 33% Grade 4 (1 RCT)
  - Ahlback Grade 1-2 (1 RCT)
- Mean symptom duration 6.5 years (4.4 to 10.3) (4 RCTs)
- Bilateral (4 RCTs), Unilateral (2 RCTs), Both (2 RCTs), NR (1 RCT)
- PRP Injections
  - Injections: 1 (4 RCTs), 2 (2 RCTs), 3 (6 RCT); primarily weekly if multiple (2 weeks, 2 RCTs; 1 month, 1 RCT)
  - Platelet count varied; Leukocyte-poor (4 RCTs), Leukocyte-rich (4 RCTs), NR (1 RCT)
  - Volume primarily 5 mL per injection (range 4 to 8 mL)
  - Use of activating agent: calcium chloride (2 RCTs), none (3 RCTs), NR (4 RCTs)

KQ 2a: PRP vs. Saline – Function

WOMAC Physical Function (0-68)



Short term*
4 RCTs (N=775)
Pooled MD: -5.06 (-9.44, -1.78), I^2=55%
Small improvement (SOE: moderate)

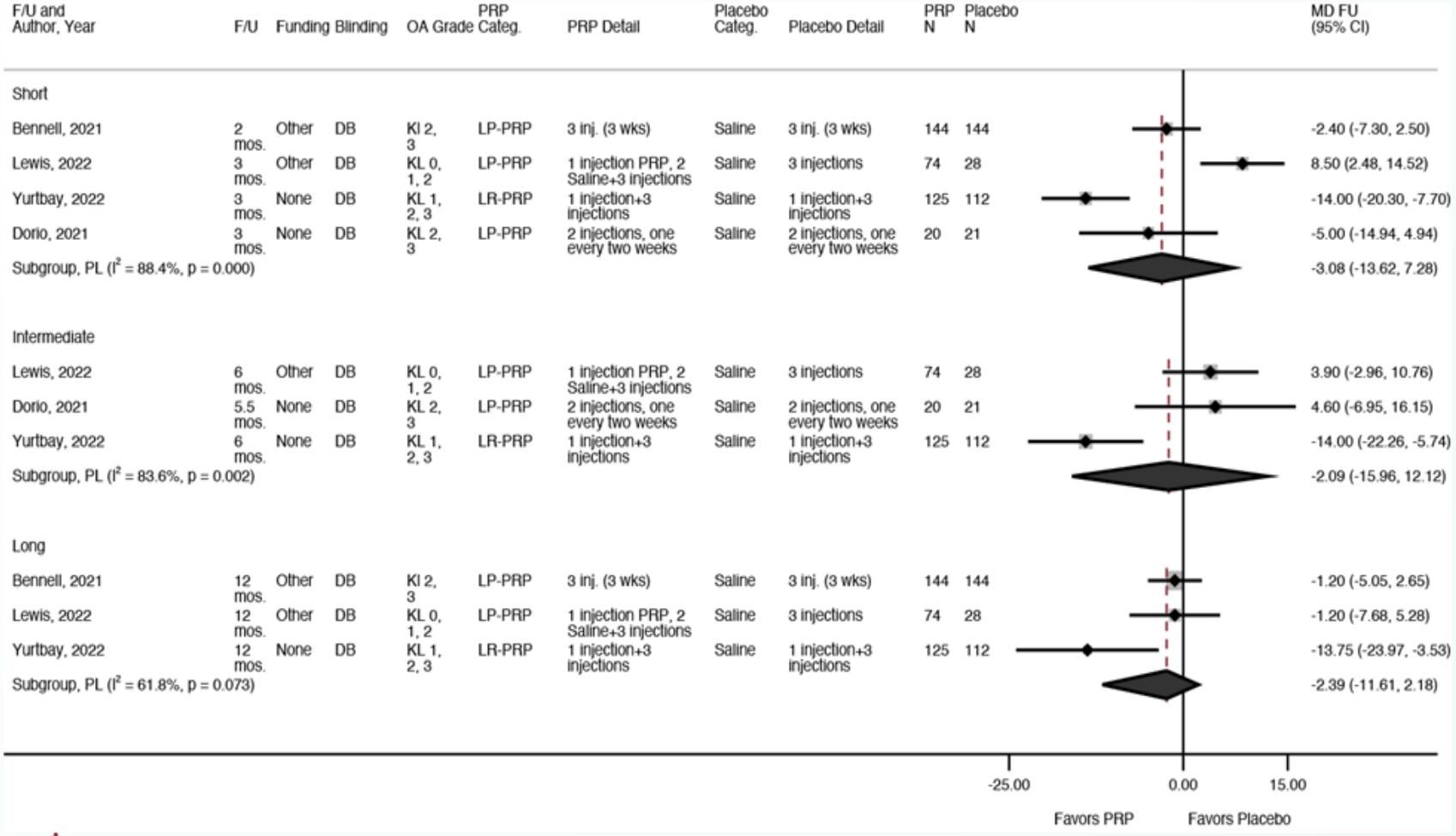
Intermediate term*
3 RCTs (N=815)
Pooled MD: -14.11 (-19.29, -8.92), I^2=82%
Mod. Improvement (SOE: low)

Long term
2 RCTs (N=677)
Large Improvement (SOE: low)

*excluding outlier trials

KQ 2a: PRP vs. Saline – Function, cont.

KOOS ADL (0-100)



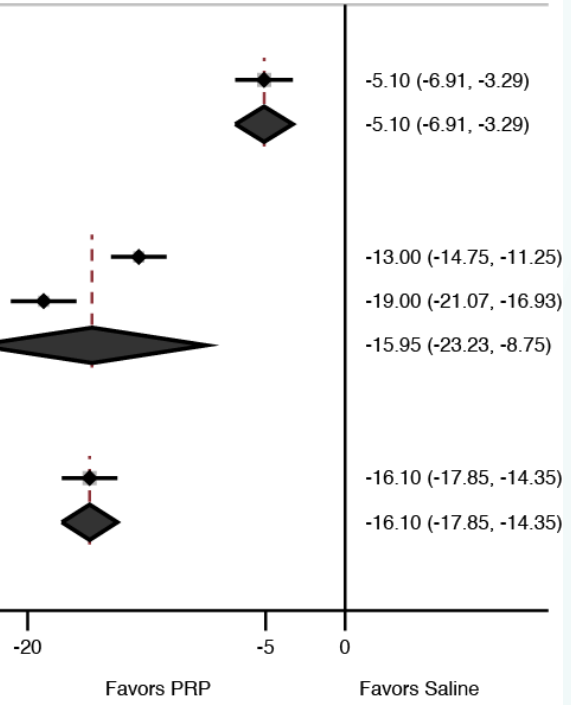
SOE: low (for all)

- Similar results for **KOOS Sport/Recreation** across same trials, see appendix slides

KQ 2a: PRP vs. Saline – Function, cont.

IKDC (0-100)

F/U and Author, Year	F/U (mos)	Funding*	Blinding	OA Grade (KL)	PRP Categ.	PRP Detail	Saline Detail	PRP N	Saline N	MD F/U (95% CI)
Short										
Chu, 2022	3	Other	DB	1, 2, 3	LP	3 inj., 1/wk	3 inj., 1/wk	308	302	-5.10 (-6.91, -3.29)
Subgroup, PL (I^2 = 0.0%, p = .)										-5.10 (-6.91, -3.29)
Intermediate										
Chu, 2022	6	Other	DB	1, 2, 3	LP	3 inj., 1/wk	3 inj., 1/wk	308	302	-13.00 (-14.75, -11.25)
Gormeli, 2017	6	NR	DB	1 or 2 (67%), 3 or 4 (33%)	LR	1 inj. + 2 saline inj., 1/wk+3 inj., 1/wk	3 inj., 1/wk	83	40	-19.00 (-21.07, -16.93)
Subgroup, PL (I^2 = 94.7%, p = 0.000)										-15.95 (-23.23, -8.75)
Long										
Chu, 2022	12	Other	DB	1, 2, 3	LP	3 inj., 1/wk	3 inj., 1/wk	308	302	-16.10 (-17.85, -14.35)
Subgroup, PL (I^2 = 0.0%, p = .)										-16.10 (-17.85, -14.35)



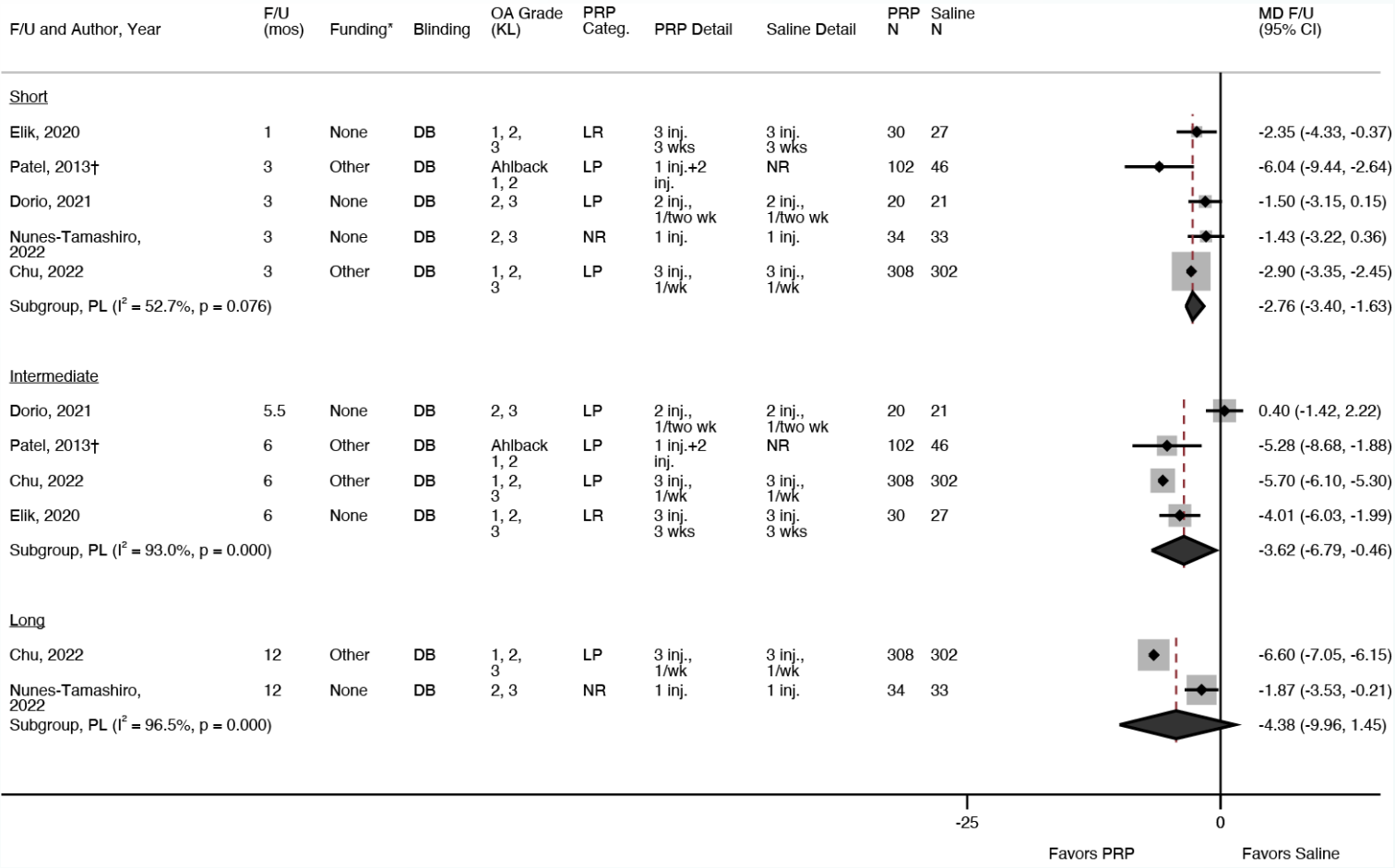
Short and long term: small and moderate improvement, respectively, with PRP (SOE: low); one large fair-quality RCT*

Intermediate term: Insufficient evidence due to imprecision and substantial heterogeneity

KQ 2a: PRP vs. Saline – Pain

WOMAC Pain (0-20)

F/U and Author, Year	F/U (mos)	Funding*	Blinding	OA Grade (KL)	PRP Categ.	PRP Detail	Saline Detail	PRP N	Saline N	MD F/U (95% CI)
Short										
Elik, 2020	1	None	DB	1, 2, 3	LR	3 inj. 3 wks	3 inj. 3 wks	30	27	-2.35 (-4.33, -0.37)
Patel, 2013†	3	Other	DB	Ahlback 1, 2	LP	1 inj.+2 inj.	NR	102	46	-6.04 (-9.44, -2.64)
Dorio, 2021	3	None	DB	2, 3	LP	2 inj., 1/two wk	2 inj., 1/two wk	20	21	-1.50 (-3.15, 0.15)
Nunes-Tamashiro, 2022	3	None	DB	2, 3	NR	1 inj.	1 inj.	34	33	-1.43 (-3.22, 0.36)
Chu, 2022	3	Other	DB	1, 2, 3	LP	3 inj., 1/wk	3 inj., 1/wk	308	302	-2.90 (-3.35, -2.45)
Subgroup, PL (I^2 = 52.7%, p = 0.076)										-2.76 (-3.40, -1.63)
Intermediate										
Dorio, 2021	5.5	None	DB	2, 3	LP	2 inj., 1/two wk	2 inj., 1/two wk	20	21	0.40 (-1.42, 2.22)
Patel, 2013†	6	Other	DB	Ahlback 1, 2	LP	1 inj.+2 inj.	NR	102	46	-5.28 (-8.68, -1.88)
Chu, 2022	6	Other	DB	1, 2, 3	LP	3 inj., 1/wk	3 inj., 1/wk	308	302	-5.70 (-6.10, -5.30)
Elik, 2020	6	None	DB	1, 2, 3	LR	3 inj. 3 wks	3 inj. 3 wks	30	27	-4.01 (-6.03, -1.99)
Subgroup, PL (I^2 = 93.0%, p = 0.000)										-3.62 (-6.79, -0.46)
Long										
Chu, 2022	12	Other	DB	1, 2, 3	LP	3 inj., 1/wk	3 inj., 1/wk	308	302	-6.60 (-7.05, -6.15)
Nunes-Tamashiro, 2022	12	None	DB	2, 3	NR	1 inj.	1 inj.	34	33	-1.87 (-3.53, -0.21)
Subgroup, PL (I^2 = 96.5%, p = 0.000)										-4.38 (-9.96, 1.45)



Short term* and Intermediate term†
Mod. improvement (SOE: moderate) for both

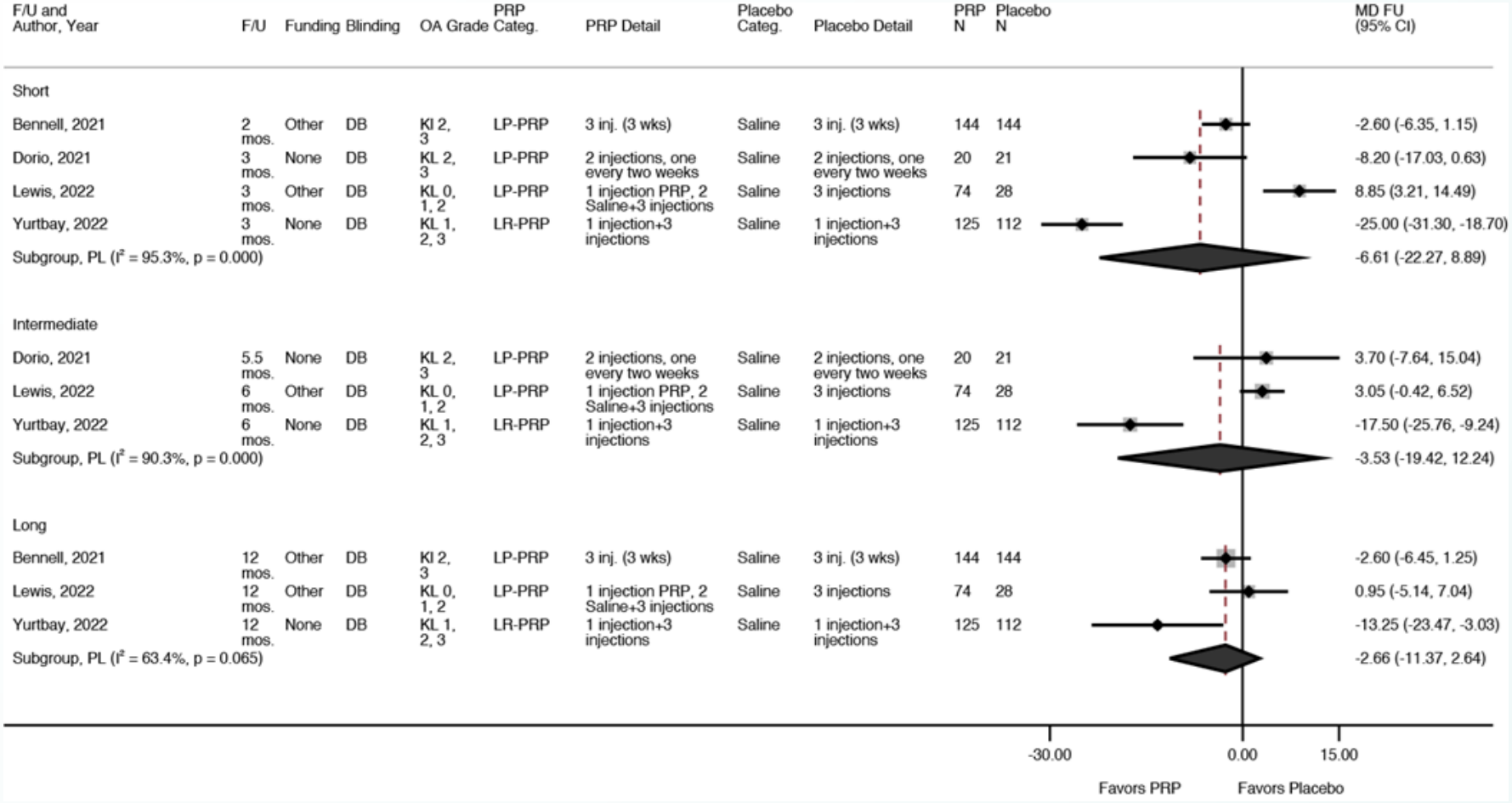
Long term
Insufficient evidence (↑ RoB, inconsistent, imprecise)

*exclusion of outlier did not change conclusions
†exclusion of outlier resulted in large improvement with PRP

Aggregate Analytics

KQ 2a: PRP vs. Saline – Pain, cont.

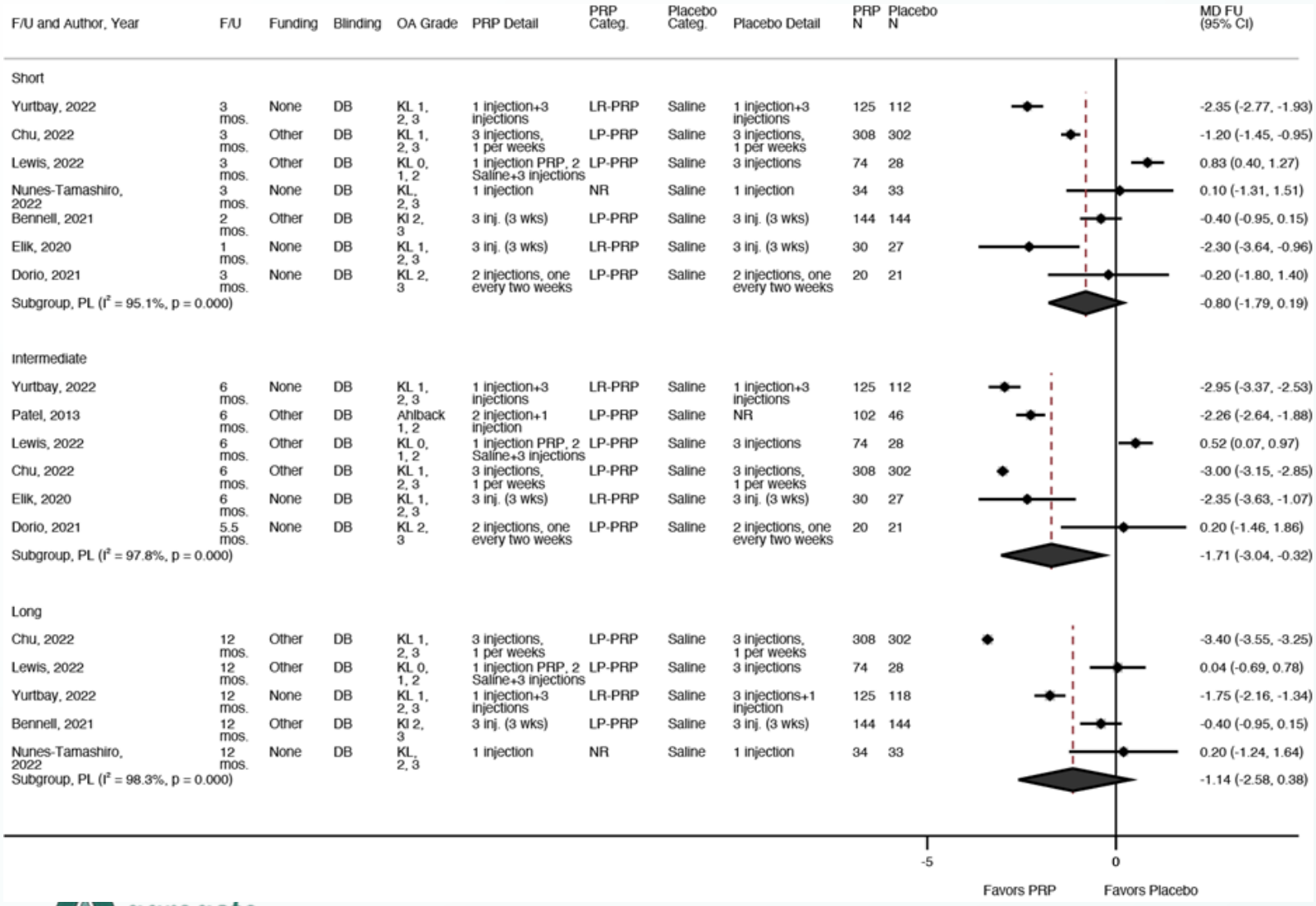
KOOS Pain (0-100)



No differences at any timepoint (**SOE: Low**); estimates were imprecise, heterogeneity was high.

KQ 2a: PRP vs. Saline – Pain, cont.

VAS Pain (0-10)



Short term: no difference

Intermediate term: moderate improvement

Long term: no difference

SOE: low (for all): inconsistent, imprecise

KQ 2a: PRP vs. Saline – OMERACT-OARSI criteria

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

Small increase in the likelihood of achieving response with PRP vs. saline short term, no difference intermediate term (**SOE: low for both**).

Aggregate Analytics

KQ 2a: PRP vs. Saline – Secondary invasive procedures

Outcome*	RCTs	F/U	PRP vs. Placebo (saline) RR (95% CI) Conclusion	Quality (SoE)
Total knee arthroplasty	2 (N=545) Bennell 2021 Yurtbay 2022	12-24 mos.	**PRP:** 2.2% (6/271); **Placebo:** 2.6% (7/274); **RR** 0.87, 95% CI 0.30 to 2.55 Conclusion: No difference.	⊕⊕◯◯ LOW (imprecision, consistency unknown)

Aggregate Analytics

KQ 2a: PRP vs. Corticosteroid (Knee OA)

Patient and Intervention Characteristics

(See Appendix G – Tables G11a-G11c)

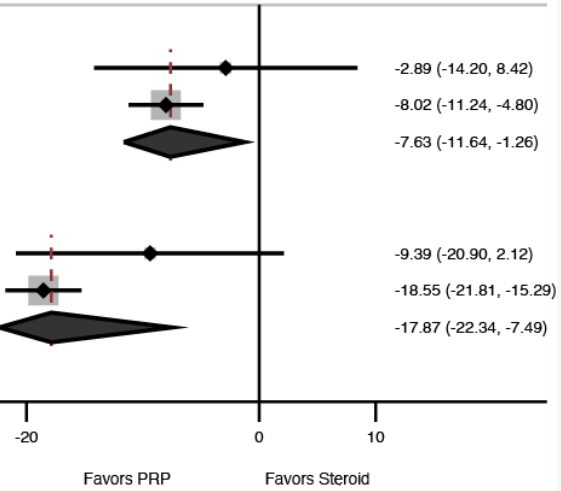
9 RCTs, N=598 (range 51 to 70)

- Mean age: 57 years (52 to 68)
- Female: 68% (15% to 91%)
- Kellgren-Lawrence OA Grade (*primarily Grades 2-3*)
  - Grade 1-2 (1 RCT), Grade 2 only (1 RCT), Grade 2-3 (6 RCTs); Grades 3-4 (1 RCT, 58% Grade 4)
- Mean symptom duration 5.1 years (2 RCTs); ≥3 mos. (2 RCTs); NR (5 RCTs)
- Unilateral (2 RCTs), Bilateral (1 RCT), Both (2 RCTs), NR (4 RCTs)
- PRP Injections
  - Injections: 1 (5 RCTs), 2 (1 RCTs), 3 (2 RCT), unclear (1 RCT); primarily every 4 weeks if multiple (weekly, 1 RCT; unclear, 1 RCT)
  - Platelet count varied; Leukocyte-poor (3 RCTs), Leukocyte-rich (1 RCT), NR (5 RCT)
  - Volume primarily 4–5 mL per injection (range 4–8 mL)
  - Use of activating agent: calcium gluconate (1 RCT), none (1 RCT), NR (5 RCT)
- Steroid Injections (same number as PRP)
  - Triamcinolone (6 RCTs), betamethasone (1 RCT), NR (2 RCTs); volume varied 1–6 mL

KQ 2a: PRP vs. Steroid – Function

KOOS ADL (0-100)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Steroid Categ.	Steroid Detail	PRP N	Steroid N	MD FU (95% CI)
Short											
Joshi, 2017	3 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	-2.89 (-14.20, 8.42)
Naderi, 2018	3 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-8.02 (-11.24, -4.80)
Subgroup, PL (I^2 = 0.0%, p = 0.393)											-7.63 (-11.64, -1.26)
Intermediate											
Joshi, 2017	6 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	-9.39 (-20.90, 2.12)
Naderi, 2018	6 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-18.55 (-21.81, -15.29)
Subgroup, PL (I^2 = 55.6%, p = 0.134)											-17.87 (-22.34, -7.49)



INSUFFIENT EVIDENCE (↑ RoB, inconsistent, imprecise):

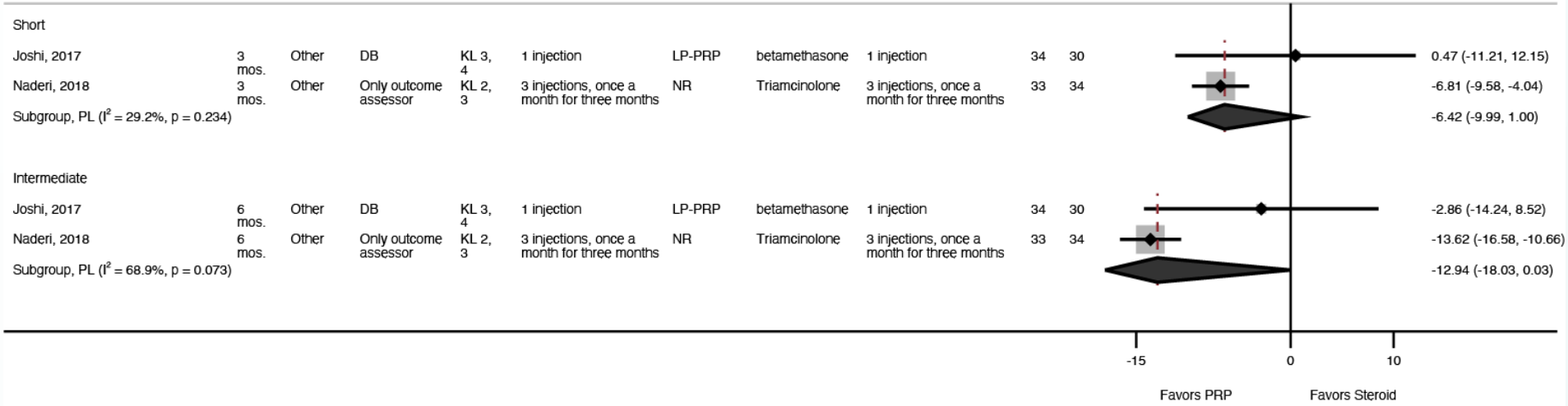
- Small improvement short term, moderate improvement intermediate term with PRP; however, individual trial results conflicted.
- Differences in injection regimens, OA grades, steroid type

Aggregate Analytics

KQ 2a: PRP vs. Steroid – Function, cont.

KOOS Sport/Recreation (0-100)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Steroid Categ.	Steroid Detail	PRP N	Steroid N	MD FU (95% CI)
Short											
Joshi, 2017	3 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	0.47 (-11.21, 12.15)
Naderi, 2018	3 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-6.81 (-9.58, -4.04)
Subgroup, PL (I^2 = 29.2%, p = 0.234)											-6.42 (-9.99, 1.00)
Intermediate											
Joshi, 2017	6 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	-2.86 (-14.24, 8.52)
Naderi, 2018	6 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-13.62 (-16.58, -10.66)
Subgroup, PL (I^2 = 68.9%, p = 0.073)											-12.94 (-18.03, 0.03)



INSUFFIENT EVIDENCE (↑ RoB, inconsistent, imprecise):

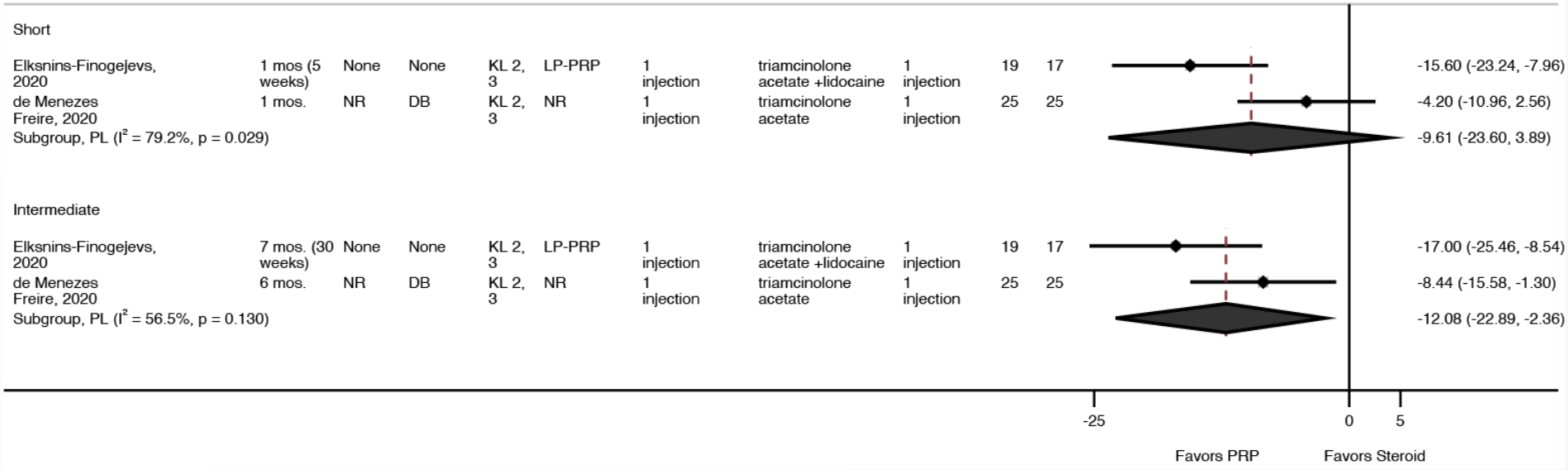
- No difference between groups; however, individual trial results conflicted.
- Differences in injection regimens, OA grades, steroid type

Aggregate Analytics

KQ 2a: PRP vs. Steroid – Function, cont.

Knee Society Score (0-100)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Categ.	PRP Detail	Steroid Categ.	Steroid Detail	PRP N	Steroid N	MD FU (95% CI)
Short											
Elksnins-Finogejevs, 2020	1 mos (5 weeks)	None	None	KL 2, 3	LP-PRP	1 injection	triamcinolone acetate +lidocaine	1 injection	19	17	-15.60 (-23.24, -7.96)
de Menezes Freire, 2020	1 mos.	NR	DB	KL 2, 3	NR	1 injection	triamcinolone acetate	1 injection	25	25	-4.20 (-10.96, 2.56)
Subgroup, PL (I^2 = 79.2%, p = 0.029)											-9.61 (-23.60, 3.89)
Intermediate											
Elksnins-Finogejevs, 2020	7 mos. (30 weeks)	None	None	KL 2, 3	LP-PRP	1 injection	triamcinolone acetate +lidocaine	1 injection	19	17	-17.00 (-25.46, -8.54)
de Menezes Freire, 2020	6 mos.	NR	DB	KL 2, 3	NR	1 injection	triamcinolone acetate	1 injection	25	25	-8.44 (-15.58, -1.30)
Subgroup, PL (I^2 = 56.5%, p = 0.130)											-12.08 (-22.89, -2.36)



SOE Low (↑ RoB, imprecision):

- **Short term**: *no difference* between groups (individual trial results conflicted)
- **Intermediate term**: *moderate improvement* with PRP

Aggregate Analytics

KQ 2a: PRP vs. Steroid – Function, cont.

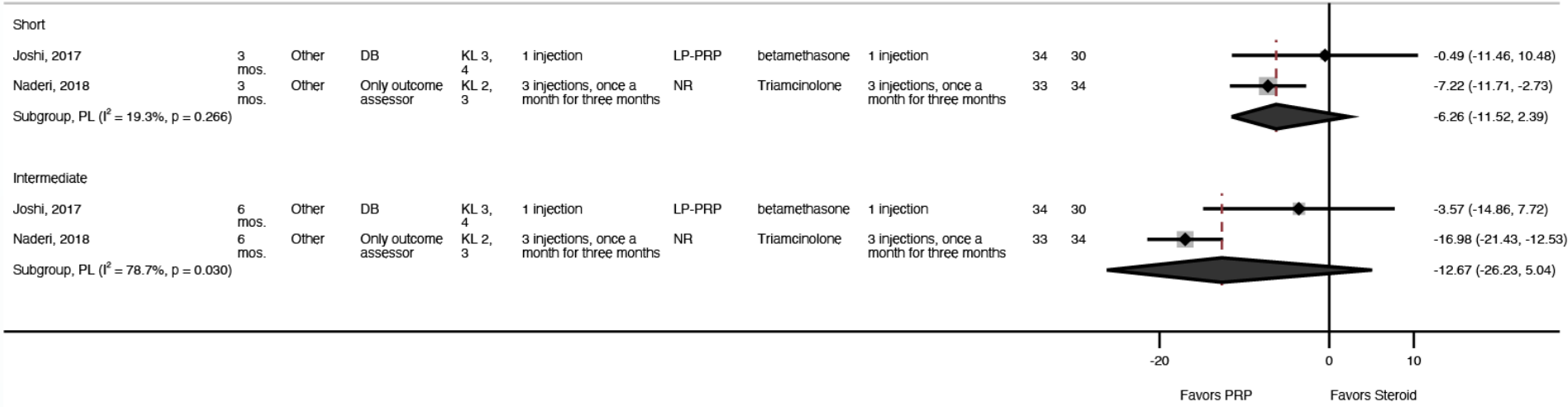
Other Outcomes, not amenable to pooling

Outcome*	RCTs Quality	F/U	PRP vs. Steroid, MD (95% CI) Conclusion	Quality (SoE)
WOMAC physical function scores (0-68 lower score = better)	1 (N=67) Nunes-Tamashiro, 2022 Fair	3, 12 mos.	3 months (short term) **MD:** 1.4, 95% CI -3.58 to 6.38 12 months (long term) **MD:** -2.2, 95% CI -7.70 to 3.30 Conclusion: No difference.	⊕⊕◯◯ LOW (imprecision, consistency unknown)
	1 RCT (N=103) Khan, 2018 Poor	6 mos.	6 months (intermediate term) **MD:** 1.6, 95% CI -0.89 to 4.17 Conclusion: No difference; one poor-quality trial.	⊕◯◯◯ INSUFFICIENT (↑ RoB, imprecision, consistency unknown)
IKDC scores (0-100 lower score = better)	1 RCT (N=36) Elksnins-Finogejevs, 2020 Poor	3, 7, 13 mos.	3 months **MD:** -20.5, 95% CI -29.63 to -11.37 7 months **MD:** -21.2, 95% CI -31.65 to -10.75 13 months **MD:** -22.2, 95% CI -32.65 to -11.75 Conclusion: Large improvement with PRP; one-poor quality trial.	⊕◯◯◯ INSUFFICIENT (↑ RoB, imprecision, consistency unknown)

KQ 2a: PRP vs. Steroid – Pain

KOOS Pain (0-100)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Steroid Categ.	Steroid Detail	PRP N	Steroid N	MD FU (95% CI)
Short											
Joshi, 2017	3 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	-0.49 (-11.46, 10.48)
Naderi, 2018	3 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-7.22 (-11.71, -2.73)
Subgroup, PL (I^2 = 19.3%, p = 0.266)											-6.26 (-11.52, 2.39)
Intermediate											
Joshi, 2017	6 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	-3.57 (-14.86, 7.72)
Naderi, 2018	6 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-16.98 (-21.43, -12.53)
Subgroup, PL (I^2 = 78.7%, p = 0.030)											-12.67 (-26.23, 5.04)



No difference short (**SOE: low;** ↑RoB, imprecision) or intermediate term (**SOE: insufficient;** ↑RoB, inconsistency, imprecision)

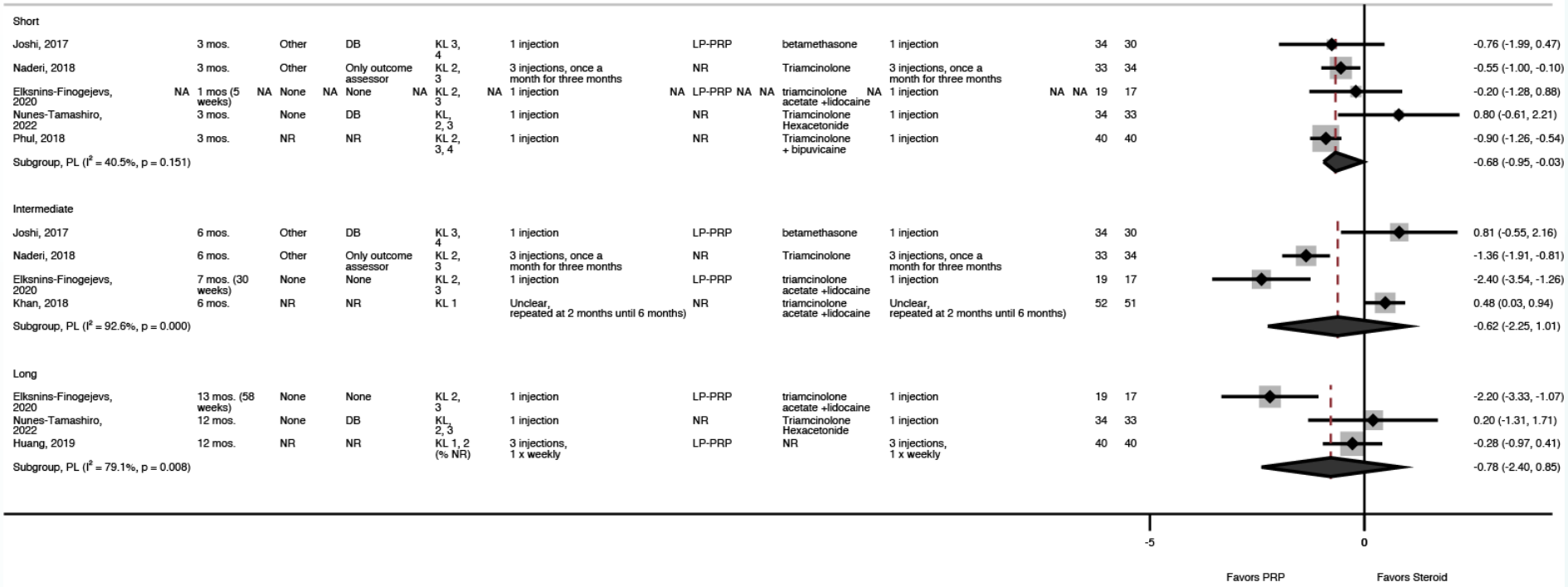
- Individual trial results differed
- Differences in injection regimens, OA grades, steroid type

Aggregate Analytics

KQ 2a: PRP vs. Steroid – Pain, cont.

VAS Pain (0-10)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Steroid Categ.	Steroid Detail	PRP N	Steroid N	MD FU (95% CI)
Short											
Joshi, 2017	3 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	-0.76 (-1.99, 0.47)
Naderi, 2018	3 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-0.55 (-1.00, -0.10)
Elksnins-Finogejevs, 2020	1 mos (5 weeks)	None	None	KL 2, 3	1 injection	LP-PRP	triamcinolone acetate +lidocaine	1 injection	19	17	-0.20 (-1.28, 0.88)
Nunes-Tamashiro, 2022	3 mos.	None	DB	KL 2, 3	1 injection	NR	Triamcinolone Hexacetonide	1 injection	34	33	0.80 (-0.61, 2.21)
Phul, 2018	3 mos.	NR	NR	KL 2, 3, 4	1 injection	NR	Triamcinolone + bipuvicaine	1 injection	40	40	-0.90 (-1.26, -0.54)
Subgroup, PL (I^2 = 40.5%, p = 0.151)											-0.68 (-0.95, -0.03)
Intermediate											
Joshi, 2017	6 mos.	Other	DB	KL 3, 4	1 injection	LP-PRP	betamethasone	1 injection	34	30	0.81 (-0.55, 2.16)
Naderi, 2018	6 mos.	Other	Only outcome assessor	KL 2, 3	3 injections, once a month for three months	NR	Triamcinolone	3 injections, once a month for three months	33	34	-1.36 (-1.91, -0.81)
Elksnins-Finogejevs, 2020	7 mos. (30 weeks)	None	None	KL 2, 3	1 injection	LP-PRP	triamcinolone acetate +lidocaine	1 injection	19	17	-2.40 (-3.54, -1.26)
Khan, 2018	6 mos.	NR	NR	KL 1	Unclear, repeated at 2 months until 6 months)	NR	triamcinolone acetate +lidocaine	Unclear, repeated at 2 months until 6 months)	52	51	0.48 (0.03, 0.94)
Subgroup, PL (I^2 = 92.6%, p = 0.000)											-0.62 (-2.25, 1.01)
Long											
Elksnins-Finogejevs, 2020	13 mos. (58 weeks)	None	None	KL 2, 3	1 injection	LP-PRP	triamcinolone acetate +lidocaine	1 injection	19	17	-2.20 (-3.33, -1.07)
Nunes-Tamashiro, 2022	12 mos.	None	DB	KL 2, 3	1 injection	NR	Triamcinolone Hexacetonide	1 injection	34	33	0.20 (-1.31, 1.71)
Huang, 2019	12 mos.	NR	NR	KL 1, 2 (% NR)	3 injections, 1 x weekly	LP-PRP	NR	3 injections, 1 x weekly	40	40	-0.28 (-0.97, 0.41)
Subgroup, PL (I^2 = 79.1%, p = 0.008)											-0.78 (-2.40, 0.85)



- *Small improvement* with PRP short term (**SOE: low**);
- *No differences* intermediate (**SOE: insufficient**) and long term (**SOE: low**)
- ↑ RoB, imprecision, inconsistency (intermediate term)

Aggregate Analytics

KQ 2a: PRP vs. Steroid – Secondary invasive procedures

Outcome*	RCTs	F/U	PRP vs. Placebo (saline) RR (95% CI) Conclusion	Quality (SoE)
Total knee arthroplasty	1 (N=40) Elksnins-Finogejevs, 2020	13 mos.	**PRP:** 0% (0/20) **Steroid:** 15% (3/20) Conclusion: Insufficient evidence precludes a conclusion.	⊕◯◯◯ INSUFFICIENT (RoB, imprecision, consistency unknown)

KQ 2a: PRP vs. Oral Analgesics (Knee OA)

Patient and Intervention Characteristics

(See Appendix G – Table G12)

3 RCTs, N=195 (range 60 to 70)

- Mean age: 56 years (53 to 57)
- Female: 46% (33% to 54%)
- Kellgren-Lawrence OA Grade: Grade 1-2 (2 RCTs), Grade 2-3 (1 RCT)
- Mean symptom duration NR; ≥3 months for inclusion (1 RCT)
- Unilateral or Bilateral
- PRP Injections
  - Injections: 1, 5 ml (1 RCT); 2, 3 ml (2 weeks apart, 1 RCT); 3, 3 ml (2 weeks apart, 1 RCT)
  - Platelet count varied; all leukocyte-poor PRP
  - All used an activating agent: calcium chloride (2 RCTs), calcium gluconate (1 RCT)
- Analgesics
  - NSAIDs 60-200 mg (2 RCTs), APAP 500 mg (1 RCT); regimens varied

KQ 2a: PRP vs. Analgesics – Function

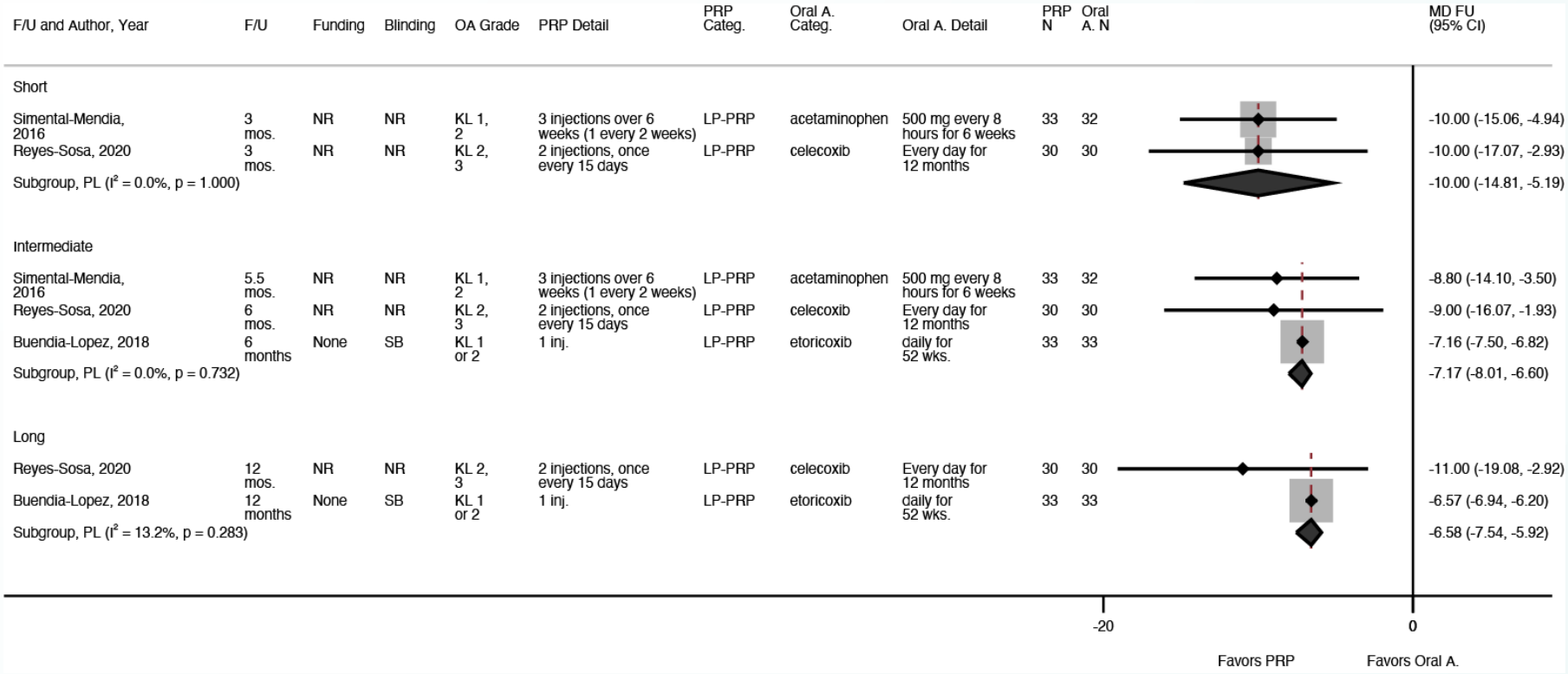
Responder Analysis

Outcome*	RCTs Quality	PRP vs. NSAID, RR (95% CI) Conclusion	Quality (SoE)
"Success" (Responders): ≥20% decrease in WOMAC Physical Function scores	1 (N=66) Buendia-Lopez, 2018 Fair	6 months (intermediate term) **PRP:** 46% (15/33) **Etoricoxib** 60 mg.: 12% (4/33) **RR**: 3.75, 95 CI 1.39 to 10.11 12 months (long term) **PRP:** 24% (8/33) **Etoricoxib** 60 mg.: 0% (0/33) Conclusion: Large increase in the likelihood of response with PRP	⊕⊕◯◯ LOW (imprecision, consistency unknown)

KQ 2a: PRP vs. Analgesics – Function, cont.

WOMAC Physical Function scores (0-68)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Oral A. Categ.	Oral A. Detail	PRP N	Oral A. N	MD FU (95% CI)
Short											
Simental-Mendia, 2016	3 mos.	NR	NR	KL 1, 2	3 injections over 6 weeks (1 every 2 weeks)	LP-PRP	acetaminophen	500 mg every 8 hours for 6 weeks	33	32	-10.00 (-15.06, -4.94)
Reyes-Sosa, 2020	3 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-10.00 (-17.07, -2.93)
Subgroup, PL (I^2 = 0.0%, p = 1.000)											-10.00 (-14.81, -5.19)
Intermediate											
Simental-Mendia, 2016	5.5 mos.	NR	NR	KL 1, 2	3 injections over 6 weeks (1 every 2 weeks)	LP-PRP	acetaminophen	500 mg every 8 hours for 6 weeks	33	32	-8.80 (-14.10, -3.50)
Reyes-Sosa, 2020	6 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-9.00 (-16.07, -1.93)
Buendia-Lopez, 2018	6 months	None	SB	KL 1 or 2	1 inj.	LP-PRP	etoricoxib	daily for 52 wks.	33	33	-7.16 (-7.50, -6.82)
Subgroup, PL (I^2 = 0.0%, p = 0.732)											-7.17 (-8.01, -6.60)
Long											
Reyes-Sosa, 2020	12 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-11.00 (-19.08, -2.92)
Buendia-Lopez, 2018	12 months	None	SB	KL 1 or 2	1 inj.	LP-PRP	etoricoxib	daily for 52 wks.	33	33	-6.57 (-6.94, -6.20)
Subgroup, PL (I^2 = 13.2%, p = 0.283)											-6.58 (-7.54, -5.92)



Consistent improvement with PRP (**SOE: low** for all; RoB, imprecision)

- Short and intermediate term *(moderate)*, long term *(small)*

*excluding outlier trials

All fair quality

KQ 2a: PRP vs. Analgesics – Pain

Responders ("success"): ≥20% decrease for following pain measures

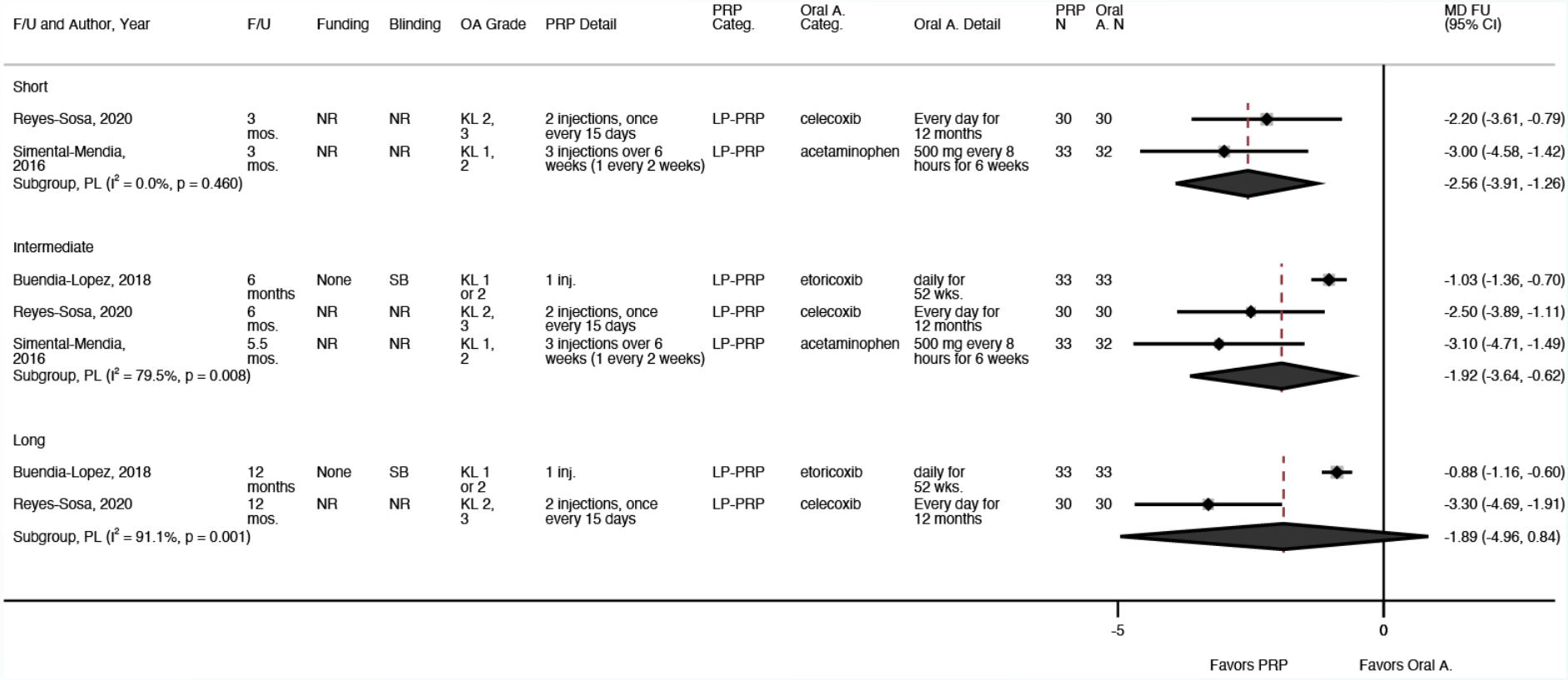
RCTs Quality	Outcome	PRP vs. NSAID, RR (95% CI)	Conclusion Quality (SoE)
1 (N=66) Buendia-Lopez, 2018 Fair	**WOMAC Pain scores**	6 months (intermediate term) **PRP:** 49% (16/33) vs. **Etoricoxib** 60 mg.: 15% (5/33); **RR**: 3.20, 95 CI 1.33 to 7.72 12 months (long term) **PRP:** 30% (10/33) vs. **Etoricoxib** 60 mg.: 0% (0/33)	Conclusion: Large increase in the likelihood of achieving response with PRP ⊕⊕◯◯ **LOW** (imprecision, consistency unknown)
	VAS Pain scores	6 months (intermediate term) **PRP:** 49% (16/33) vs. **Etoricoxib** 60 mg.: 18% (6/33); **RR**: 2.67, 95 CI 1.19 to 5.96 12 months (long term) **PRP:** 15% (5/33) vs. **Etoricoxib** 60 mg.: 6% (2/33); **RR**: 2.50, 95% CI 0.52 to 11.98	

Aggregate Analytics

KQ 2a: PRP vs. Analgesics – Pain, cont.

WOMAC Pain scores (0-20)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Oral A. Categ.	Oral A. Detail	PRP N	Oral A. N	MD FU (95% CI)
Short											
Reyes-Sosa, 2020	3 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-2.20 (-3.61, -0.79)
Simental-Mendia, 2016	3 mos.	NR	NR	KL 1, 2	3 injections over 6 weeks (1 every 2 weeks)	LP-PRP	acetaminophen	500 mg every 8 hours for 6 weeks	33	32	-3.00 (-4.58, -1.42)
Subgroup, PL (I^2 = 0.0%, p = 0.460)											-2.56 (-3.91, -1.26)
Intermediate											
Buendia-Lopez, 2018	6 months	None	SB	KL 1 or 2	1 inj.	LP-PRP	etoricoxib	daily for 52 wks.	33	33	-1.03 (-1.36, -0.70)
Reyes-Sosa, 2020	6 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-2.50 (-3.89, -1.11)
Simental-Mendia, 2016	5.5 mos.	NR	NR	KL 1, 2	3 injections over 6 weeks (1 every 2 weeks)	LP-PRP	acetaminophen	500 mg every 8 hours for 6 weeks	33	32	-3.10 (-4.71, -1.49)
Subgroup, PL (I^2 = 79.5%, p = 0.008)											-1.92 (-3.64, -0.62)
Long											
Buendia-Lopez, 2018	12 months	None	SB	KL 1 or 2	1 inj.	LP-PRP	etoricoxib	daily for 52 wks.	33	33	-0.88 (-1.16, -0.60)
Reyes-Sosa, 2020	12 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-3.30 (-4.69, -1.91)
Subgroup, PL (I^2 = 91.1%, p = 0.001)											-1.89 (-4.96, 0.84)

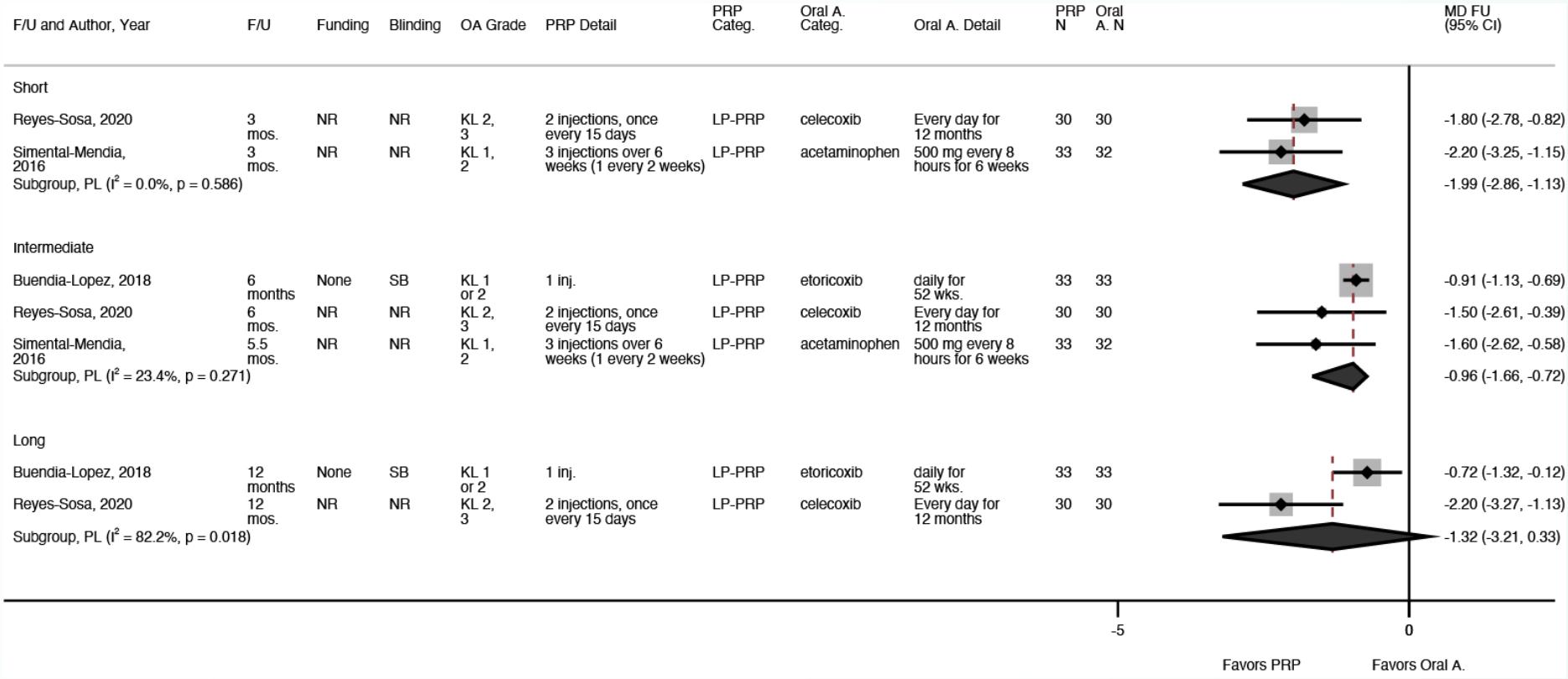


- *Moderate* improvement short term and *small* improvement intermediate term in pain with PRP (**SOE: low**)
- *No difference* in pooled analysis long term (**SOE: insufficient**)
  - Individually, results conflicted (both fair quality RCTs)
  - Differences in the severity of OA, treatment regimens

KQ 2a: PRP vs. Analgesics – Pain, cont.

VAS Pain scores (0-10)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	PRP Detail	PRP Categ.	Oral A. Categ.	Oral A. Detail	PRP N	Oral A. N	MD FU (95% CI)
Short											
Reyes-Sosa, 2020	3 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-1.80 (-2.78, -0.82)
Simental-Mendia, 2016	3 mos.	NR	NR	KL 1, 2	3 injections over 6 weeks (1 every 2 weeks)	LP-PRP	acetaminophen	500 mg every 8 hours for 6 weeks	33	32	-2.20 (-3.25, -1.15)
Subgroup, PL (I^2 = 0.0%, p = 0.586)											-1.99 (-2.86, -1.13)
Intermediate											
Buendia-Lopez, 2018	6 months	None	SB	KL 1 or 2	1 inj.	LP-PRP	etoricoxib	daily for 52 wks.	33	33	-0.91 (-1.13, -0.69)
Reyes-Sosa, 2020	6 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-1.50 (-2.61, -0.39)
Simental-Mendia, 2016	5.5 mos.	NR	NR	KL 1, 2	3 injections over 6 weeks (1 every 2 weeks)	LP-PRP	acetaminophen	500 mg every 8 hours for 6 weeks	33	32	-1.60 (-2.62, -0.58)
Subgroup, PL (I^2 = 23.4%, p = 0.271)											-0.96 (-1.66, -0.72)
Long											
Buendia-Lopez, 2018	12 months	None	SB	KL 1 or 2	1 inj.	LP-PRP	etoricoxib	daily for 52 wks.	33	33	-0.72 (-1.32, -0.12)
Reyes-Sosa, 2020	12 mos.	NR	NR	KL 2, 3	2 injections, once every 15 days	LP-PRP	celecoxib	Every day for 12 months	30	30	-2.20 (-3.27, -1.13)
Subgroup, PL (I^2 = 82.2%, p = 0.018)											-1.32 (-3.21, 0.33)



- *Moderate* improvement short term and *small* improvement intermediate term in pain with PRP (**SOE: low**)
- *No difference* in pooled analysis long term (**SOE: insufficient**)
  - Individually, results conflicted (both fair quality RCTs)
  - Differences in the severity of OA, treatment regimens

KQ 2a: PRP + exercise vs. Exercise (Knee OA)

Patient and Intervention Characteristics

(See Appendix G – Table G13)

3 RCTs, N=179 (range 52 to 65)

- Mean age: 59 years (55 to 62)
- Female: 90% (80% to 97%)
- Kellgren-Lawrence OA Grade: Grades 1 to 3 (1 RCT) or 4 (1 RCT), distribution NR; Grade 4 only (1 RCT)
- Symptom duration ≥3 mos. for inclusion in all RCTs (78% with sx >12 mos. in 1 RCT)
- Unilateral/Bilateral NR
- PRP Injections
  - Injections: 1, 6 ml (1 RCT); 2, 4–6 ml (details NR, 1 RCT); 3 (ml NR, 2 weeks apart, 1 RCT)
  - Platelet count poorly reported (1 RCT); all leukocyte-rich PRP
  - Activating agent: calcium chloride (1 RCT), calcium gluconate (1 RCT), NR (1 RCT)
- Exercise
  - Home exercise (ROM, strengthening) without (2 RCTs) and with (1 RCT) TENS

KQ 2a: PRP (+ exercise) vs. Exercise

RCTs F/U Quality	Outcome	PRP vs. Exercise MD (95% CI) Conclusion	Quality (SoE)
2 (N=122) Akan, 2018 Rayegani, 2014 6 mos. (intermediate term) Fair	**WOMAC PF scores** (0-68; lower = better)	**Pooled MD:** -1.48, 95% CI -7.25 to 3.94, I^2=0% Conclusion: No difference	⊕⊕◯◯ **LOW** (RoB, imprecision)
	WOMAC Pain scores (0-20; lower = better)	**Pooled MD:** -2.14, 95% CI -3.89 to 0.14, I^2=53.4% Conclusion: No difference	

KQ 2a: PRP (+ exercise) vs. Exercise

INSUFFICIENT EVIDENCE:

Function

- **WOMAC PF**
  - Short term (3 mos.), 1 RCT (N=60): no difference
- **KOOS ADL and Sports/Recreation**
  - Short term (2 mos.), 1 RCT (N=50): moderate improvement with PRP for ADL; below threshold for small effect for Sport/Rec

Pain

- **WOMAC Pain**
  - Short term (3 mos.), 1 RCT (N=60): small improvement with PRP
- **KOOS Pain and VAS Pain**
  - Short term (2 mos.), 1 RCT (N=50): small improvement with PRP on KOOS, no difference on VAS

Need for TKA

- 12 mos., 1 RCT (N=60): no difference (3% vs. 0%)

KQ 2a: PRP vs. Other

(See Appendix F for patient and intervention characteristics)

INSUFFICIENT EVIDENCE:

PRP vs. PT

- 1 poor-quality RCT (N=40), short term (3 mos.)
- Large improvement in WOMAC PF and VAS pain scores with PRP

PRP vs. Prolotherapy

- 2 poor-quality RCTs, short (1-2 mos.) and intermediate term (6 mos.)
- Small improvement in WOMAC PF and WOMAC pain (1 RCT, N=42) and VAS pain (1 RCT, N=60) scores with PRP

Aggregate Analytics

KQ 2a: PRP – number of injections (Knee OA)

Patient and Intervention Characteristics

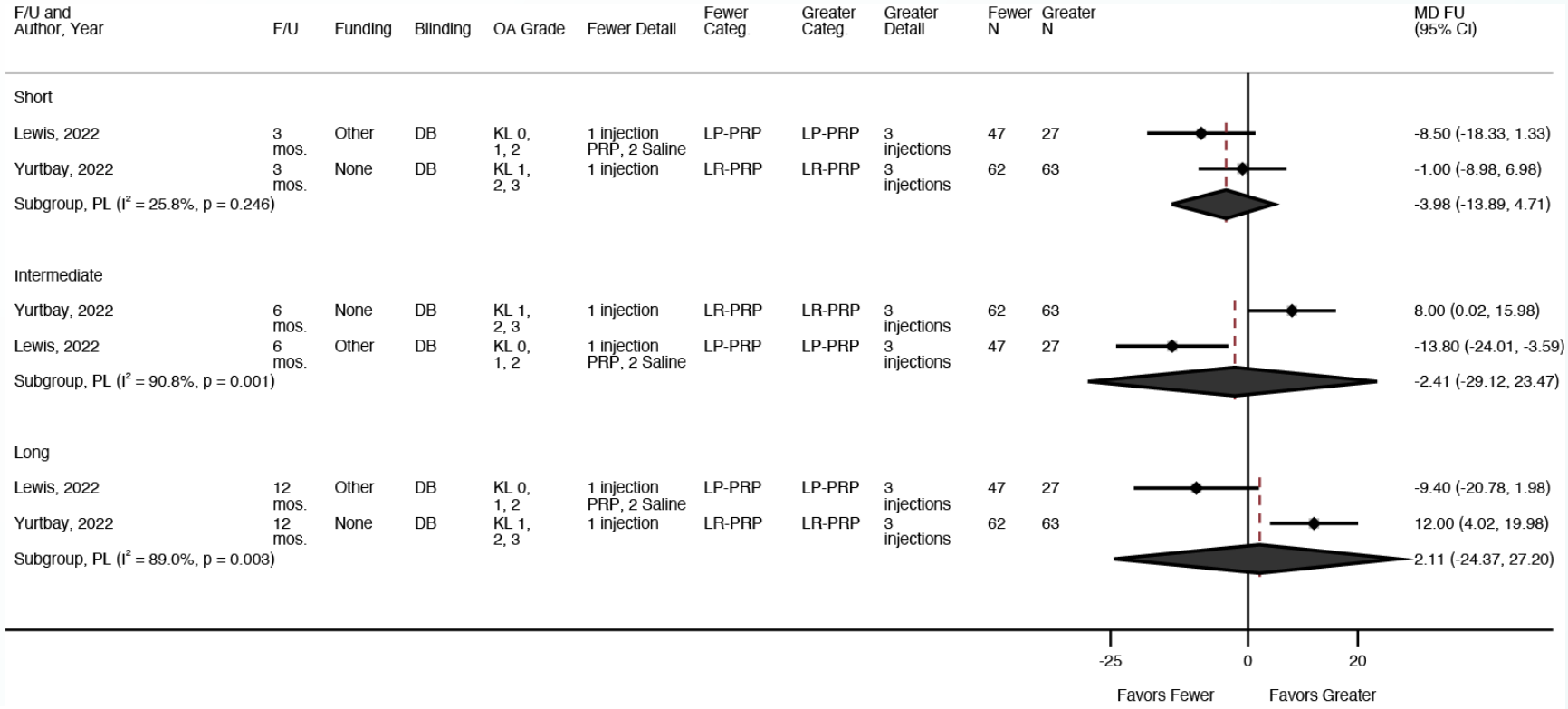
(See Appendix G – Tables G15a-b)

6 RCTs, N=508 (range 52 to 133)

- Mean age: 56 years (52 to 66)
- Female: 58% (13% to 85%)
- OA Grade:
  - Kellgren-Lawrence Grades 1-2 (1 RCT), 2-3 (1 RCT), 3 only (1 RCT), and 1-4 (1 RCT, 33% Grade 4)
  - Ahlback Grades 1-2 (2 RCTs)
- Mean symptom duration 4.7 years (1 RCT); ≥4 or 6 months for inclusion (3 RCTs)
- Unilateral (2 RCTs), Bilateral (2 RCTs), Both (1 RCT), NR (1 RCT)
- PRP Injections
  - No. of injections: 1 vs. 3 (4 RCTs), 1 vs. 2 (3 RCTs), 2 vs. 3 (1 RCT)
  - 4 to 8 ml given at weekly (2 RCTs), 2-week (2 RCTs), 3-week (1 RCT) or monthly (1 RCT) intervals
  - Platelet count poorly reported; LR-PRP (4 RCTs), LP-PRP (2 RCTs)
  - Activating agent: calcium chloride (3 RCTs), NR (3 RCTs)

KQ 2a: PRP – fewer vs. greater number of injections

KOOS Sports and Recreation scores (0-100)



SOE: low

SOE: insuff.

- ***No difference*** in pooled analyses at any timepoint
  - At intermediate and long term, individual point estimates went in opposite directions, substantial heterogeneity
  - Difference in intervals between injections (weekly vs. monthly) may explain some of the variation.

KQ 2a: PRP – fewer vs. greater number of injections

INSUFFICIENT EVIDENCE:

Function

- **Responders (WOMAC PF ≥30% and ≥50% decrease):** 1 vs. 2 injections, 1 RCT (N=56), short term (3 mos.)
  - Moderate increase in likelihood to response with 2 vs. 1 injection using ≥30% but not ≥50% cut-off
- **WOMAC PF scores:** 1 vs. 2 injections (3 RCTs), 1 vs. 2 and vs. 3 injections (1 RCT); short (3 mos.) and intermediate (6 mos.) term
  - Moderate improvement with 3 vs. 1 injection; no difference for 2 vs. 3 injections
- **KOOS ADL scores:** 1 vs. 3 injections (2 RCTs); short (3 mos.), intermediate (6 mos.) and long (12 mos.) term
  - No difference in pooled estimate, individual point estimates in opposite directions
- **IKDC scores**: 1 vs. 3 injections; intermediate term (6 mos.)
  - Moderate improvement with 3 vs. 1 injection

KQ 2a: PRP – fewer vs. greater number of injections

INSUFFICIENT EVIDENCE:

Pain

- **Responders (WOMAC Pain ≥30%, ≥50% decrease; VAS Pain ≥50% decrease):** 1 vs. 2 injections, 1 RCT (N=56), short term (3 mos.)
  - Greater likelihood of pain response with 2 vs. 1 injection
- **VAS pain scores:** 1 vs. 2 injections (3 RCTs), short (3 mos.) and intermediate (6 mos.) term; 1 vs. 3 injections (3 RCTs), short (3 mos.), intermediate (6 mos.) and long (12 mos.) term; 2 vs. 3 (1 RCT), short (3 mos.) and intermediate (6 mos.) term
  - No difference between any groups at any timepoint; difference in intervals b/w multiple PRP injections may explain some of the heterogeneity
- **WOMAC Pain scores:** 1 vs. 2 injections (3 RCTs), 1 vs. 2 and vs. 3 injections (1 RCT); short (3 mos.) and intermediate (6 mos.) term
  - Improvement in pain with 3 injections (vs. 1 and 2); no difference for 1 vs. 2 injections
- **KOOS Pain scores:** 1 vs. 3 injections (2 RCTs); short (3 mos.), intermediate (6 mos.) and long (12 mos.) term
  - No difference in pooled estimates, individual trials went in opposite direction (interval difference)

KQ 2a: PRP – leukocyte rich (LR) vs. leukocyte poor (LP) (Knee OA)

Patient and Intervention Characteristics

(See Appendix G – Table GX)

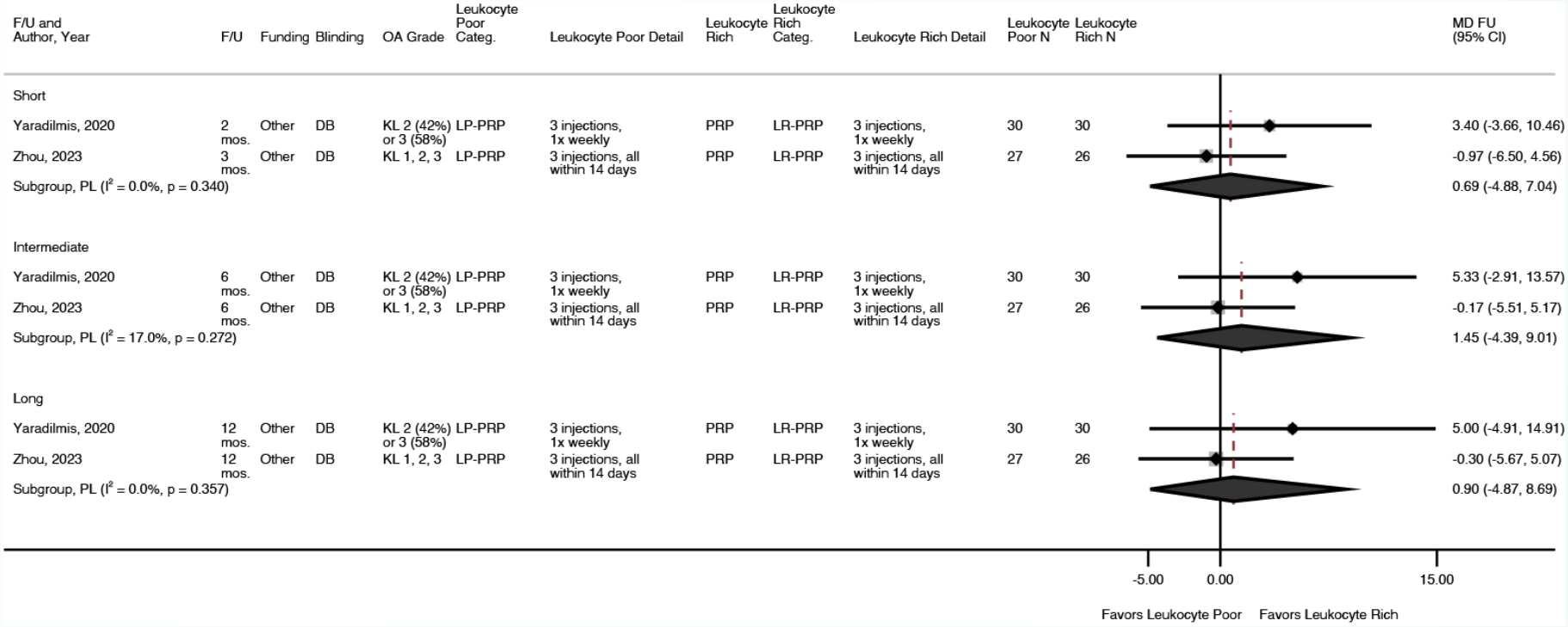
2 RCTs, N=130 (60 and 70)

- Mean age: 61 years (59 to 62)
- Female: 81% (70% to 90%)
- Kellgren-Lawrence OA Grades: 1 to 3 (1 RCT) or 2 to 3 (1 RCT)
- Symptom duration ≥3 mos. for inclusion in 1 RCT (NR by other RCT)
- Unilateral/Bilateral NR
- PRP Injections
  - 3 injections at weekly (1 RCT) or 2-week intervals (1 RCT)
  - Platelet and leukocyte counts varied
  - Activating agent: NR

KQ 2a: LP-PRP vs. LR- PRP – Function

WOMAC Physical Function Scores (0-68)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	Leukocyte Poor Categ.	Leukocyte Poor Detail	Leukocyte Rich	Leukocyte Rich Categ.	Leukocyte Rich Detail	Leukocyte Poor N	Leukocyte Rich N	MD FU (95% CI)
Short												
Yaradilmis, 2020	2 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	PRP	LR-PRP	3 injections, 1x weekly	30	30	3.40 (-3.66, 10.46)
Zhou, 2023	3 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	PRP	LR-PRP	3 injections, all within 14 days	27	26	-0.97 (-6.50, 4.56)
Subgroup, PL (I^2 = 0.0%, p = 0.340)												0.69 (-4.88, 7.04)
Intermediate												
Yaradilmis, 2020	6 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	PRP	LR-PRP	3 injections, 1x weekly	30	30	5.33 (-2.91, 13.57)
Zhou, 2023	6 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	PRP	LR-PRP	3 injections, all within 14 days	27	26	-0.17 (-5.51, 5.17)
Subgroup, PL (I^2 = 17.0%, p = 0.272)												1.45 (-4.39, 9.01)
Long												
Yaradilmis, 2020	12 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	PRP	LR-PRP	3 injections, 1x weekly	30	30	5.00 (-4.91, 14.91)
Zhou, 2023	12 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	PRP	LR-PRP	3 injections, all within 14 days	27	26	-0.30 (-5.67, 5.07)
Subgroup, PL (I^2 = 0.0%, p = 0.357)												0.90 (-4.87, 8.69)

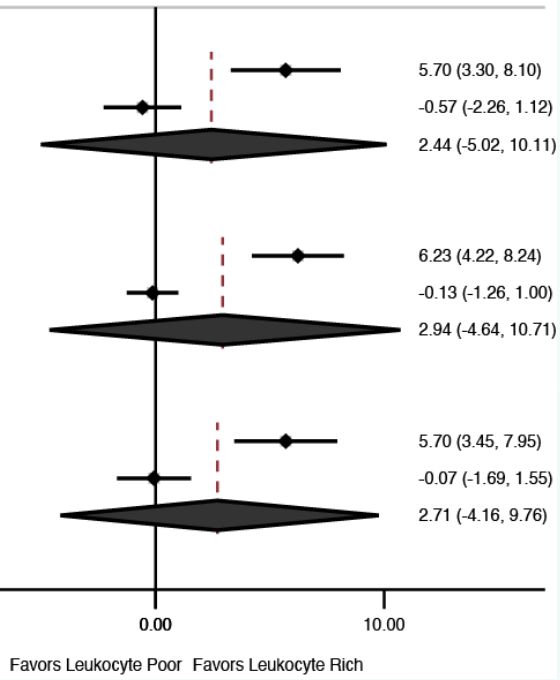


- *No difference* at any timepoint (**SOE: low**)

KQ 2a: LP-PRP vs. LR- PRP – Pain

WOMAC Pain Scores (0-68)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	Leukocyte Poor Categ.	Leukocyte Poor Detail	Leukocyte Rich Categ.	Leukocyte Rich Detail	Leukocyte Poor N	Leukocyte Rich N	MD FU (95% CI)
Short											
Yaradilmis, 2020	2 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	LR-PRP	3 injections, 1x weekly	30	30	5.70 (3.30, 8.10)
Zhou, 2023	3 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	LR-PRP	3 injections, all within 14 days	27	26	-0.57 (-2.26, 1.12)
Subgroup, PL (I^2 = 94.3%, p = 0.000)											2.44 (-5.02, 10.11)
Intermediate											
Yaradilmis, 2020	6 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	LR-PRP	3 injections, 1x weekly	30	30	6.23 (4.22, 8.24)
Zhou, 2023	6 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	LR-PRP	3 injections, all within 14 days	27	26	-0.13 (-1.26, 1.00)
Subgroup, PL (I^2 = 96.6%, p = 0.000)											2.94 (-4.64, 10.71)
Long											
Yaradilmis, 2020	12 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	LR-PRP	3 injections, 1x weekly	30	30	5.70 (3.45, 7.95)
Zhou, 2023	12 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	LR-PRP	3 injections, all within 14 days	27	26	-0.07 (-1.69, 1.55)
Subgroup, PL (I^2 = 94.0%, p = 0.000)											2.71 (-4.16, 9.76)



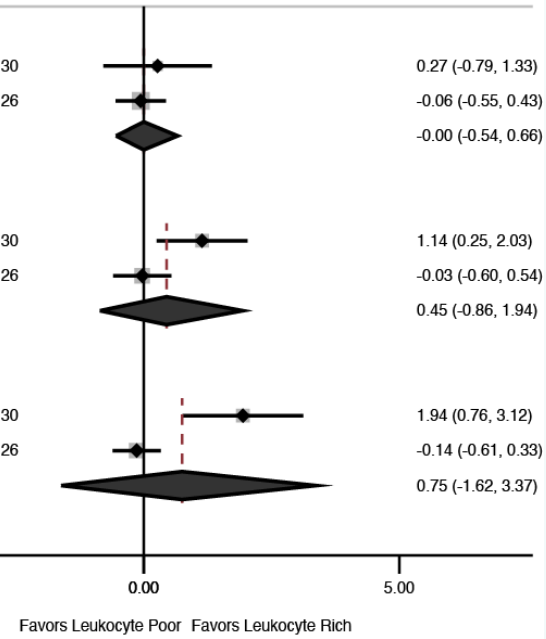
- ***No difference*** in pooled estimates at any timepoint (**SOE: insufficient**)
  - Individual trials reported conflicting results (good quality RCT showed no difference; fair-quality RCT favored LR-PRP); treatment regimens differed

Aggregate Analytics

KQ 2a: LP-PRP vs. LR-PRP – Pain, cont.

VAS Pain Scores (0-10)

F/U and Author, Year	F/U	Funding	Blinding	OA Grade	Leukocyte Poor Categ.	Leukocyte Poor Detail	Leukocyte Rich Categ.	Leukocyte Rich Detail	Leukocyte Poor N	Leukocyte Rich N	MD FU (95% CI)
Short											
Yaradilmis, 2020	2 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	LR-PRP	3 injections, 1x weekly	30	30	0.27 (-0.79, 1.33)
Zhou, 2023	3 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	LR-PRP	3 injections, all within 14 days	27	26	-0.06 (-0.55, 0.43)
Subgroup, PL (I^2 = 0.0%, p = 0.581)											-0.00 (-0.54, 0.66)
Intermediate											
Yaradilmis, 2020	6 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	LR-PRP	3 injections, 1x weekly	30	30	1.14 (0.25, 2.03)
Zhou, 2023	6 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	LR-PRP	3 injections, all within 14 days	27	26	-0.03 (-0.60, 0.54)
Subgroup, PL (I^2 = 78.8%, p = 0.030)											0.45 (-0.86, 1.94)
Long											
Yaradilmis, 2020	12 mos.	Other	DB	KL 2 (42%) or 3 (58%)	LP-PRP	3 injections, 1x weekly	LR-PRP	3 injections, 1x weekly	30	30	1.94 (0.76, 3.12)
Zhou, 2023	12 mos.	Other	DB	KL 1, 2, 3	LP-PRP	3 injections, all within 14 days	LR-PRP	3 injections, all within 14 days	27	26	-0.14 (-0.61, 0.33)
Subgroup, PL (I^2 = 90.3%, p = 0.001)											0.75 (-1.62, 3.37)



SOE: low

SOE: insuff.

- ***No differences*** in pooled analyses at any timepoint
  - At intermediate and long term, individual point estimates in opposite directions (good-quality RCT no difference; fair-quality RCT favored LR-PRP), substantial heterogeneity
  - Differences in treatment regimen, OA grades may explain some of the variation

Key Question 2b: Safety of PRP (Knee OA)

KQ 2b: PRP Safety

- 14 RCTs, 1 NRSI (randomized by knee) that evaluated PRP reported adverse events; small sample sizes
  - 9 RCTs, 1 NRSI reported **SAEs (SOE: Insufficient)**
    - Comparators: saline (4 RCTs, 1 NRSI), steroids (1 RCT), exercise (1 RCT), and prolotherapy (1 RCT); # PRP injections (2 RCTs) and LP- vs. LR-PRP (1 RCT)
  - 9 RCTs reported other AEs
    - Comparators: saline (5 RCTs), steroids (3 RCTs), exercise (2 RCTs); # PRP injections (1 RCT) and LP- vs. LR-PRP (1 RCT)
- Harms, complications, AEs poorly reported.
- It is unclear whether patients could have >1 event
- Substantial heterogeneity regarding types of adverse events, how they were categorized and how they were reported.

KQ 2b: PRP Safety – Serious AEs

Adverse event	Study	Comparison	PRP % (n/N)	Control % (n/N)
Serious treatment related AEs*	Bennell, 2021	PPR vs. Placebo	0% (0/138)	0% (0/140)
	Pishgahi, 2020	PRP vs. Prolotherapy	0% (0/30)	0% (0/30)
Serious AEs	Chu, 2022†	PRP vs. Placebo	0% (0/308	NR
	Elik, 2020‡	PRP vs. Placebo	0% (0/30)	0% (0/27)
	Ghai, 2019§	PRP vs. Placebo	5% (1/20 knees)	0% (0/20 knees)
	Patel, 2013**	PRP (1 inj.) vs. Placebo	0% (0/26)	0% (0/23)
		PRP (2 inj.) vs. Placebo	0% (0/25)	0% (0/23)
		PRP (1 inj.) vs. PRP (2 inj.)	0% (0/26)	0% (0/25)
	Elksnins-Finogejevs, 2020**	PRP vs. Steroid	0% (0/19)	0% (0/17)
	Angoorani, 2015**	PRP vs. Exercise	0% (0/26)	0% (0/24)
	Kavadar, 2015**	PRP (1 inj.) vs. PRP (2 inj.)	0% (0/34)	0% (0/34)
		PRP (1 inj.) vs. PRP (3 inj.)	0% (0/34)	0% (0/34)
		PRP (2 inj.) vs. PRP (3 inj.)	0% (0/34)	0% (0/34)
	Zhou, 2023††	P-PRP vs. L-PRP	0% (0/27)	11.5% (3/26)
Treatment-related AEs *(unclear if serious)*	Wu, 2018	PRP vs. Placebo	0% (0/20 knees)	0% (0/20 knees)
	Nabi, 2018	PRP vs. Steroid	0% (0/33)	0% (0/34)

§severe inflammation with swelling, stiffness post-inj.
††serious swelling and fever not beyond 37.5 C/99.5 F.

➢ **INSUFFICIENT EVIDENCE**

Aggregate Analytics

KQ 2b: PRP Safety – Other AEs

Adverse event	Study	Comparison	PRP % (n/N)	Control % (n/N)	RR (95% CI)
Mild pain	Bennell, 2021	PPR vs. Saline	18.1% (25/138)	15.0% (21/140)	1.21 (0.71 to 2.05)
	Elik, 2020	PRP vs. Saline	16.7% (5/30)	11.1% (3/27)	1.5 (0.4 to 5.69)
	Akan, 2018	PRP vs. Exercise	33.3% (7/30)	NR	-
Swelling	Bennell, 2021	PRP vs. Saline	2.2% (3/138)	0% (0/140)	-
Swelling & pain	Angoorani, 2015	PRP vs. Exercise	11.5% (3/26)	4.2% (1/24)	2.77 (0.31 to 24.85)
	Akan, 2018	PRP vs. Exercise	20.0% (6/30)	NR	-
	Zhou, 2023[†††]	P-PRP vs. L-PRP	14.8% (4/27)	30.8% (8/26)	0.48 (0.16 to 1.41)
Knee stiffness	Bennell, 2021	PRP vs. Saline	3.6% (5/138)	0% (0/140)	-
Mild synovitis	Elksnins-Finogejevs, 2020	PRP vs. Steroid	78.9% (15/19)	0% (0/17)	-
Other mixed or undefined	Bennell, 2021[‡‡]	PRP vs. Saline	22.5% (31/138)	16.4% (23/140)	1.37 (0.84 to 2.22)
	Nunes-Tamashiro, 2022	PRP vs. Saline	0% (0/34)	0% (0/33)	-
		PRP vs. Steroid	0% (0/34)	0% (0/33)	
	Patel, 2013[§§]	PRP (1 inj.) vs. Saline	23.1% (6/26)	0% (0/23)	-
		PRP (2 inj.) vs. Saline	44% (11/25)	0% (0/23)	-
		PRP (1 inj.) vs. PRP (2 inj.)	23.1% (6/26)	44% (11/25)	0.52 (0.23 to 1.20)
	Wu, 2018	PRP vs. Saline	0% (0/20 knees)	0% (0/20 knees)	-
	Jubert, 2017	PRP vs. Steroid	0% (0/40)	0% (0/40)	-
	Akan, 2018[***]	PRP vs. Exercise	0% (0/30)	NR	-

KQ 2c: Differential effectiveness of PRP (Knee OA)

KQ 2c: Differential Effects of PRP

- 1 fair-quality RCT of **PRP vs. saline** from prior report
- OA stage *may* modify treatment (PRP patients with early OA better function, QOL than those with advanced OA); 6 months
  - MDs differ for the early and advanced OA groups; there is no overlap in the confidence intervals; no test for interaction reported
- Evidence is insufficient

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

KQ 2d: Cost-effectiveness of PRP

- No evidence other than that for HA vs. PRP summarized in HA section (KQ 1d)

Summary of Findings
KQ 1: HA

Knee OA
Hip OA

Summary: KQ 1a
HA vs. placebo (saline) for knee OA

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

Improvement favors HA unless otherwise indicated

Summary: KQ 1a
HA vs. PRP for Knee OA

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success	No difference (SOE: Low); 4 RCTs	HA – **lower likelihood** (SOE: Low); 1 RCT	HA – **lower likelihood** (SOE: Low), 1 RCT
WOMAC PF Scores	No difference (SOE: Low); 4 RCTs	Small - **PRP Favored** (SOE: Low); 4 RCTs	Small - **PRP Favored** (SOE: Low); 4 RCTs
IKCD	No difference (SOE: Low); 2 RCTs	Small - **PRP Favored** (SOE: Low); 3 RCTs	Small - **PRP Favored** (SOE: Low); 42RCTs
Lysholm	No difference (SOE: Low); 2 RCTs	INSUFFICIENT	INSUFFICIENT
WOMAC pain Success	No difference (SOE: Low); 4 RCTs	Small - **PRP Favored** (SOE: Low); 1 RCT	No evidence
WOMAC Pain	No difference (SOE: Low); 6 RCTs	Small - **PRP Favored** (SOE: Low);4 RCTs	Small - **PRP Favored** (SOE: Low); 5 RCTs
VAS pain	Small - **PRP Favored** (SOE: Low); 5 RCTs	Small - **PRP Favored** (SOE: Low); 6 RCTs	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

Aggregate Analytics

Improvement favors HA unless otherwise indicated

Summary: KQ 1a
HA vs. steroid for knee OA

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

Improvement favors HA unless otherwise indicated

Aggregate Analytics

Summary: KQ 1a
HA vs. NSAIDs for knee OA

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success	No evidence	No difference (SOE: Low); 1 RCT (oral NSAID)	No difference (SOE: Low); 1 RCTs (oral NSAID)
WOMAC PF Scores	No evidence	Small (SOE: Low); 1 RCT (oral NSAID)	Small -***favoring oral NSAIDs*** (SOE: Low); 1 RCT
WOMAC Pain VAS Pain Success	No evidence	No difference (SOE: Low); 1 RCTs (oral NSAID)	No difference (SOE: Low); 1 RCT (oral NSAID)
WOMAC Pain Scores	No evidence	Moderate (SOE: Low); 1 RCTs (oral NSAID)	No difference (SOE: Low); 1 RCT (oral NSAID)
VAS pain scores	No evidence	Small (SOE: Low); 1 RCT (oral NSAID)	Small - ***favoring oral NSAIDs*** (SOE: Low); 1 RCT
		No difference (SOE: Low); 1 RCTs (IM NSAID)	No difference (SOE: Low); 1 RCTs (IM NSAID)

Aggregate Analytics

Improvement favors HA unless otherwise indicated

Summary: KQ 1a
HA vs. PT and prolotherapy for knee OA

Both PT and prolotherapy were favored over HA at short term

No evidence at either intermediate or long term

HA vs. Physical Therapy

	Short term (≤3 months)
KOOS ADL	No difference (SOE: Low); 1 RCTs
KOOS S&R	Small - **favoring PT** (SOE: Low);1 RCT
VAS pain scores	Moderate - **favoring PT** SOE: Low); 1 RCT
KOOS Pain	Small - **favoring PT** (SOE: Low); 1 RCT

HA vs. Prolotherapy

	Short term (≤3 months)
KOOS ADL	INSUFFICIENT
KOOS S&R	Small **- favoring Prolotherapy** (SOE: Low);1 RCT
VAS pain scores	Large - **favoring Prolotherapy** SOE: Low); 1 RCT
KOOS Pain	Small - **favoring Prolotherapy** SOE: Low); 1 RCT

Aggregate Analytics

Summary: KQ 1a
HA (animal derived) vs. HA (nonanimal derived) for knee OA

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

Aggregate Analytics

Summary: KQ 1b
Harms and Safety of HA for knee OA

- Harms poorly described; substantial heterogeneity in classification, reporting
- Serious AEs: uncommon, no difference with HA (0% to 4.3%) vs. saline (0% to 3.2%); **(SOE: Insufficient)**
- Serious treatment-related AEs: HA 0% - 1.55% vs. saline 0% (1 RCT) **(SOE Insufficient)**
- Treatment-related AEs: more common; *generally*, no differences HA vs. comparators;
  - HA (0% to 26.9%) vs. Saline (0% to 25.8): Significant differences, 1 RCT (15.7% vs. 5.5%, RR 2.89, 95% CI 1.18 to 7.04)
  - Higher risk, treatment-related AEs with HA in single RCTs; significant difference
    - HA vs. steroid: 21.7% vs. 6.8%, RR 3.20, 95% CI 1.85 to 5.54
    - HA vs. usual care: 45% vs. 18%, RR 2.56, 95% CI 1.50 to 4.38
- "Other" AEs:
  - HA (0% - 49.5%) vs. saline (0% - 54%); HA (0% -54.3%) vs. steroid (0% to 64.3%)

SOE: Low for reported treatment-related, "other" AEs and swelling

Summary: KQ 1b
Harms and Safety of HA for knee OA (continued)

HA vs. PRP (SOE Insufficient)

- No serious treatment AEs (1 RCT);
- Withdrawals: HA (6.3% to 4.3%) vs. 0% to 4.3% (2 RCTs)

HA (animal derived) vs. HA (nonanimal derived)
No differences SOE Low

- Severe AE (not specified): 4.6% vs. 3.4%
- Serious AE (not specified): 3.4% vs. 1.7%
- Any treatment-related AE: 9.8% vs. 13.1%
- Pts with ≥ 1 AE: 42.5% vs. 47.4%

Aggregate Analytics

Summary: KQs 1a and 1b
HA vs. placebo (saline) for *hip OA*

	Short	Intermediate	Long
WOMAC PF or Lequesne	No difference (SOE: low); 2 RCTs	No difference (SOE: low); 1 RCT	No evidence
WOMAC pain Success	No difference (SOE: low); 1 RCT	No difference (SOE: low); 1 RCT	No evidence
WOMAC Pain VAS pain	No difference (SOE: low); 2 RCTs	No difference (SOE: low);1 RCT	No evidence
WOMAC Total	INSUFFICIENT	INSUFFICIENT	No evidence
OMERACT	INSUFFICIENT	INSUFFICIENT	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	No evidence
Serious AEs	INSUFFICIENT	INSUFFICIENT	No evidence
Tx-Related* AEs	Any time; No difference (SOE: low); 1 RCT		No evidence
Withdrawal due to AE	Any time; No difference (SOE: low); 1 RCT		No evidence

Improvement favors HA unless otherwise indicated

Summary: KQs 1a and 1b
HA vs. PRP for *hip* OA

	Short	Intermediate	Long
WOMAC PF	No difference (SOE: low); 1 RCT	No evidence	No difference (SOE: low); 1 RCT
WOMAC Pain VAS pain	No difference (SOE: low); 1RCT	No evidence	No difference (SOE: low); 1 RCT
WOMAC Total	No difference (SOE: low); 1 RCT	No evidence	No difference (SOE: low); 1RCT
Harris Hip	No difference (SOE: low); 1 RCT	No evidence	No difference (SOE: low); 1 RCT
OMERACT	No difference (SOE: low); 1 RCT	No difference (SOE: low); 1 RCT	No difference (SOE: low); 1 RCT
Arthroplasty	Any time: No difference (SOE: low); 1 RCT		
Serious AEs	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

Aggregate Analytics

Improvement favors HA unless otherwise indicated

Summary: KQs 1a and 1b
HA vs. Steroids for *hip* OA

	Short	Intermediate	Long
Lequesne	No difference (SOE: low);1 RCT	No evidence	No evidence
VAS pain	INSUFFICIENT	No evidence	No evidence
WOMAC Total	INSUFFICIENT	No evidence	No evidence
OMERACT	INSUFFICIENT	No evidence	No evidence
Arthroplasty	INSUFFICIENT	No evidence	No evidence
Serious AEs	INSUFFICIENT	No evidence	No evidence

Improvement favors HA unless otherwise indicated

Aggregate Analytics

Summary: KQs 1c and 1d

- Differential effectiveness: Insufficient
- Cost-effectiveness of HA vs. conventional care
  - Knee OA: 7 economic studies, most funded by industry conclude that HA is cost-effectives vs. conventional care
  - Hip OA: 1 poor quality non-US based study
- Cost-effectiveness of PRP vs. HA
  - Poor quality study concluded that PRP is not more cost-effective than HA, but at 1 year PRP is more effective

Aggregate Analytics

Summary of Findings
KQ 2: PRP

Knee OA

Aggregate Analytics

Summary: KQ 2a
PRP vs. saline for knee OA

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

Aggregate Analytics

Improvement favors PRP unless otherwise indicated

Summary: KQ 2a
PRP vs. steroid for knee OA

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

Aggregate Analytics

Improvement favors PRP unless otherwise indicated

Summary: KQ 2a
PRP vs. oral analgesics for knee OA

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

Improvement favors PRP unless otherwise indicated

Aggregate Analytics

Summary: KQ 2a
PRP vs. exercise for knee OA

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

Improvement favors PRP unless otherwise indicated

Aggregate Analytics

Summary: KQ 2a
PRP vs. PT and vs. prolotherapy for knee OA

All evidence ***insufficient*** to draw conclusions due to study quality (all poor-quality):

- **PRP vs. PT**: 1 RCT (N=40): WOMAC physical function scores and VAS pain scores short term (3 months).
- **PRP vs. Prolotherapy**: 2 RCTs (N=42 and 60): WOMAC physical function scores, WOMAC pain scores and VAS pain scores short (1-2 months) and intermediate term (6 months)

Aggregate Analytics

Summary: KQ 2a
Greater vs. fewer number of PRP injections for knee OA

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

Aggregate Analytics

Improvement favors greater number of PRP injections unless otherwise indicated

Summary: KQ 2a
LP- vs. LR-PRP injections for knee OA

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

Improvement favors LP-PRP unless otherwise indicated

Aggregate Analytics

Summary KQ 2b: PRP Safety – Serious AEs

- 9 RCTs, 1 NRSI evaluating PRP reported SAEs
- Comparators included placebo (4 RCTs, 1 NRSI), steroids (1 RCT), exercise (1 RCT), and prolotherapy (1 RCT); number of PRP injections (2 RCTs) and LP- vs. LR-PRP (1 RCT)
- Only 2 studies reported a SAE as defined by the authors:
  - **Severe swelling and mild fever**: 3/26 (12%) LR-PRP patients vs. no patient LP-PRP patient; 1 required arthroscopic debridement to treat symptoms (1 RCT)
  - **Severe inflammation with swelling and stiffness immediately post-injection**: 1/20 knees (5%) randomized to LP-PRP vs. none with saline injection; sx persisted for 2 weeks and then improved (1 NRSI).
- Across the other 8 RCTs, no serious treatment-related adverse events were reported to have occurred.

Aggregate Analytics

Summary KQ 2b: PRP Safety – Serious AEs, cont.

- Evidence on safety/harms for PRP was considered **INSUFFICIENT** due to generally poor reporting of SAEs and small sample sizes.
- Substantial heterogeneity regarding how AEs were categorized, reported and described (if described at all); many trials simply state that “no serious adverse events occurred”.

Aggregate Analytics

Summary: KQs 2c and 2d

- **Differential effectiveness**: Insufficient evidence

- **Cost-effectiveness** of PRP vs. HA
  - Poor quality study concluded that PRP is not more cost-effective than HA, but at 1 year, PRP is more effective (see KQ 1d)

Aggregate Analytics

Considerations

Considerations

HA for treatment of knee and hip OA

- Heterogeneity in available products, study protocols, methods
- Lack of standardization: High vs. low molecular weight, treatment protocols (dose, injection frequency and timing)
- Few RCTs: HA vs. conservative measures; hip OA
- Most RCTs industry funded

PRP for treatment of knee and hip OA

- There is substantial heterogeneity across studies
- Lack of standardization: LR vs. LP-PRP; treatment protocols
- No U.S.-based trials

HA and PRP:

- Insufficient evidence: differential effectiveness/harms
- Harms: poor reporting, heterogeneity of classification, power

Appendix

Summaries

HA vs. Saline

PRP vs. Saline

HA vs. PRP

Aggregate Analytics

Summary: KQ 1a
HA vs. placebo (saline) for knee OA

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

Improvement favors HA unless otherwise indicated

Summary: KQ 2a
PRP vs. saline for knee OA

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

Aggregate Analytics

Improvement favors PRP unless otherwise indicated

Summary: KQ 1a
HA vs. PRP for Knee OA

	Short term (≤3 months)	Intermediate term (>3 to <12 months)	Long term (≥12 months)
WOMAC PF Success	No difference (SOE: Low); 4 RCTs	HA – **lower likelihood** (SOE: Low); 1 RCT	HA – **lower likelihood** (SOE: Low), 1 RCT
WOMAC PF Scores	No difference (SOE: Low); 4 RCTs	Small - **PRP Favored** (SOE: Low); 4 RCTs	Small - **PRP Favored** (SOE: Low); 4 RCTs
IKCD	No difference (SOE: Low); 2 RCTs	Small - **PRP Favored** (SOE: Low); 3 RCTs	Small - **PRP Favored** (SOE: Low); 42RCTs
Lysholm	No difference (SOE: Low); 2 RCTs	INSUFFICIENT	INSUFFICIENT
WOMAC pain Success	No difference (SOE: Low); 4 RCTs	Small - **PRP Favored** (SOE: Low); 1 RCT	No evidence
WOMAC Pain	No difference (SOE: Low); 6 RCTs	Small - **PRP Favored** (SOE: Low);4 RCTs	Small - **PRP Favored** (SOE: Low); 5 RCTs
VAS pain	Small - **PRP Favored** (SOE: Low); 5 RCTs	Small - **PRP Favored** (SOE: Low); 6 RCTs	No evidence
Invasive procedures	INSUFFICIENT	INSUFFICIENT	INSUFFICIENT

Aggregate Analytics

Improvement favors HA unless otherwise indicated

HTCC Coverage and Reimbursement Determination
Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.

Based on Legislative mandate: RCW 70.14.100(2).

The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

3. *Factors for Consideration - Importance*

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the

task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical committee evidence votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Serious related adverse events		
Serious adverse events		
Treatment-related adverse events		
Other adverse events		
Swelling, Pain		
Treatment/study withdrawal		
Knee Stiffness		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Physical function scores (WOMAC, IKDC, Lysholm, KOOS)		
Activities of daily living (ADL) (KOOS, KSL)		
Pain scores (WOMAC, VAS, KOOS)		
Responder criteria (OMERACT-OARSI)		
QOL (EQ-VAS)		
Secondary invasive procedures (e.g. TKA)		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost-effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Osteoarthritis stage		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is:

Not covered	Covered unconditionally	Covered with conditions

Discussion item

Is the determination consistent with identified national coverage determinations issued by the Centers for Medicare and Medicaid services and expert guidelines, and if not, what evidence is relied upon.

Medicare Coverage

[See page 43-47 of Final Evidence Report]

Hyaluronic acid:
There is no current National Coverage Decision for hyaluronic acid for treatment of osteoarthritis.

Platelet-rich plasma:
There is a National Coverage Determinate for Platelet-rich plasma for certain non-healing wounds, however, it is not for conditions included in this report.

Clinical Practice Guidelines

[See pages 19-20 of Final Evidence Report]

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

			PRP use in both the knee and hip	
Osteoarthritis Research Society International (OARSI)	2019	• NR	• HA: OARSI conditionally recommends use of IAHA • PRP: OARSI strongly recommends against use of PRP	• HA: • PRP: Extremely low quality
Arthroscopy Association of Canada (AAC)	2019	• NR	• HA: Intra-articular injections of HMW HA provide improved pain relief and the restoration of function compared with placebo and can be considered in patients with mild to moderate knee OA • PRP: We cannot recommend for or against the use of PRP until further high-quality clinical studies become available	• HA: Good - A • PRP: Conflicting or poor-quality - C
EUROpean VIScosupplementation COnsensus Group (EUROVISCO)	2018	• NR	• HA: Recommended when NSAIDs are not effective	• NR
American Medical Society for Sports Medicine (AMSSM)	2016	• 11 studies	• AMSSM recommends the use of HA for the appropriate patients with knee OA (OMERACT-OARSI criteria)	• Over 60 years old: High quality • Under 60 years old: Moderate quality
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)	2016	• NR	• ESCEO task force recommends the use of IA HA in knee OA patients with mild-moderate disease, and for more severe patients who are either contraindicated to TKR surgery or wishing to delay the surgical procedure	• Good
National Institute for Health and Care Excellence (NICE)	2014	• 1 SR, 20 comparative studies	• Do not offer intra-articular hyaluronan injections for the	• Moderate/Low (based on study

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

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

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.

Washington State Health Care Authority

FINAL Key Questions and Background

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

Background

Osteoarthritis (OA) is one of the most common disabilities affecting people in the United States, with roughly 32.5 million Americans currently affected.[1] This number is projected to grow in the coming years, with estimates as high as 29.5% of US adults over the age of 45 by 2032.[2] Osteoarthritis, which most commonly occurs in the knee and hip, often causes pain, fatigue, disability, and general limitations to daily life activities that impact physical, mental, and emotional wellbeing.[1] There is no cure for this condition and, as such, treatment can become considerably expensive long term. Healthcare cost due to osteoarthritis in the United States is estimated at $45.4 billion per year, with affected individuals paying an additional $1778 per year in healthcare costs on average.[3] Reduced ability to work results in additional wage loss of $1114 per year, more than double that of those without osteoarthritis ($517).[3]

Osteoarthritis is a progressive disease that may often lead to joint failure requiring total joint replacement. Given the generally slow rate of progression of the disease, however, care in the interim before eligibility or need for replacement surgery is of the utmost importance. Conservative management of osteoarthritis commonly includes exercise and physical therapy, use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, use of supportive devices, weight loss, corticosteroid injections and may include hyaluronic acid (HA, viscosupplementation) and intra-articular platelet-rich plasma (PRP).[4] Exercise and physical therapy are currently considered front-line treatments for knee and hip osteoarthritis and provide considerable benefit both for pain relief and maintenance of functionality, but may be difficult to begin for overweight or obese individuals and time commitments and costs may present challenges to some.[5] Pain medications such as NSAIDs and acetaminophen are commonly recommended or prescribed for relief of pain and inflammation caused by osteoarthritis. These medications are generally easy to access and carry relatively low cost, but long-term use increases risk of potentially serious adverse events such as stomach, kidney, and liver damage, heart attack, and stroke.[6,7] Supportive devices are commonly used by osteoarthritis patients, with between 40% and 76% of patients utilizing an assisted walking device such as a cane, walker, or crutches.[8] Evidence on the efficacy of these devices for pain reduction and slowing of disease progression, however, is limited and contradictory to professional consensus.[8,9] Weight loss has shown to be effective at reducing pain and increasing functionality in osteoarthritis patients, but this benefit is only available to overweight and obese individuals and there may be significant barriers to achieving weight loss, including pain and reduced functionality from the disease itself.[10] Less commonly, conservative care may include use of opiate medications, acupuncture, and supplements such as turmeric or glucosamine chondroitin.

Intra-articular corticosteroid injections may be effective at reducing pain in knee and hip osteoarthritis patients in short- and medium-term settings, but carry risk of adverse events such as pain flare and rapid destructive osteoarthritis of the joint[11,12] as well as increased risk of post-operative surgical infection months following injection, transient increases in blood sugar and hypertension and transient decrease in immune response. Viscosupplementation is an increasingly popular treatment for knee and hip osteoarthritis over the last twenty years. Viscosupplementation with intra-articular hyaluronic acid (IAHA) is most commonly provided to individuals who are unable to utilize or do not respond well to other front-line or preferred treatments; it may provide anti-inflammatory, analgesic, and

chondroprotective effects.[13] Hyaluronic acid products require approval from the Food and Drug Administration (FDA), which notes numerous mild to moderate adverse events such as swelling, pain, and edema at injection site and lack of sufficient evidence for non-knee indications.[14] PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with a similar adverse event risk profile, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated.[15]

While IAHA and PRP are not curative, they may provide some longer-term relief compared with some primary treatment modalities and may be more acceptable to some patients. Previous reviews of the effectiveness of HA and PRP report mixed results on the effectiveness of these for pain reduction and/or functional improvement. There has been a considerable increase in available evidence on the use of HA and PRP for knee and hip OA since the publication of prior reviews for the Washington State Health Technology Assessment Program in 2013 and 2016, respectively, and re-review of the evidence is therefore warranted.

Policy context

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

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

Final Key Questions and Scope of this HTA

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

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

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

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

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

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

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

PICOTS/Scope:

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

Study Component	Inclusion	Exclusion
	• Arthroscopic lavage and/or debridement • Prolotherapy • Corticosteroid injection • Placebo or sham • No treatment	blood products [e.g., autologous conditioned serum"] medicinal signaling cells, mesenchymal stem cells, "stem cell", adipose, fat, or microfat injections); peptide injections • Ozone treatment • Non-FDA approved treatments • Herbal treatments • Acupuncture • Nerve ablation
Outcomes	**Primary** • Function • Pain • Need for secondary invasive procedures (e.g., surgery) • Adverse events or harms **Secondary** • Symptom Recurrence (e.g., persistent or increased pain, reduced function) resulting in need for additional injection of HA or PRP within 2 months after protocol completion • Quality of life • Medication use • Return to normal activities (sports, work, or activity level) **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome	• Non-clinical outcomes • Non-validated measures (e.g., for pain, function, QOL)
Timing	Review will focus on persistence of relief 1 or more months post-treatment	
Study design	**Focus will be on studies with the least potential for bias with ≥ 1 month post treatment results** **Key Questions 1 and 2 parts a and b:** • High quality systematic reviews of RCTs will be considered if available and they address the key questions. • Randomized controlled trials (RCTs) • In the absence of RCTs, high quality non-randomized comparative studies will be	• Indirect comparisons • Comparisons with historical cohorts • Noncomparative studies (case series, single arm studies, pre-post) • Nonrandomized studies which do not control for confounding • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients per treatment group • Case reports

Study Component	Inclusion	Exclusion
	considered in the absence of RCTs with a focus on comparative prospective studies **Key Question 1b and 2b:** • KQ2: In the absence of RCTs, high-quality non-randomized studies designed specifically to evaluate harms/adverse events that are rare or occur long-term **Key Question 1c and 2c:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest and test for interaction. **Key Question 1d and 2d:** Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Studies in which <80% of patients have a condition of interest • Studies that do not report on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)	• Abstracts, conference proceedings, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

Study Component	Inclusion	Exclusion
Population	Adults with symptomatic knee or hip osteoarthritis Subpopulations based on patient characteristics, primary or secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options	• Conditions other than knee or hip OA • Patients <18 years old • Asymptomatic individuals
Intervention	Autologous PRP injection(s) or hyaluronic acid (HA) (viscosupplementation) injection(s) used as the primary intervention or in conjunction with common conservative care options	• Non-FDA-approved HA (viscosupplementation) formulations; products undergoing phase III trials may be considered • PRP or HA used in conjunction with another intervention not listed for inclusion (e.g., open, arthroscopic or minimally invasive surgery, invasive procedures are not included) • Combinations of HA with PRP together

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

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

References

1. Osteoarthritis Action Alliance, Thurston Arthritis Research Center at the University of North Carolina. OA Prevalence and Burden - Osteoarthritis Action Alliance. OA. Published 2021. Accessed September 21, 2022. https://oaaction.unc.edu/oa-module/oa-prevalence-and-burden/
2. Turkiewicz A, Petersson IF, Björk J, et al. Current and future impact of osteoarthritis on health

care: a population-based study with projections to year 2032. *Osteoarthr Cartil*. 2014;22(11):1826-1832. doi:10.1016/J.JOCA.2014.07.015
3. Zhao X, Shah D, Gandhi K, et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. *Osteoarthr Cartil*. 2019;27(11):1618-1626. doi:10.1016/j.joca.2019.07.002
4. Centers for Disease Control, Prevention. Osteoarthritis (CDC). *Website*. Published online 2015:Osteoarthritis (OA). Accessed September 21, 2022. https://www.cdc.gov/arthritis/types/osteoarthritis.htm
5. Skou ST, Roos EM. Physical therapy for patients with knee and hip osteoarthritis: supervised, active treatment is current best practice. *Clin Exp Rheumatol*. 2019;37(5):112-117. Accessed September 21, 2022. https://www.clinexprheumatol.org/abstract.asp?a=14740
6. Da Costa BR, Pereira T V., Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ*. 2021;375. doi:10.1136/BMJ.N2321
7. Can arthritis pain medications be harmful? - Mayo Clinic. Accessed September 21, 2022. https://www.mayoclinic.org/diseases-conditions/arthritis/expert-answers/arthritis-pain-medications/faq-20058391
8. Carbone LD, Satterfield S, Liu C, et al. Assistive Walking Device Use and Knee Osteoarthritis: the Health, Aging, and Body Composition Study (Health ABC Study). *Arch Phys Med Rehabil*. 2013;94(2):332. doi:10.1016/J.APMR.2012.09.021
9. Anandacoomarasamy A, March L. Current Evidence for Osteoarthritis Treatments. *Ther Adv Musculoskelet Dis*. 2010;2(1):17. doi:10.1177/1759720X09359889
10. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons – a scoping review. *Obes Rev*. 2014;15(7):578. doi:10.1111/OBR.12173
11. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ Br Med J*. 2004;328(7444):869. doi:10.1136/BMJ.38039.573970.7C
12. Choueiri M, Chevalier X, Eymard F. Intraarticular Corticosteroids for Hip Osteoarthritis: AReview. *Cartilage*. 2021;13(1 Suppl):122S. doi:10.1177/1947603520951634
13. Food and Drug Administration. Federal Register :: Intent To Consider the Appropriate Classification of Hyaluronic Acid Intra-articular Products Intended for the Treatment of Pain in Osteoarthritis of the Knee Based on Scientific Evidence. Published 2018. Accessed September 21, 2022. https://www.federalregister.gov/documents/2018/12/18/2018-27351/intent-to-consider-the-appropriate-classification-of-hyaluronic-acid-intra-articular-products
14. Margerrison E, Argentieri M, Kommala D, Schabowsky CN. Hyaluronic Acid (HA) Safety Profile Report Details Date of Submission ECRI Corporate Governance Project Manager. Published online 2021.
15. Bennell KL, Hunter DJ, Paterson KL. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. *Curr Rheumatol Rep*. 2017;19(5). doi:10.1007/S11926-017-0652-X