2.01.98	Orthopedic Applications of Platelet-Rich Plasma		
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Section:	2.0 Medicine	**Page:**	Page 1 of 38

Policy Statement

I. Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations:
   A. Primary use (injection) for the following conditions:
      1. Achilles tendinopathy
      2. Lateral epicondylitis
      3. Plantar fasciitis
      4. Osteochondral lesions
      5. Osteoarthritis
   B. Adjunctive use in the following surgical procedures:
      1. Anterior cruciate ligament (ACL) reconstruction
      2. Hip fracture
      3. Long-bone nonunion
      4. Patellar tendon repair
      5. Rotator cuff repair
      6. Spinal fusion
      7. Subacromial decompression surgery
      8. Total knee arthroplasty (TKA)

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

Description

The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Related Policies

- Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions
- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)
- Prolotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract

language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1,270 and 1,271. Blood products such as platelet-rich plasma are included in these regulations. Under these regulations, certain products including blood products such as platelet-rich plasma are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated platelet-rich plasma. A number of platelet-rich plasma preparation systems are available, many of which were cleared for marketing by the FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of platelet-rich plasma outside of this setting (eg, an office injection) would be considered off-label. The Aurix System® (previously called AutoloGel™; Nuo Therapeutics) and SafeBlood®

(SafeBlood Technologies) are 2 related but distinct autologous blood-derived preparations that can be used at the bedside for immediate application. Both AutoloGel™ and SafeBlood® have been specifically marketed for wound healing. Other devices may be used during surgery (eg, autoLog® Autotransfusion system [Medtronic], the SmartPRePÒ [Harvest Technologies] device). The Magellan® Autologous Platelet Separator System (Isto Biologics) includes a disposable kit for use with the Magellan Autologous Platelet Separator portable tabletop centrifuge. GPS® II (BioMet Biologics), a gravitational platelet separation system, was cleared for marketing by the FDA through the 510(k) process for use as disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site (GPS® III [Zimmer Biomet] is now available). Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. The use of different devices and procedures can lead to variable concentrations of activated platelets and associated proteins, increasing variability between studies of clinical efficacy.

Rationale

Background

Platelet-Rich Plasma

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of platelet-derived growth factor, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant platelet-derived growth factor has also been extensively investigated for clinical use in wound healing (see Blue Shield of California Medical Policy: Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions).

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, platelet-rich

plasma has been investigated as an adjunct to various periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factor , and thus platelet-rich plasma has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, platelet-rich plasma may be injected directly into various tissues. Platelet -rich plasma injections have been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren contracture.

Injection of platelet-rich plasma for tendon and ligament pain is theoretically related to prolotherapy (see Blue Shield of California Medical Policy: Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions). However, prolotherapy differs in that it involves the injection of chemical irritants intended to stimulate inflammatory responses and induce the release of endogenous growth factors.

Platelet-rich plasma is distinguished from fibrin glues or sealants, which have been used as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and VITASEAL™ (Johnson & Johnson Surgical Technologies) are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.
To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

At present, there are a large number of techniques available for the preparation of platelet-rich plasma or platelet-rich plasma gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is also uncertain whether platelet activation before the injection is necessary.[1,2,3,4,5,6,]

Platelet-Rich Plasma as a Primary Treatment for Tendinopathy

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, and anti-inflammatory agents, in individuals with tendinopathy.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with tendinopathy.

Interventions

The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, and anti-inflammatory agents.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for tendinopathy has varying lengths of follow-up, ranging from 6 months to 2 years. While studies described below all reported at least 1 outcome of interest, longer follow-up is necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Many systematic reviews have evaluated platelet-rich plasma for treating mixed tendinopathies. They include trials on tendinopathies of the Achilles, rotator cuff, patella, and/or lateral epicondyle (tennis elbow). Select, recent (i.e., 2019 to present) systematic reviews of RCTs and/or nonrandomized studies are described next. A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A1). Characteristics and results of these systematic reviews are found in Tables 1 and 2.

Masiello et al (2022) conducted a systematic review and meta-analysis of 33 RCTs (N=2025) comparing ultrasound-guided platelet-rich plasma to control (injection of steroids, saline, autologous whole blood, mesenchymal stem cells, or local anesthetic; dry needling; prolotherapy; or other non-injection intervention) for the treatment of tendinopathy.[7,] Tendinopathies included lateral epicondylitis (n=8), plantar fasciitis (n=5), Achilles tendinopathy (n=5), rotator cuff tendinopathy (n=7), patellar tendinopathy (n=3), and carpal tunnel syndrome (n=3). Most trials (n=20) administered platelet-rich plasma as a single injection; however, up to 4 injections were administered in some

trials. Few differences in efficacy between control and platelet-rich plasma were found with the exception of patients with carpal tunnel where pain and severity scores were reduced in the short and medium term. Results were reported for individual tendinopathies and, therefore, are not included in Table 2. However, overall mean differences in pain scores were: -0.24 (95% confidence interval [CI], -0.73 to 0.25) for lateral epicondylitis, -3.62 (95% CI, -8.16 to 0.91) for plantar fasciitis, -0.17 (95% CI, -4.25 to 3.90) for Achilles tendinopathy, 0.16 (95% CI, -0.18 to 0.50) for rotator cuff tendinopathy, 0.17 (95% CI, -0.64 to 0.98) for patellar tendinopathy, and -0.24 (95% CI, -0.32 to -0.16) for carpal tunnel syndrome. The evidence was rated as low quality due to risk of bias, imprecision, and inconsistency. Dai et al (2023) conducted a systematic review and meta-analysis of RCTs evaluating platelet-rich plasma versus control (saline injection, dry needling, or no treatment) for the treatment of tendinopathy.[8,] A total of 13 trials met the eligibility criteria and included patients with lateral epicondylitis (5 RCTs), Achilles tendinopathy (4 RCTs), rotator cuff tendinopathy (2 RCTs), and patellar tendinopathy (2 RCTs). Among the 13 RCTs, 7 studies were judged to be at low risk of bias and 6 were found to have a high risk of bias. The meta-analysis demonstrated that platelet-rich plasma was not superior to control for the primary outcomes of change in pain intensity or function at 12 weeks; these trends also persisted at 24 weeks. The authors noted that included trials displayed significant heterogeneity with respect to platelet-rich plasma preparation and patient characteristics, and had important methodological limitations.

Muthu et al (2021) conducted a systematic review with meta-analysis of RCTs comparing platelet-rich plasma, autologous blood, corticosteroids, local anesthetics, laser therapy, and surgery for patients with lateral epicondylitis.[9,] A total of 25 trials met the eligibility criteria (N=2040). Results demonstrated that based on data from 22 trials, only leukocyte-rich platelet-rich plasma significantly improved visual analog scale (VAS) pain scores compared to saline control (weighted mean difference [MD], -14.8; 95% CI, -23.18 to -6.39); in a subgroup analysis of 14 studies with at least 12 months of follow up, the weighted MD did not reach statistical significance (-7.69; 95% CI, -27.28 to 11.90). Based on data from 11 trials, none of the interventions were superior to saline control for improvement in the Disabilities of the Arm, Shoulder and Hand (DASH) score. Treatment ranking based on the P-score approach demonstrated that leukocyte-rich platelet-rich plasma was most likely to be the best treatment amongst autologous blood, corticosteroids, laser therapy, local anesthetics, and leukocyte-poor platelet-rich plasma.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs on platelet-rich plasma for various orthopedic indications, including 10 RCTs of lateral epicondylitis.[10,] The meta-analysis evaluated the standardized MD in pain at both 3 and 12 months. Systematic review authors used the Cochrane Collaboration risk of bias tool to assess study quality. At 12 months, pain scores were statistically significantly lower for platelet-rich plasma versus its comparators (i.e., steroids, whole blood, dry needling, local anesthetics). However, these results should be interpreted with caution due to important limitations including high statistical heterogeneity (I^2 =73%), lack of a clinically significant difference (i.e., < effect size threshold of 0.5 for a clinically important difference), and moderate to high risk of bias in study conduct.

Table 1. Systematic Reviews & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Masiello et al (2022)[7,]	Through 2021	33	Patients with tendinopathy	2025 (NR)	RCT	3 to 36 mo
Dai et al (2023)[8,]	2010-2020	13	Patients with tendinopathy	576 (23 to 79)	RCT	4 to ≥24 wk
Muthu et al (2021)[9,]	2010-2020	25	Patients with lateral epicondylitis	2040 (25 to 230)	RCT	3 to 24 mo
Johal et al (2019)[10,]	2010-2016	10	Patients with lateral epicondylitis	25 to 231	RCT	6 wk to 24 mo

NR: not reported; RCT: randomized controlled trial.

Table 2. Systematic Reviews & Meta-Analysis Results

Study	SMD in Pain for PRP	SMD in functional disability for PRP	WMD in pain reduction (between LR-PRP and control)	WMD in functional disability (between LR-PRP and control)	WMD in pain reduction at 3 months (between LR-PRP and control)	WMD in pain reduction at 1 year (between LR-PRP and control)
Dai et al (2023)[8,]	-0.14	0.18				
95% CI	-0.55 to 0.26	-0.13 to 0.49				
Muthu et al (2021)[9,]			-14.8	-8.77		-7.69
95% CI			-23.18 to -6.39	-30.60 to 13.07		-27.28 to 11.90
Johal et al (2019)[10,]	-0.69					
95% CI	-1.15 to -0.23					

CI: confidence interval; LR: leukocyte-rich; PRP: platelet-rich plasma; SMD: standard mean difference; WMD: weighted mean difference;.

Randomized Controlled Trials

One larger RCT not included in the above systematic reviews was published in 2021 (N=240) comparing platelet-rich plasma to sham control.[11,] Victorian Institute of Sport Assessment-Achilles (VISA-A) score was not significantly different between groups. Tables 3 and 4 summarize the RCT characteristics and results, respectively, and Tables 5 and 6 describe study design and conduct limitations.

Table 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	Comparator 1	Comparator 2
Kearney et al (2021)[11,]	UK	24	2016-2020	Adults with painful midportion Achilles tendinopathy lasting longer than 3 months	PRP (n=121)	Sham (n=119)	

PRP: platelet-rich plasma; RCT: randomized controlled trial; UK: United Kingdom.

Table 4. Summary of Key RCT Results

Study	Other pain / disability assessment
Kearney et al (2021)[11,]	6 mo VISA-A score
PRP	54.4
Sham	53.4
Adjusted MD; 95% CI	-2.7 (-8.8 to 3.3)

CI: confidence interval; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VISA-A: Victorian Institute of Sport Assessment-Achilles score..

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow Up[e]
Kearney et al (2021)[11,]		1. 37 participants received additional treatments during the 6-month follow up	1. 40 participants received additional treatments during the 6-month follow up		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Kearney et al (2021)[11],		1. Single blinded (participants only)				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. 4. Underpowered
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Tendinopathy

Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of platelet-rich plasma injections in individuals who have tendinopathy. The majority of the more recently published systematic reviews and meta-analyses that only included RCTs failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. Although 1 systematic review found statistically significantly lower pain scores at 12 months with platelet-rich plasma versus the comparators, its results should be interpreted with caution due to important study conduct limitations. Additionally, in a recent RCT compared to sham control, platelet-rich plasma did not significantly improve pain after 6 or 12 months.

Platelet-Rich Plasma as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, and anti-inflammatory agents, in individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, and anti-inflammatory agents.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence
In individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis), there are no large double-blind RCTs of sufficient duration (i.e., 2 years) to demonstrate efficacy.

Systematic Reviews
Seth et al (2023) published a systematic review comparing corticosteroid injections to either platelet-rich plasma or extracorporeal shock wave therapy in patients with plantar fasciitis.[12,] The studies were limited to RCTs up to April 2021. A total of 18 studies were included, 12 of which evaluated platelet-rich plasma compared to corticosteroid injections. VAS scores were higher in the corticosteroid group than the platelet-rich plasma group at both 3 (MD, 0.62; 95% CI, 0.13 to 1.12; p=.01) and 6 months (MD, 1.49; 95% CI, 0.22 to 2.76; p=.02). Notably, numerical differences between groups were small.

Functional outcomes were similar with corticosteroids compared to platelet-rich plasma at 3 months but worse with corticosteroids at 6 months (American Orthopaedic Foot and Ankle Society [AOFAS] MD, -11.53; 95% CI, -16.62 to -6.43; p<.0001). The authors deemed the evidence very low quality, and most studies had either high or unclear risk of bias.

Randomized Controlled Trials
There are several additional RCTs not included in the Seth et al (2023) review.[13,14,15,] None were large double-blind RCTs of sufficient duration (i.e., 2 years) to conclusively demonstrate efficacy. The RCTs compared platelet-rich plasma treatment with corticosteroid injection or saline injection. The platelet-rich plasma protocols differed across RCTs. The RCTs were small, ranging in size from 28[15,] to 155 participants.[13,] Follow-up duration ranged from 6 months[15,16,] to 18 months.[14,] Two were conducted in single centers in either the United Kingdom,[15,]or India.[14,] The other was a multicenter RCT of 5 sites in the Netherlands.[15,] None prespecified any methods to assess potential harms. Results were mixed

across RCTs. The largest RCT (N=115) by Peerbooms et al (2019) compared platelet-rich plasma with corticosteroid injection and had a follow-up to 12 months.[13,] In the RCT by Peerbooms et al (2019), the proportion of patients with at least a 25% improvement in Foot Function Index Pain Scores between baseline and 12 months was significantly greater in the platelet-rich plasma group (88.4% vs. 55.6%; p =.003). Additionally, mean Foot Function Index Disability Scores were significantly lower in the platelet-rich plasma group at 12 months (MD, 12.0; 95% CI, 2.3 to 21.6). But, these improvements did not translate into significantly greater quality of life in the platelet-rich plasma group. Also, important study design and conduct gaps exist that seriously limit the interpretation of these findings, including that analysis excluded 29% of the randomized patients, which was less than the calculated sample size. Therefore, although evidence continues to develop, important uncertainties in efficacy and safety remain and larger double-blind RCTs are still needed.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation

Several small RCTs, multiple prospective observational studies, and systematic reviews of these studies have evaluated the efficacy of platelet-rich plasma injections in individuals with chronic plantar fasciitis. The preparation of platelet-rich plasma and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the RCTs showed that treatment using platelet-rich plasma compared with corticosteroids resulted in statistically significant improvements in pain and disability, but not quality of life. Larger RCTs completed over a sufficient duration of time (i.e., 2 years) are still needed to address important uncertainties in efficacy and safety.

Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery in individuals with osteochondral lesions.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with osteochondral lesions.

Interventions

The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for osteochondral lesions has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 28 weeks of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Comparative Studies

No high-quality RCTs on the treatment of osteochondral lesions were identified. Mei-Dan et al (2012) reported on a quasi-randomized study of 29 patients with 30 osteochondral lesions of the talus assigned to 3 intra-articular injections of hyaluronic acid or platelet-rich plasma.[17,] At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale improved to a greater extent in the platelet-rich plasma group (from 68 to 92) than in the hyaluronic acid group (from 66 to 78) ($p<.05$). Subjective global function also improved to a greater extent in the platelet-rich plasma group (from 58 to 91) than in the hyaluronic acid group (from 56 to 73). Interpretation of the composite measures of VAS scores for pain and function is limited by differences between the groups at baseline. Also, neither the patients nor the evaluators were blinded to treatment in this small study.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions

A single quasi-randomized study has evaluated the efficacy of platelet-rich plasma injections in individuals who have osteochondral lesions. Compared with hyaluronic acid, treatment with platelet-rich plasma resulted in statistically significant improvements in AOFAS Ankle-Hindfoot Scale scores and global function, indicating improved outcomes. Adequately powered and blinded RCTs are required to confirm these findings.

Platelet-Rich Plasma as a Primary Treatment of Knee or Hip Osteoarthritis

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery, in individuals with knee or hip osteoarthritis.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with knee or hip osteoarthritis.

Interventions

The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for knee or hip osteoarthritis has varying lengths of follow-up, ranging from 6 to 12 months. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 12 months of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

A number of RCTs and several systematic reviews of RCTs evaluating the use of platelet-rich plasma for knee osteoarthritis have been published.[18,19,20,21,22,23,24,25,26,10,] Protocols used in platelet-rich plasma interventions for knee osteoarthritis varied widely. For example, in the studies identified in the Laudy et al (2015) systematic review, platelet-rich plasma was prepared using single, double, or triple spinning techniques, and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.[20,]

Systematic Reviews

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, findings from 6 systematic reviews are reported.[18,19,10,27,20,21,] A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A2); the systematic review by Anil et al (2021) did not delineate which of its included studies evaluated platelet-rich plasma, therefore, is not included in Table A2. The systematic reviews have varied in their outcomes of interest and their findings. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct.

Anil et al (2021) published a systematic review with network meta-analysis to compare the efficacy of nonoperative injectable treatments for knee osteoarthritis (see Tables 7 and 8).[18,] A total of 79 RCTs (N=8761) were included and the follow-up ranged from 4 weeks to 24 months. Intra-articular injectable treatments included platelet-rich plasma, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, and stromal vascular fraction; the publication did not delineate the number of RCTs that specifically evaluated on platelet-rich plasma. At 12 months, the treatment with the highest P-Score for the MD in Western Ontario and McMaster Osteoarthritis Index (WOMAC) scale score and VAS score was stromal vascular fraction. However, the MD in WOMAC scale and VAS scores for leukocyte-poor platelet-rich plasma and leukocyte-rich platelet-rich plasma versus saline placebo at 12 months did not reach statistical significance.

Trams et al (2020) published a systematic review that included 38 RCTs (N=2962) evaluating the effects of platelet-rich plasma on patients with knee osteoarthritis (see Tables 7 and 8).[19,] The meta-analysis focused on the review of 33 blinded studies. Follow-up ranged from 6 months to 2 years. Comparators included hyaluronic acid in 23 studies, placebo (e.g., saline, no injection, physical therapy) in 10 studies, corticosteroids in 4 studies, and acetaminophen in 2 studies. Twenty-two

studies reported VAS pain outcomes for placebo (n=5), hyaluronic acid (n=15), and corticosteroids (n=2). Placebo and hyaluronic acid subgroups showed significant VAS differences in favor of platelet-rich plasma (p<.00001). The corticosteroid subgroup was not significantly different from platelet-rich plasma (p=.23). Six studies comparing single versus multiple injections of platelet-rich plasma showed a significant difference in favor of 3 platelet-rich plasma injections (p<.00001). Functional outcomes were reported via the WOMAC scale for placebo (n=9), corticosteroids (n=1), and hyaluronic acid (n=15). Both pooled and subgroup analyses favored platelet-rich plasma (p<.00001). In 5 studies assessing multiple versus single platelet-rich plasma injections, significant differences in favor of multiple injections were found (p<.00001). Functional outcomes assessed via International Knee Documentation Committee (IKDC) scores were reported in 2 placebo studies and 5 hyaluronic acid studies. While a significant difference was found for hyaluronic acid (p=.004), no significant difference was found for placebo (p=.24). Pooled estimates for 6 studies comparing platelet-rich plasma to corticosteroids, hyaluronic acid, or mesenchymal stem cells found no significant differences in Knee injury and Osteoarthritis Outcome Score (KOOS) sport, quality of life, activities of daily living, symptoms, or pain subscales. The pooled estimates for adverse events showed non-significant differences in favor of the control groups (p=.15). The risk of bias was assessed using Cochrane criteria. One study was at high risk of bias for 3 domains, 2 studies were at high risk of bias for 2 domains, and 12 studies were at high risk of bias for 1 domain. The most impacted domains were performance bias and reporting bias.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials, n=927), placebo (2 trials, n=105), no platelet-rich plasma (2 trials, n=123), acetaminophen (1 trial, n=75), or a corticosteroid (1 trial, n=48).[10,] Meta-analysis of VAS pain scores showed that platelet-rich plasma was more effective than its comparators at 12 months (standard MD, −0.91; 95% CI, −1.41 to −0.41). However, the systematic review authors noted that important limitations of this finding included lack of a clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically important difference), high residual statistical heterogeneity between studies (I^2=89%), and high risk of bias in study conduct.

Xu et al (2017) conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee osteoarthritis (see Tables 7 and 8).[27,] Risk of bias was assessed using Cochrane criteria. Four studies were assessed as being of low-quality, 3 as moderate-quality, and 3 as high-quality. Meta-analyses including 7 of the trials comparing platelet-rich plasma with hyaluronic acid showed that platelet-rich plasma significantly improved the WOMAC or IKDC scores compared with hyaluronic acid at 6-month follow-up; however, when meta-analyses included only the 2 high-quality RCTs, there was not a significant difference between platelet-rich plasma and hyaluronic acid (see Table 8). Also, note that the WOMAC evaluates 3 domains: pain, scored from 0 to 20; stiffness, scored from 0 to 8; and physical function, scored from 0 to 68. Higher scores represent greater pain and stiffness as well as worsened physical capability. The IKDC is a patient-reported, knee-specific outcome measure that measures pain and functional activity. In the meta-analysis comparing platelet-rich plasma with placebo, a third trial was included, which had 4 treatment groups, 2 of which were platelet-rich plasma and placebo. This analysis showed that platelet-rich plasma significantly improved the WOMAC or IKDC scores compared with placebo; however, only 1 of the trials was considered high-quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials (I^2≥90%).
Laudy et al (2015) conducted a systematic review of RCTs and nonrandomized clinical trials to evaluate the effect of platelet-rich plasma on patients with knee osteoarthritis (see Tables 7 and 8).[20,] Ten trials (N=1110) were selected. Cochrane criteria for risk of bias were used to assess study quality, with 1 trial rated as having a moderate-risk of bias and the remaining 9 trials as high-risk of bias. While meta-analyses showed that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function (see Table 8), larger randomized studies with a lower risk of bias are needed to confirm these results.

Chang et al (2014) published a systematic review that included 5 RCTs, 3 quasi-randomized controlled studies, and 8 single-arm prospective series (N=1543) (see Tables 7 and 8).[21,] The Jadad scale was used to assess RCTs, and the Newcastle-Ottawa Scale was used to assess the other studies; however, results of the quality assessments were not reported. Meta-analysis of functional outcomes at 6 months found that the effectiveness of platelet-rich plasma (effect size, 1.5; 95% CI, 1.0 to 2.1) was greater than that of hyaluronic acid (effect size, 0.7; 95% CI, 0.6 to 0.9; when only RCTs were included). However, there was no significant difference at 12-month follow-up between platelet-rich plasma (effect size, 0.9; 95% CI, 0.5 to 1.3) and hyaluronic acid (effect size, 0.9; 95% CI, 0.5 to 1.2; when only RCTs were included). Fewer than 3 injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. Platelet-rich plasma also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs but asymmetry in funnel plots suggested significant publication bias.

Table 7. Systematic Review Characteristics for Knee Osteoarthritis

Study	Search Date	Trials	Participants	Design
Anil et al (2021)[18,]	Through 2020	RCTs of patients receiving PRP, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, or stromal vascular fraction	Patients with knee OA	79 RCTs
Trams et al (2020)[19,]	2005-2020	-10 PRP vs. placebo -23 PRP vs. HA -4 PRP vs. corticosteroid -2 PRP vs. acetaminophen -6 PRP, single vs. multiple injections	Patients with knee OA	38 RCTs
Johal et al (2019)[10,]	Through Feb 2017	-8 PRP vs. HA -2 PRP vs. placebo -2 PRP vs. no PRP -1 PRP vs. corticosteroid -1 PRP vs. acetaminophen	Patients with knee OA	14 RCTs
Xu et al (2017)[27,]	Through May 2016	-8 PRP vs. HA -2 PRP vs. placebo	Patients with knee OA	10 RCTs
Laudy et al (2015)[20,]	Through Jun 2014	- 8 PRP vs. HA -1 PRP vs. placebo - 1 PRP, different preparations	Patients with knee OA	6 RCTs; 4 nonrandomized
Chang et al (2014)[21,]	Through Sep 2013	-6 PRP vs. HA -1 PRP vs. placebo -1 PRP, different preparations -8 single-arm PRP	Patients with knee OA	5 RCTs; 3 quasi-randomized; 8 single-arm

HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

Table 8. Systematic Review Functional Score Results for Knee Osteoarthritis

Study	Change in Functional Scores (95% CI)[a]
	6 Months to 2 Years
Anil et al (2021)[18,]	WOMAC at 1 year: Leukocyte-poor PRP vs. saline placebo, -7.65 (-27.18 to 11.88); Leukocyte-rich PRP vs. saline placebo, -13.28 (-28.74 to 2.18)
Trams et al (2020)[19,]	WOMAC: All trials, -12.10 (-14.12 to -7.24); PRP vs. placebo, -14.56 (-21.17 to -7. 96); PRP vs. steroid, -16.10 (-19.61 to -12.59); PRP vs. HA, -10,68 (-14.12 to -7.24) IKDC: All trials, 6.94 (2.53 to 11.34); PRP vs. placebo, 8.96 (-5.88 to 23.81); PRP vs. HA, 6.58 (2.12 to 11.05) KOOS - ADL: All trials, 1.23 (-4.85 to 7.31)
	6 Months 12 Months

Study	Change in Functional Scores (95% CI)[a]	
Xu et al (2017)[27,]	PRP vs. HA: All trials: -0.9 (-1.4 to -0.3); Low quality: -13.3 (-33.9 to 3.7); Moderate quality: -1.3 (-1.6 to -1.0); High quality: -0.1 (-0.3 to 0.1) PRP vs. placebo:· All trials (3): -2.1 (-3.3 to -1.0)	NR
Laudy et al (2015)[20,]	PRP vs. HA: -0.8 (-1.0 to -0.6)	PRP vs. HA: -1.3 (-1.8 to -0.9)
Chang et al (2014)[21,]	PRP, baseline vs. post-treatment:· All studies: 2.5 (1.9 to 3.1); Single-arm: 3.1 (2.0 to 4.1); Quasi-randomized: 3.1 (1.4 to 3.8); RCT: 1.5 (1.0 to 2.1)	PRP, baseline vs. posttreatment:· All studies: 2.9 (1.0 to 4.8); Single-arm: 2.6 (-0.4 to 5.7); Quasi-randomized: 4.5 (4.1 to 5.0); RCT: 0.9 (0.5 to 1.3)

ADL: activities of daily living; CI: confidence interval; CS: corticosteroid; HA: hyaluronic acid; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritic Outcome Score; NR: not reported; OA: osteoarthritic; PRP: platelet-rich plasma; RCT: randomized controlled trial; WOMAC: Western Ontario McMaster Osteoarthritis Index.

[a] Functional outcomes were measured by the IKDC, KOOS, or WOMAC.

In individuals with hip osteoarthritis undergoing platelet-rich plasma injections, findings from 2 systematic reviews are reported. Belk et al (2022) identified 6 RCTs comparing the efficacy of platelet-rich plasma (n=211) and hyaluronic acid injections (n=197).[28,] The mean follow-up was approximately 12 months. In an analysis of 4 RCTs, platelet-rich plasma and hyaluronic acid groups had similar improvements in VAS score (MD, 5.9; 95% CI, -0.741 to 1.92) and WOMAC score (MD, 0.27; 95% CI, -0.05 to 0.59). Gazendam et al (2020) identified 11 RCTs (N=1353) assessing the efficacy of platelet-rich plasma, corticosteroids, and saline injections.[29,] Pooled pain and functional outcomes were reported for 2 to 4 and 6 months follow-up. No intervention significantly outperformed saline intra-articular injection at any time point. Clinically significant improvements in pain from baseline were observed for all treatment groups, including placebo.

Randomized Controlled Trials

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, 3 RCTs with a follow-up of at least 12 months have been published subsequent to several of the above-described systematic reviews (Tables 9 to 12).[30,31,32,] All trials were conducted outside of the United States. Sample sizes ranged from 40 to 200 patients. Comparator treatments included corticosteroids, celecoxib, or hyaluronic acid. Two RCTs found statistically significantly greater 1-year reductions in pain and function scores with platelet-rich plasma versus corticosteroids or celecoxib. Sdeek et al (2021) reported on the results of a 36-month RCT that compared 3 intraarticular injections of either platelet-rich plasma (n=95) or hyaluronic acid (n=94) in patients with knee osteoarthritis.[30,] Both platelet-rich plasma and hyaluronic acid were effective in improving pain and functional status. Statistical analyses were not performed, however, trends for pain and function scores showed greater improvement in the group that received platelet-rich plasma. The findings of these RCTs should be interpreted with caution due to important study conduct limitations, including potential inadequate control for selection bias and limited or unclear blinding. No significant differences in pain or function scores were observed within the first month of treatment in either study.

Dallari et al (2016) reported on results of an RCT that compared platelet-rich plasma with hyaluronic acid alone or with a combination platelet-rich plasma plus hyaluronic acid in 111 patients with hip osteoarthritis.[33,] Although this well-conducted RCT reported positive results, with statistically significant reductions in VAS score (lower scores imply less pain) at 6 months in the platelet-rich plasma arm (21; 95% CI, 15 to 28) versus the hyaluronic acid arm (35; 95% CI, 26 to 45) or the platelet-rich plasma plus hyaluronic acid arm (44; 95% CI, 36 to 52), the impact of treatment on other secondary outcome measures such as Harris Hip Score and the WOMAC scores was not observed. Notably, there was no control for type I error for multiple group comparisons at different time points, and the trial design did not incorporate a sham-control arm. Nouri et al (2022) also conducted an RCT comparing platelet-rich plasma with hyaluronic acid in patients with hip osteoarthritis.[34,] A total of 105 patients were randomized to platelet-rich plasma, hyaluronic acid, or the combination. There were no differences in VAS scores between groups at 6 months; however, functional outcomes were improved in the platelet-rich plasma groups compared with hyaluronic acid alone.

Table 9. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	Comparator 1	Comparator 2
Nouri et al (2022)[34,]	Iran	1	2019-2020	Patients with hip OA, grade II to III	PRP (n=35); 2 x 5 mL 14 days apart	HA (n=35); 2 x 2.5 mL 14 days apart	HA + PRP (n=35); 2 x 5 mL PRP + 2.5 mL HA 14 days apart
Sdeek et al (2021)[30,]	Egypt	NR	2016-2020	Patients with knee OA, grade II to III	PRP (n=95); 3 x 2.5 mL 14 days apart	HA (n=94); 3 x 2.5 mL 14 days apart	
Reyes-Sosa et al (2020)[31,]	Mexico	1	NR	Patients with knee OA, grade II to III, who were previously treated with acetaminophen without improvement	Activated PRP (n=30); 2 x 3 mL 15 days apart	NSAID: (n=30); 200 mg celecoxib every 24 hours for 1 year	
Elksnins-Finogejevs et al (2020)[32,]	Latvia	1	2016 - 2017	Patients with knee OA, grade II to III	PRP (n=20); 8 ml single-dose	CS (n=20); 1 mL 40 mg/mL triamcinolone + 5 mL 2% lidocaine	
Dallari et al (2016)[33,]	Italy	NR	2010 - 2011	Patients with hip OA	PRP (n=44)	PRP+HA (n=31)	HA (n=36)

CS: corticosteroid; HA: hyaluronic acid; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

Table 10. Summary of Key RCT Results

Study	Pain Outcomes	Functional Outcomes
Knee OA		
Sdeek et al (2021)[30,]	Mean VAS Score	Mean IKDC and WOMAC Scores
PRP	Baseline: 57.8 12 months: 47.1 36 months: 40.9	IKDC: Baseline: 49.1 12 months: 67.9 36 months: 55.2 WOMAC: Baseline: 66.5 12 months: 52.8 36 months: 60.6
HA	Baseline: 59.3 12 months: 50.3 36 months: 60.3	IKDC: Baseline: 47.3 12 months: 61.6 36 months: 46.1 WOMAC: Baseline: 66.9 12 months: 54.9 36 months: 64.2
Reyes-Sosa et al (2020)[31,]	Change in VAS Score from Baseline at 12 mo, %	Change in WOMAC Score from Baseline at 12 mo
PRP	-68.69 (p<.001)	-11.5[a]
Celecoxib	-40.94 (p<.001)	-4[a]
***P*-value for Difference**	p<.001	p<.001
Elksnins-Finogejevs et al (2020)[32,]	Mean VAS Score, 95% CI	Mean IKDC Score, 95% CI
PRP	Baseline: 6.1 (5.4 to 6.6) 30 weeks: 1.6 (0.7 to 2.6) 58 weeks: 2.9 (2.2 to 3.6)	Baseline: 36.3 (31.2 to 41.4) 30 weeks: 77.5 (70.6 to 84.3) 58 weeks: 62.0 (54.5 to 69.6)

Study	Pain Outcomes	Functional Outcomes
CS	Baseline: 6.0 (5.2 to 6.8) 30 weeks: 4.0 (3.2 to 4.8) 58 weeks: 5.1 (4.1 to 6.0)	Baseline: 28.0 (24.6 to 33.1) 30 weeks: 56.3 (47.4 to 65.3) 58 weeks: 39.8 (32.8 to 46.8)
Hip OA		
Nouri et al (2022)[34],	VAS at 6 mo	WOMAC at 6 mo
PRP	3.13 ± 1.29	21.53 ± 10.40
HA	3.90 ± 1.40	27.21 ± 9.25
PRP + HA	3.13 ± 1.18	21.16 ± 8.00
Dallari et al (2016)[35],	VAS Score at 6 mo	NR
PRP	21	
HA	35	
PRP + HA	44	

CI: confidence interval; CS: corticosteroids; HA: hyaluronic acid; IKDC: International Knee Documentation Score; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[a] Calculated estimate.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow Up[e]
Nouri et al (2022)[34],					1. Only 6 months follow-up
Sdeek et al (2021)[30],					
Reyes-Sosa et al (2020)[31],			3. Unclear adherence to treatment.	5. Clinically significant difference not defined.	
Elksnins-Finogejevs et al (2020)[32],					
Dallari et al (2016)[33],					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Binding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Nouri et al (2022)[34],		1. Patients not fully blind due to differences in administration procedures				
Sdeek et al (2021)[30],					1. Power calculations not reported; 2. Power not	3. Confidence intervals and/or p values not

Study	Allocation[a]	Binding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
					calculated for primary outcome	reported; 4. Comparative treatment effects not calculated.
Reyes-Sosa et al (2020)[31,]	2. Allocation not concealed from patients or health care providers. 4. Inadequate control for selection bias in celecoxib group.	1-3. Blinding of outcome assessors not clear.	1. Not registered.		1. Power not calculated.	2. Confidence intervals not reported.
Elksnins-Finogejevs et al (2020)[32,]	2. Allocation not concealed from patients or health care providers.	1-3. Not double-blinded.				
Dallari et al (2016)[33,]	2. Allocation not concealed from patients or health care providers	1. Only data collectors and outcome assessors blinded to treatment assignment				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Knee or Hip Osteoarthritis

Multiple RCTs and systematic reviews with meta-analysis have evaluated the efficacy of platelet-rich plasma injections in individuals with knee or hip osteoarthritis. Most trials have compared platelet-rich plasma with hyaluronic acid for knee osteoarthritis. A single RCT compared platelet-rich plasma with hyaluronic acid alone or combination platelet-rich plasma plus hyaluronic acid in hip osteoarthritis. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in pain and function outcomes, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and limited or unclear blinding. Also, benefits were not maintained at 5 years. Using hyaluronic acid as a comparator is questionable because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. Two systematic reviews evaluating hip osteoarthritis did not report any statistically or clinically significant differences in pain or functional outcomes compared to hyaluronic acid, corticosteroids, or placebo. Additional larger controlled studies comparing platelet-rich plasma with placebo and alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and

hip osteoarthritis. Further studies are also needed to determine the optimal protocol for delivering platelet-rich plasma.

Platelet-Rich Plasma as an Adjunct to Surgery

Anterior Cruciate Ligament Reconstruction

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with anterior cruciate ligament (ACL) reconstruction.
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with ACL reconstruction.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for ACL reconstruction has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A Cochrane review by Moraes et al (2014) on platelet-rich therapies for musculoskeletal soft tissue injuries identified 2 RCTs and 2 quasi-randomized studies (N=203) specifically on platelet-rich plasma used in conjunction with ACL reconstruction.[36,] Pooled data found no significant difference in IKDC scores between the platelet-rich plasma and control groups.

A systematic review and meta-analysis by Trams et al (2020) identified 16 RCTs (N=740).[19,] Five studies showed no significant overall difference with respect to pain (p=.43). In 4 studies reporting IKDC scores, no significant differences were noted (p=.83). In 4 studies, no significant differences in functional outcomes as measured by the Lysholm score were reported (p=.19). Pooled estimates for

Tegner scale activity assessments in 5 studies showed no significant differences (p=.38) in favor of the control. Twelve studies were deemed to be at high risk of bias in at least 1 domain.

A systematic review and meta-analysis by Lv et al (2022) identified 17 RCTs (N=970) in patients undergoing ACL reconstruction.[37,] Compared to controls, platelet-rich plasma improved VAS score (MD, -1.12; 95% CI, -1.92 to -0.31; p=.007), Lysholm score (MD, 8.49; 95%CI, 1.63 to 15.36) and subjective IKDC score (MD, 6.08; 95% CI, 4.39 to 7.77; p<.00001) at 6 months. The authors only considered the difference in pain score to be clinically relevant, and they did not consider any differences between groups at 12 months to be clinically meaningful (VAS MD, -0.47 and subjective IKDC score MD, 3.99). Overall, the evidence was determined to be of moderate quality.

Randomized Controlled Trials

One of the largest RCTs, reported by Nin et al (2009), randomized 100 patients to arthroscopic ACL reconstruction with or without platelet-rich plasma.[38,] The use of platelet-rich plasma on the graft and inside the tibial tunnel in patients treated with bone-patellar tendon-bone allografts had no discernable clinical or biomechanical effect at 2-year follow-up.

Retrospective Cohort Studies

Bailey et al (2021) reported on a retrospective matched case-control study evaluating the effects of intraoperative platelet-rich plasma on postoperative knee function and complications at 2 years after ACL reconstruction with meniscal repair.[39,] The study was conducted between 2013 and 2017 and included 162 patients who received platelet-rich plasma and 162 patients who did not. Results demonstrated that there were no differences in knee function scores between the platelet-rich plasma and matched-control groups at 2 years, as well as no differences in the timing of return to activity (mean, 7.8 vs. 8.0 months; p=.765). However, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group (13.6% vs. 4.6%; p<.001).

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment of Anterior Cruciate Ligament Reconstruction

Several systematic reviews that included multiple RCTs, quasi-randomized studies, and/or prospective studies have evaluated the efficacy of platelet-rich plasma injections in individuals undergoing ACL reconstruction. Three systematic reviews conducted a meta-analysis. Two showed that adjunctive platelet-rich plasma treatment did not result in a significant effect on function and activity outcomes, including IKDC score. One systematic review did find statistically significant benefit with platelet-rich plasma compared with control in terms of VAS, Lysholm score, and IKDC at 6 months; however, the authors only considered the differences in pain scores to be clinically relevant. By 12 months, none of the differences between groups were clinically relevant. Individual studies have shown mixed results. A retrospective matched case-control study found no differences in knee function scores or time to return of activity between platelet-rich plasma and matched-control groups at 2 years; however, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group (13.6% vs 4.6%).

Hip Fracture

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with hip fracture.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with hip fracture.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for hip fracture has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
One RCT was identified for the treatment of a hip fracture with platelet-rich plasma. Griffin et al (2013) reported on a single-blind randomized trial assessing the use of platelet-rich plasma for the treatment of hip fractures in patients ages 65 years and older.[40,] Patients underwent internal fixation of a hip fracture with cannulated screws and were randomized to standard-of-care fixation (n=99) or standard-of-care fixation plus injection of platelet-rich plasma into the fracture site (n=101). The primary outcome measure was the failure of fixation within 12 months, defined as any revision surgery. The overall risk of revision by 12 months was 36.9%, and the risk of death was 21.5%. There was no significant risk reduction (39.7% control vs. 34.1% platelet-rich plasma; absolute risk reduction, 5.6%; 95% CI, -10.6% to 21.8%) or significant difference between groups for most of the secondary outcome measures. For example, mortality was 23% in the control group and 20% in the platelet-rich plasma group. The length of stay was significantly reduced in the platelet-rich plasma-treated group (median difference, 8 days). For this measure, there is a potential for bias from the nonblinded treating physician.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Hip Fracture
A single open-label RCT has evaluated the efficacy of platelet-rich plasma injections in individuals with a hip fracture. This trial failed to show any statistically significant reductions in the need for revision surgery after platelet-rich plasma treatment.

Long Bone Nonunion
Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as recombinant human bone morphogenetic protein-7 (rhBMP-7) plus orthopedic surgery, in individuals with long bone nonunion.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with long bone nonunion.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include rhBMP-7 plus orthopedic surgery.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for long bone nonunion has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.
e.

Review of Evidence
Systematic Reviews
A Cochrane review by Griffin et al (2012) found only 1 small RCT (N=21) evaluating platelet-rich plasma for long bone healing.[41,] However, because only studies comparing platelet-rich plasma with no additional treatment or placebo were eligible for inclusion, reviewers did not select a larger RCT by Calori et al (2008; discussed below).[42,]

Randomized Controlled Trials
The trial by Dallari et al (2007), which was included in the Cochrane review, compared platelet-rich plasma plus allogenic bone graft with allogenic bone graft alone in patients undergoing corrective osteotomy for medial compartment osteoarthrosis of the knee.[35,] According to Cochrane reviewers, the risk of bias in this study was substantial. Results showed no significant differences in patient-reported or clinician-assessed functional outcome scores between groups at 1 year. However, the proportion of bones united at 1 year was statistically significantly higher in the platelet-rich plasma plus allogenic bone graft arm (8/9) compared with the allogenic bone graft alone arm (3/9; relative risk [RR], 2.67; 95% CI, 1.03 to 6.91). This benefit, however, was not statistically significant when assuming poor outcomes for participants who were lost to follow-up (8/11 vs. 3/10; RR, 2.42; 95% CI, 0.88 to 6.68). Tables 13 and 14 describe this RCT and the subsequent RCT's characteristics and results, respectively. Tables 15 and 16 describe study design and conduct limitations.

Calori et al (2008) compared the application of platelet-rich plasma with rhBMP-7 for the treatment of long bone nonunions in an RCT involving 120 patients and 10 surgeons.[42,] Inclusion criteria were

posttraumatic atrophic nonunion for at least 9 months, with no signs of healing over the last 3 months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and 21 cases in the platelet-rich plasma group. Computer-generated randomization created 2 homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, patients underwent surgery for nonunion, including bone grafts according to the surgeon's choice (66.6% of rhBMP-7 patients, 80% of platelet-rich plasma patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the platelet-rich plasma group (68%) than in the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13% to 14% with platelet-rich plasma.

Samuel et al (2017) conducted a controlled trial in which patients with delayed unions (15 to 30 weeks old) were randomized to 2 platelet-rich plasma injections at the fracture site at baseline and 3 weeks (n=23) or no treatment (n=17).[43,] The delayed unions were in the tibia (n=29), femur (n=8), forearm (n=2), and the humerus (n=1). The main outcome was long bone union, defined as no pain or tenderness on weight bearing, no abnormal mobility, and bridging at 3 or more cortices in x-ray. Examinations were conducted every 6 weeks for 36 weeks or until union. Percent union did not differ significantly between the 2 groups (78% in the platelet-rich plasma group vs. 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the platelet-rich plasma group vs. 13.1 weeks for the control group).

Table 13. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	*Comparator 1*	*Comparator 2*
Dallari et al (2007)[35,]	Italy	NR	NR	Patients undergoing high tibial osteotomy to treat genu varum	Implantation of lyophilized bone chips with platelet gel (n=11)	Implantation of lyophilized bone chips with platelet gel and bone marrow stromal cells (n=12)	Implantation of lyophilized bone chips without gel (n=10)
Calori et al (2008)[42,]	Italy	1	2005-2007	Patients undergoing treatment of long bone nonunions	PRP (n=60)	rhBMP-7 (n=60)	
Samuel et al (2017)[43,]	India	1	2010-2014	Patients with delayed unions	PRP (n=23)	No treatment (n=17)	

NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; rhBMP-7: recombinant human bone morphogenetic protein-7.

Table 14. Summary of Key RCT Results

Study	Knee Society Score at 1 yr	Knee Society Functional Score at 1 yr	Union Rate	Median Healing Time
Dallari et al (2007)[35,]				
PRP	91.3 ± 2	99.0 ± 0.6		
PRP+bone marrow	89.9 ± 4	99.2 ± 0.5		
Non-PRP	90.3 ± 4	98.8 ± 0.6		
Calori et al (2008)[42,]				
PRP			41 (68.3%)	4 ± 0.61 months
rhBMP-7			52 (86.7%)	3.5 ± 0.48
p-value			.016	
Samuel et al (2017)[43,]				
PRP			18 (78%)	15.3 weeks

Study	Knee Society Score at 1 yr	Knee Society Functional Score at 1 yr	Union Rate	Median Healing Time
Control			10 (59%)	13.1 weeks
p-value			.296	.54

PRP: platelet-rich plasma; RCT: randomized controlled trial; rhBMP-7: recombinant human bone morphogenetic protein-7.

Table 15. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow Up[e]
Dallari et al (2007)[35,]	3. Only 33 patients included				
Calori et al (2008)[42,]					
Samuel et al (2017)[43,]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 16. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Dallari et al (2007)[35,]	3. Allocation concealment unclear	1,2,3. No blinding described			1,2. Study was underpowered and nonparametric statistical tests were performed	
Calori et al (2008)[42,]	2. Allocation not concealed	1,2,3. No blinding described				
Samuel et al (2017)[43,]	1. Randomization procedure not described, 3. Allocation concealment unclear	1,2,3. No blinding described				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2.

Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Long Bone Nonunion

Three RCTs have evaluated the efficacy of platelet-rich plasma injections in individuals with long bone nonunion. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between patients who received platelet-rich plasma plus allogenic bone graft versus those who received only allogenic bone graft. While the trial showed statistically significant increases in the proportion of bones that healed in patients receiving platelet-rich plasma in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. An RCT that compared platelet-rich plasma with rhBMP-7 also failed to show any clinical and radiologic benefits of platelet-rich plasma over rhBMP-7. The third RCT found no difference in the number of unions or time to union in patients receiving platelet-rich plasma injections or no treatment.

Rotator Cuff Repair

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with rotator cuff repair.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with rotator cuff repair.

Interventions

The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include orthopedic surgery alone.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for rotator cuff repair has varying lengths of follow-up, ranging from 6 months to 3.5 years. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 3.5 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

The literature on platelet-rich plasma for rotator cuff repair consists of several RCTs and systematic reviews that have evaluated the efficacy of platelet-rich plasma membrane or matrix combined with surgical repair of the rotator cuff. A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A3). The systematic reviews have varied in their outcomes of interest and findings (Tables 17 and 18).[10,36,44,45,46,47,48,] For pain outcomes, systematic reviews generally found significant reductions with platelet-rich plasma at 12 months.[46,10,] However, systematic review authors noted that the pain findings should be interpreted with caution due to significant residual statistical heterogeneity,[46,] lack of a clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically important difference),[10,] and high risk of bias in study conduct.[10,48,]. Some systematic reviews generally did not show a statistically or clinically significant benefit of platelet-rich plasma on other outcomes, including function, retear rate, and Constant scores.[47,] One systematic review found a statistically significant reduction in retear rate in a subgroup analysis of 4 long-term RCTs that were at least 24 months in duration.[48,] No reviews have demonstrated a consistent statistically and clinically significant benefit of platelet-rich plasma across multiple outcomes of interest for the 3.5 years of follow-up that is considered necessary to conclusively demonstrate efficacy. The systematic review by Wang et al (2019) reported on adverse effects, and noted that complications were only reported in 1 of the included RCTs, occurring in 5.6% of participants in the platelet-rich plasma groups and none in the control groups. The complications included infection, hematoma, and an exanthematous itchy skin lesion in 1 patient each.

Table 17. Systematic Reviews & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Li et al (2021)[48,]	Through Oct 2020	16 (PRP)	Patients undergoing surgery for rotator cuff repair	1440 (28 to 120)	RCT	1.5 to 60 mo
Chen et al (2020)[47,]	2011-2017	17	Patients with rotator cuff tears	1116[a] (36 to 120)	RCT	NR
Johal et al (2019) [10,]	2011-2016	13	Patients undergoing surgery for rotator cuff repair	858 (25 to 120)	RCT	7w to 24mo
Chen et al (2018)[46,]	2011-2016	37	Patients with tendon and ligament injuries	1031[a] (NR)	RCT	NR
Fu et al (2017)[49,]	2011-2015	11	Patients with rotator cuff injury or tendinopathy	638 (NR)	RCT	NR
Zhao et al (2015)[44,]	2011-2013	8	Patients with rotator cuff injury	464 (28 to 88)	RCT	NR
Moraes et al (2014)[36,]	2008-2013	19	Patients undergoing rotator cuff repair	1088 (23 to 150	RCT and quasi-randomized trials	NR

NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial.
[a] Number of participants which could be included in the quantitative analysis.

Table 18. Systematic Reviews & Meta-Analysis Results

Study	VAS Reduction	VAS Reduction at 1 Year	Difference in Retear Rate	Difference in Function	Difference in Function at 1 Year
Li et al (2021)[48,]	10 RCTs; n=559		12 RCTs; n=700 RCTs ≥24 months: 4 RCTs, n=255	UCLA Score: 7 RCTs; n=437	
Point estimate	10 RCTs: MD -0.13		12 RCTs: RR, 0.56 RCTs ≥24 months: RR, 0.40	7 RCTs: MD, 1.55	
95% CI	10 RCTs: -0.56 to -0.06		12 RCTs: RR, 0.56 RCTs ≥24 months: 0.22 to 0.73	7 RCTs: MD, 0.86 to 2.24	
Chen et al (2020)[47,]		8 RCTs; N=469			UCLA Score: 6 RCTs; N=386
WMD		-0.34			1.39
95% CI		-0.76 to 0.09			0.35 to 2.43
I^2		87.5%			37.8%
Johal et al (2019)[10,]		7 RCTs, N=324			
SMD		-0.261			
95% CI		-0.46 to -0.05			
I^2		0%			
Chen et al (2018)[46,]					
WMD		-0.84			
95% CI		-1.23 to -0.44			
p-value		<.01			
Fu et al (2017)[49,]					
SMD		0.142[a]			
95% CI		-0.08 to 0.364			
p-value		.209			
Zhao et al (2015)[44,]					
RR			0.94		
95% CI			0.70 to 1.25		
p-value			.66		
Moraes et al (2014)[36,]					
SMD					0.25
95% CI					-0.07 to 0.57
p-value					.12

[a] Change from baseline at final follow-up. Follow-up durations ranged from 6 weeks to 24 months.
CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio; SMD: standard mean difference; UCLA: University of California at Los Angeles (UCLA) activity score; VAS: visual analog scale; WMD: weighted mean difference.

Randomized Controlled Trials

Data from a 2011 double-blind RCT by Randelli et al that included 53 patients randomized to receive arthroscopic rotator cuff repair with or without the addition of platelet-rich plasma is included in multiple meta-analyses summarized above. Randelli et al (2021) published results of a 10-year follow-up of this trial, which included data for 17 patients who received platelet-rich plasma and 21 control group patients.[50,] At the 10-year follow-up, both platelet-rich plasma and control groups experienced

improvements in the median (interquartile range [IQR]) University of California at Los Angeles activity score (34 [29 to 35] and 33 [29 to 35] points, respectively) and VAS score (0.34 [0 to 1.85] and 0.70 [0 to 2.45] points, respectively); the between-group differences did not reach statistical significance. Furthermore, approximately 37% of the operated patients had a re-rupture in each group. Retears occurred in 6% of the patients who received platelet-rich plasma treatment and 14% of patients in the control group (p=.61).

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Rotator Cuff Repair
For individuals undergoing rotator cuff repair who receive platelet-rich plasma injections, the evidence includes multiple systematic reviews with meta-analyses and an RCT. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. While the systematic reviews and meta-analyses generally failed to show a statistically and/or clinically significant impact on other outcomes, 1 meta-analysis found a statistically significant reduction in retear rate in a subgroup analysis of 4 RCTs that were at least 24 months in duration. Findings of a subsequently published 10-year follow-up of a small RCT failed to demonstrate the superiority of platelet-rich plasma over control for clinical and radiologic outcomes. The variability in platelet-rich plasma preparation techniques and platelet-rich plasma administration limits the generalizability of the available evidence.

Spinal Fusion

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with spinal fusion.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with spinal fusion.

Interventions

The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include orthopedic surgery alone.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for spinal fusion has varying lengths of follow-up.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
One small (N=62), unblinded, single-center RCT for spinal fusion conducted in Japan and published by Kubota et al (2019) was identified that compared platelet-rich plasma to no platelet-rich plasma.[51,] Follow-up was 24 months. Although fusion rates were significantly improved with platelet-rich plasma, there were no significant differences in VAS scores between the 2 groups. Major limitations of this RCT include that patients were unblinded to treatment, and there was no placebo comparator.

Prospective Cohort Studies
Two prospective observational studies found no differences in fusion rates with the use of a platelet gel or platelet glue compared with historical controls.[52,53,]

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Spinal Fusion
For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and a few observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain).

Subacromial Decompression Surgery
Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with subacromial decompression surgery.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with subacromial decompression surgery.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for subacromial decompression surgery has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

One small RCT evaluated the use of platelet-rich plasma as an adjunct to subacromial decompression surgery. Everts et al (2008) reported on a rigorously conducted, small (N=40), double-blinded RCT of platelet and leukocyte-rich plasma gel following open subacromial decompression surgery in a carefully selected patient population.[54,] Neither self-assessed nor physician-assessed instability improved. Both subjective pain and use of pain medication were lower in the platelet and leukocyte-rich plasma group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the platelet and leukocyte-rich plasma group (close to 4 in the control group, close to 2 in the platelet and leukocyte-rich plasma group), and only 1 (5%) patient in the platelet and leukocyte-rich plasma group was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvements in the platelet and leukocyte-rich plasma group across the 6-week assessment period, with patients reporting improvements in activities of daily living, such as the ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Subacromial Decompression Surgery

A single small RCT has evaluated the efficacy of platelet-rich plasma injections in individuals undergoing subacromial decompression surgery. Compared with controls, platelet-rich plasma treatment did not improve self-assessed or physician-assessed instability. However, subjective pain, use of pain medication, and objective measures of range of motion showed clinically significant improvements with platelet-rich plasma. Larger RCTs would be required to confirm these benefits.

Total Knee Arthroplasty

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with total knee arthroplasty.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with total knee arthroplasty.

Interventions

The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for total knee arthroplasty has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Trams et al (2020) published a systematic review and meta-analysis that included 6 RCTs (N=621) evaluating the effects of intraoperative platelet-rich plasma as an adjunct to total knee arthroplasty.[19,] Two studies were deemed at high risk of bias. The primary aim of the studies was to assess blood loss during the procedure. While there were significant differences in favor of platelet-rich plasma in the overall effect on blood parameters in comparison to the control groups (standard MD, -0.29; 95% CI, -0.46 to -0.11), no significant differences in range of motion, functional outcomes, or long-term pain were observed.

Shu et al (2022) evaluated platelet-rich plasma in patients undergoing total joint replacement including 8 studies in patients with total knee arthroplasty (1 study for total hip arthroplasty and 1 on total hip or knee arthroplasty).[55,] Of the 3 studies reporting VAS scores in patients undergoing total knee arthroplasty (n=161), pain scores were similar during the first 2 postoperative days, but by 3 weeks and 2 months had improved with platelet-rich plasma compared with control (MD, -0.92; 95% CI, -1.25 to -0.60 and -0.93; 95% CI, -1.24 to -0.63, respectively). There were no differences in range of motion, WOMAC scores, length of hospital stay, or wound healing within 4 weeks between platelet-rich plasma or controls in patients undergoing total knee arthroplasty. The authors noted high heterogeneity and the need for more high-quality RCTs.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Total Knee Arthroplasty
Two systematic reviews have evaluated the efficacy of intraoperative platelet-rich plasma in individuals undergoing total knee arthroplasty. In the review by Trams et al (2020) there were no significant differences between the platelet-rich plasma and untreated control groups across several functional and pain outcomes. The systematic review by Shu et al (2022) found improved VAS scores in patients undergoing total knee arthroplasty; however, there were no differences in other outcomes and the authors noted high heterogeneity and the need for well-designed RCTs.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Orthopaedic Surgeons

In 2021, the American Academy of Orthopaedic Surgeons (AAOS) guidelines for the management of osteoarthritis of the knee made the following recommendation:[56,]

- "Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee. (Strength of Recommendation: Limited)" The variability of study findings was noted to have contributed to the low strength of recommendation rating.

In 2023 , the AAOS updated evidence-based guidelines on the management of osteoarthritis of the hip.[57,] In the section on intra-articular injectables, the guidelines gave a moderate recommendation based on high-quality evidence supporting the use of intra-articular corticosteroids as an option to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was also a strong recommendation based on high-quality evidence against the use of intra-articular hyaluronic acid, as it does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines did not mention any evidence or make recommendations related to the use of platelet-rich plasma for the treatment of osteoarthritis of the hip.

In 2019, the AAOS issued evidence-based guidelines on the management of rotator cuff injuries.[58,] The guideline noted the following recommendations related to the use of platelet-rich plasma in this setting:

- "There is limited evidence supporting the routine use of platelet-rich plasma for the treatment of cuff tendinopathy or partial tears (Strength of Recommendation: Limited)." The variability of study findings was noted to have contributed to the low strength of recommendation rating.
- "Strong evidence does not support biological augmentation of rotator cuff repair with platelet-derived products on improving patient reported outcomes; however, limited evidence supports the use of liquid platelet-rich plasma in the context of decreasing re-tear rates (Strength of Recommendation: Strong)."
- "In the absence of reliable evidence, it is the consensus of the work group that we do not recommend the routine use of platelet-rich plasma in the non-operative management of full-thickness rotator cuff tears (Strength of Recommendation: Consensus)."

National Institute for Health and Care Excellence

In 2013, the NICE issued guidance on the use of autologous blood injection for tendinopathy.[59,] The NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy was “inadequate” in quantity and quality.

In 2013, the NICE also issued guidance on the use of autologous blood injection (with or without techniques for producing platelet-rich plasma) for plantar fasciitis.[60,] The NICE concluded that the evidence on autologous blood injection for plantar fasciitis raised no major safety concerns but that the evidence on efficacy was “inadequate in quantity and quality."

In 2019, the NICE issued guidance on the use of platelet-rich plasma for osteoarthritis of the knee.[61,] The NICE concluded that current evidence on platelet-rich plasma injections for osteoarthritis of the knee raised “no major safety concerns”; however, the “evidence on efficacy is limited in quality." Therefore, NICE recommended that "this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05742763[a]	Platelet-Rich Plasma and the Effects of NSAIDs on Pain and Functional Scores in Knee Osteoarthritis	300	Dec 2027
NCT05742061	Intra-articular Platelet Rich Plasma vs Corticosteroid in Treatment of Knee Osteoarthritis	100	Dec 2023
NCT03734900	Comparison of Effectiveness Between Platelet Lysate and Platelet-rich Plasma on Knee Osteoarthritis: a Prospective,Randomized, Placebo-controlled Trial	150	May 2022
NCT03984955	A Prospective, Double Blind, Single Centre, RCT, Comparing the Effectiveness of Physiotherapy in Addition to One of 3 Types of Image Guided Injection of the Common Extensor Tendon, on Pain and Function in Patients With Tennis Elbow	123	Apr 2024
NCT01843504	The Clinical, Biomechanical, and Tissue Regenerating Effects of a Single Platelet-rich Plasma Injection for the Treatment of Chronic Patellar Tendinopathy: a Randomized Controlled Trial	44	Dec 2024
Unpublished			
NCT04697667	The Combination of Exercise and PRP vs Exercise Alone in Patients With Knee Osteoarthritis: A Randomized Controlled Clinical Trial	84	Feb 2022
NCT04703998	Arthroscopic Rotator Cuff Repair Augmented With Platelet Rich Plasma	103	Sep 2022

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
HCPCS	C1734	Orthopedic/device/drug matrix for opposing bone-to-bone or soft tissue-to bone (implantable)
	P9020	Platelet rich plasma, each unit

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/04/2015	BCBSA medical policy adaptation
07/01/2016	Policy revision without position change
06/01/2017	Policy revision without position change
06/01/2018	Policy revision without position change
07/01/2019	Policy revision without position change
03/01/2020	Coding update
07/01/2020	Annual review. No change to policy statement. Literature review updated.
06/01/2021	Annual review. No change to policy statement. Literature review updated.
06/01/2022	Annual review. No change to policy statement. Literature review updated.
06/01/2023	Annual review. Policy guidelines and literature review updated.
06/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Orthopedic Applications of Platelet-Rich Plasma 2.01.98 **Policy Statement:** I. Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations: A. Primary use (injection) for the following conditions: 1. Achilles tendinopathy 2. Lateral epicondylitis 3. Plantar fasciitis 4. Osteochondral lesions 5. Osteoarthritis B. Adjunctive use in the following surgical procedures: 1. Anterior cruciate ligament (ACL) reconstruction 2. Hip fracture 3. Long-bone nonunion 4. Patellar tendon repair 5. Rotator cuff repair 6. Spinal fusion 7. Subacromial decompression surgery 8. Total knee arthroplasty (TKA)	**Orthopedic Applications of Platelet-Rich Plasma 2.01.98** **Policy Statement:** I. Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations: A. Primary use (injection) for the following conditions: 1. Achilles tendinopathy 2. Lateral epicondylitis 3. Plantar fasciitis 4. Osteochondral lesions 5. Osteoarthritis B. Adjunctive use in the following surgical procedures: 1. Anterior cruciate ligament (ACL) reconstruction 2. Hip fracture 3. Long-bone nonunion 4. Patellar tendon repair 5. Rotator cuff repair 6. Spinal fusion 7. Subacromial decompression surgery 8. Total knee arthroplasty (TKA)