2.01.98	Orthopedic Applications of Platelet-Rich Plasma		
Original Policy Date:	December 4, 2015	**Effective Date:**	June 1, 2021
Section:	2.0 Medicine	**Page:**	Page 1 of 41

Policy Statement

Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations:

I. Primary use (injection) for the following conditions:
   A. Achilles tendinopathy
   B. Lateral epicondylitis
   C. Osteoarthritis
   D. Osteochondral lesions
   E. Plantar fasciitis

II. Adjunctive use in the following surgical procedures:
   A. Anterior cruciate ligament (ACL) reconstruction
   B. Hip fracture
   C. Long-bone nonunion
   D. Patellar tendon repair
   E. Rotator cuff repair
   F. Spinal fusion
   G. Subacromial decompression surgery
   H. Total knee arthroplasty (TKA)

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

Policy Guidelines

Coding

There is a CPT category III code for injections of platelet-rich plasma (PRP):

- **0232T**: Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

The instructions issued with the code state that it is not to be reported with codes 20550, 20551, 20600-20610, 20926, 76942, 77002, 77012, 77021, and 86965. Code 0232T includes the harvesting and preparation of the platelet-rich plasma.

For situations other than injection (when 0232T would be reported), no specific CPT codes describe the preparation of autologous blood-derived products, but the following CPT code can be used:

- **86999**: Unlisted transfusion medicine procedure

It is questionable whether platelet-rich plasma is appropriately considered a tissue graft, but it has been reported that providers have used the following CPT code to describe the overall procedure:

- **20926**: Tissue grafts, other (e.g., paratenon, fat, dermis)

The American Medical Association's Department of Coding instructs that placement of platelet-rich plasma into an operative site is an inclusive component of the operative procedure performed and not reported separately.

Description

The use of platelet-rich plasma (PRP) has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The

potential benefit of PRP 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
- Bone Morphogenetic Protein
- 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 1270 and 1271. Blood products such as PRP are included in these regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP.

A number of PRP 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 PRP outside of this setting (e.g., an office injection) would be consideredoff-label. The Aurix System™ (previously called AutoloGel™; Cytomedix) and SafeBlood® (SafeBlood Technologies) are two 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 (e.g., Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, the SmartPRePÒ [Harvest Technologies] device). The Magellan™ Autologous Platelet Separator System (Medtronic Sofamor Danek) 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. 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

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

Injection of PRP for tendon and ligament pain is theoretically related to prolotherapy (see Blue Shield of California Medical Policy: Prolotherapy) 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.

PRP 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 Hemaseel® (Haemacure Corp) 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.

The best evidence on the efficacy of platelet-rich plasma consists of several RCTs comparing platelet-rich plasma with conservative therapy (e.g., rest, physical therapy) and medication (e.g. , corticosteroid injection), and systematic reviews of these trials. A number of systematic reviews of RCTs, with or without the addition of observational studies on platelet-rich plasma, have been published; we focus on them in this evidence review. Individual RCTs are reviewed if no systematic reviews are available or if an individual RCT is likely to influence this evidence review but was not included in a systematic review.

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 (eg, exercise, physical therapy) analgesics, and anti-inflammatory agents, in patients with tendinopathy.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

Several 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). Recent (i.e., 2014 to present) systematic reviews of RCTs and/or nonrandomized studies are described next.

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. [7] The meta-analysis evaluated the standardized mean difference 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.

Miller et al (2017) conducted a systematic review and meta-analysis on platelet-rich plasma for symptomatic tendinopathy and included only RCTs with injection controls.[8] The literature search, conducted through November 2016, identified 16 RCTs, with 18 groups (some studies included >1 tendinopathy site) for inclusion (total N =1018 patients). The Cochrane Collaboration tool was used to assess the risk of bias: 5 studies had an uncertain risk of bias, and 11 studies had a high-risk of bias. The median sample size was 35 patients. Tendinopathy sites were lateral epicondylar (12 groups), rotator cuff (3 groups), Achilles (2 groups), and patellar (1 group). Preparation of platelet-rich plasma differed across trials as did the number of injections, with most studies administering 1 injection and a few administering 2 injections. Eight of the 18 groups reported statistically significant lower pain scores using platelet-rich plasma compared with control and the other 10 reported no differences in pain scores between trial arms. A meta-analysis reported a standard mean difference in pain scores favoring platelet-rich plasma over control (0.47; 95% confidence interval [CI], 0.21 to 0.72; I^2=67%).

Tsikopoulos et al (2016) published a meta-analysis of RCTs that compared platelet-rich plasma with placebo or dry needling in patients who had tendinopathy lasting at least 6 weeks.[9] Minimum length of follow-up was 6 months. The primary outcome was pain intensity; the secondary outcome was functional disability. Five RCTs met reviewers' eligibility criteria. Two RCTs addressed lateral epicondylitis, 2 rotator cuff tendinopathy, and 2 patellar tendinopathy. Three RCT studies had a saline control group, and 2 compared platelet-rich plasma with dry needling. In a pooled analysis of all 5 RCTs, there was no statistically significant difference in pain intensity at 2 to 3 months between platelet-rich plasma and placebo/dry needling (standard mean difference = -0.29; 95% CI, -0.60 to 0.02). The between-group difference in pain intensity was statistically significant at 6 months in a pooled analysis of 4 trials (standard mean difference = -0.48; 95% CI, -0.86 to -0.10). While statistically significant, reviewers noted that the difference between groups in pain intensity at 6 months was not clinically significant. Three trials reported on functional disability levels at 3 months, and meta-analysis of these trials found a significantly greater improvement in function disability in the platelet-rich plasma group (standard mean difference = -0.47; 95% CI, -0.85 to -0.09). Functional disability 6 months post intervention was not addressed.

A systematic review by Balasubramaniam et al (2015) included RCTs on platelet-rich plasma for tendinopathy.[10] Unlike the Tsikopoulos et al(2016) review, these reviewers did not limit inclusion criteria by type of control intervention or post intervention length of follow-up. They included 4 of the 5 RCTs in the Tsikopoulos et al (2016) review and 5 other RCTs. Four RCTs evaluated

epicondylitis, 2 rotator cuff tendinopathy, 2 patellar tendinopathy, and 1 Achilles tendinopathy. Comparison interventions included placebo (n=3), dry needling (n=2), autologous blood (n=2), extracorporeal shock wave therapy (n=1), and corticosteroid injections (n=2). One study included both placebo and corticosteroid control groups. Reviewers did not pool study findings due to a high level of heterogeneity among studies. In their qualitative analysis of the literature by anatomic site of tendinopathy, they concluded that 1 trial on platelet-rich plasma for Achilles tendinopathy was insufficient to draw conclusions about efficacy. Findings of trials of other anatomic sites were mixed. Some showed statistically significant greater benefits of platelet-rich plasma than controls on outcomes, and some did not, or some found statistically significant better outcomes at some time points but not others.

Andia et al (2014) published a systematic review on the use of platelet-rich plasma in the treatment of painful tendinopathies.[11] They included 13 prospective controlled trials (12 RCTs, 1 controlled trial that was not randomized) with data from 636 patients included in the meta-analysis. The trials assessed various tendinopathies, including 7 on chronic elbow, 2 on rotator cuff, 3 on patellar, and 1 study on Achilles. Control interventions included physical therapy (1 trial), extracorporeal shock wave therapy (1 trial), corticosteroid (3 trials), autologous blood (3 trials), saline (3 trials), and dry needling (2 trials). Risk of bias was considered to be low in 4 studies, unclear in 3, and high in 6. The meta-analysis found that platelet-rich plasma was no better than control interventions in reducing pain at 1 or 2 month follow-up. A small significant effect in pain reduction was found at 3 months (weighted mean difference, -0.61). At 1 year, the weighted mean difference between platelet-rich plasma and control interventions was significant at -1.56. Due to heterogeneity between studies, these findings had low power and precision.

Table 1. Systematic Reviews & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Johal (2019)[7]	2010-2016	10	Patients with lateral epicondylitis	25 - 231	RCT	6 w - 24 mo
Miller (2017)[8]	2006-2015	16	Patients with symptomatic tendinopathy	median, 35 (NR)	RCT	NR
Tsikopoulos (2016)[9]	2013-2014	5	Patients with tendinopathy	170 (23-40)	RCT	NR
Andia (2014)[11]	2010-2014	13	Patients with tendinopathy	636	Prospective	NR

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 at 3 Months	Year (WMD between PRP and Control)
Johal (2019)[7]	-0.69			
95% CI	-1.15 to -0.23			
Miller (2017)[8]	0.47			
95% CI	0.22-0.72			
P-value	<0.001			
Tsikopoulos (2016)[9]	-0.48	-0.47		
95% CI	-0.86 to -0.1	-0.85 to -0.09		
P-value	0.01	0.01		
Andia (2014)[11]			-0.61	-1.56
95% CI			-0.97 to -0.25	-2.29 to -0.83

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

Four small RCTs (N=297, range of 57 to 80) have been published subsequent to the above-described systematic reviews.[12,13,14,15] Tendinopathy sites were lateral epicondylar (2 RCT's), patellar (1 RCT), and gluteal (1 RCT). Follow-up durations ranged from 6 months to 1 year.

Platelet-rich plasma protocols varied across studies including a single 3mL injection using a peppering technique, or ultrasound guided injections ranging from 3.5 mL to 6-7 mL, Concurrent rehabilitation protocols also differed, ranging from 6 weeks of supervised rehabilitation to 12 weeks of unsupervised rehabilitation. Compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores. However, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, in the RCT by Martin et al (2019), compared with lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy there were no significant differences in the primary outcome of rate of patients with an improvement exceeding 25% in disability based on Disabilities of the Arm, Shoulder and Hand scores (DASH-E, Spanish version), or other pain outcomes.

Table 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	Comparator 1	Comparator 2
Martin (2019) [15]	Spain	1	2014-2017	Individuals undergoing ultrasound-guided tenotomy for recalcitrant elbow tendinopathy	PRP (n=41)	Lidocaine (n=39)	
Gupta (2019) [12]	India	1	2016-2017	Lateral epicondylitis	PRP (n=40)	CS (n=40)	
Scott (2019) [13]	US, Norway, Italy	3	2014-2017	Athletes with patellar tendinopathy	LR-PRP (n=19)	LP-PRP (n=19)	Saline (n=19)
Fitzpatrick (2019) [14]	Australia	NR	2013-2015	Gluteus tendinopathy	PRP (n=40)	CS (n=40)	

CS: corticosteroids; LR: leukocyte-rich; LP: leukocyte-poor; NR: Not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; US: United States.

Table 4. Summary of Key RCT Results

Study	VAS Score	WOMAC	Other pain / disability assessment
Martin (2019) [15]			1 y rate of patients with an improvement ≥ 25% in disability based on DASH-E scores
PRP			76%
Lidocaine			70.83%
Unadjusted odds ratio; 95% CI			0.71 95% CI, 0.13 to 3.84
Gupta (2019) [12]	12 mo mean score		
PRP	2.50		
CS	13.50		
P-value	0.024		
Scott (2019) [13]			1 y NPRS
LR-PRP			4.7
LP-PRP			5.6
Saline			5.7
P-value			NR
Fitzpatrick (2019) [14]			24 wk mHHS
PRP			77.60
CS			65.72
P-value			0.0003

CI: confidence interval; CS: corticosteroids; DASH-E: Spanish version of the Disabilities of the Arm, Shoulder and Hand questionnaires; HA: hyaluronic acid; LP: leukocyte-poor; LR: leukocyte-rich; mHHS: Modified Harris Hip Score; NPRS: Numeric Pain Rating Scale; NR: not reported; NS: not significant; PRP: platelet-rich plasma;

RCT: randomized controlled trial; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow.Up[e]
Martin (2019) [15]	4. Diagnosis was based on clinical signs and local pain alone. No imaging verification				
Gupta (2019) [12]					
Scott (2019) [13]	4. Study population may not be representative of intended use as it was focused on athletes, including some elite athletes	4. Not the intervention of interest as it included 6 weeks of supervised rehab			
Fitzpatrick (2019) [14]				1. Key health outcomes not addressed	1. Not sufficient duration for benefit

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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Martin (2019) [15]				1. High amount of excluded data (38% for DASH at 12 mo); 6. Not intention to treat		
Gupta (2019) [12]		1. Not blinded	1. Not registered			
Scott (2019) [13]				1. High loss to follow-up or missing data at 12 months (21%)	4. Underpowered	
Fitzpatrick (2019) [14]						

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. Likewise, in subsequently published RCTs, although compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, compared with lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy, there were no significant differences in pain or disability outcomes.

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 patients with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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 RCT's of sufficient duration (i.e., 2 years) to demonstrate efficacy. Franceschi et al (2014) published a qualitative systematic review of the literature on platelet-rich plasma for chronic plantar fasciitis.[16] The literature search, conducted through June 2014, identified 8 prospective studies (total N =256 patients), 3 of which were randomized. Most studies did not have a control group or report imaging evaluations as outcomes. Each study used a different device to prepare platelet-rich plasma. The 3 single-blinded RCTs (n=90 patients) compared platelet-rich plasma treatment with corticosteroids (n=60) or prolotherapy (n=30).

Two trials reported statistically significant improvements with platelet-rich plasma and 1 trial reported no difference. The largest RCT (n=40) by Monto (2014) compared platelet-rich plasma with corticosteroid injection and had a follow-up to 24 months.[17] There was an apparent difference in age and baseline scores between the platelet-rich plasma and steroid groups. Blinded assessment using American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale scores at 3, 6, 12, and 24 months showed temporary improvements in the corticosteroid group, with a return to near-baseline levels (score, 58; scoring range, 0-100, with higher scores indicating less disability) by 12 months. In the platelet-rich plasma group, the AOFAS Ankle-Hindfoot Scale score increased from 37 at baseline to 95 at 3 months and remained elevated through 24 months, with a final score of 92 (difference of 46 from controls, p=0.001). Confirmation of these results in a larger double-blind RCT would permit greater certainty on the efficacy of platelet-rich plasma in plantar fasciitis.

Subsequent to the systematic review by Franceschi et al (2014), several additional RCTs have been published.[18,19,20,21] None were large double-blind RCT s of sufficient duration (i.e., 2 years) to conclusively demonstrate efficacy. The RCT s 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[20] to 155 participants.[18] Follow-up duration ranged from 6 months[20,21] to 18 months.[19] Three were conducted in single centers in either the UK,[20] India[19], or Iran.[21] The fourth was a multicenter RCT of 5 sites in the Netherlands.[20] 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.[18] 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% versus 55.6%; p =0.003). Additionally, mean Foot Function Index Disability Scores were significantly lower in the platelet-rich plasma group at 12 months (mean difference, 12.0; 95% CI, 2.3-21.6). 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 and multiple prospective observational studies have evaluated the efficacy of platelet-rich plasma injections in individuals with chronic plantar fasciitis. 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 corticosteroid resulted in statistically significant improvements in pain and disability, but not quality of life. Larger RCTs 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 patients with osteochondral lesions.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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
No 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.[22] At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale score 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) ($p<0.05$). 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 visual analog scale (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 (eg, exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery, in patients with knee or hip osteoarthritis.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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 6-12 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.[23,24,25,26,27,28,29,30,7,] 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.[24,]

Systematic Reviews

In individuals with hip osteoarthritis undergoing platelet-rich plasma injections, findings from 1 systematic review are reported. Gazendam et al (2020) identified 11 RCTs (total N=1353) assessing the efficacy of platelet-rich plasma, corticosteroids, and saline injections.[31,] Pooled pain and functional outcomes were reported for 2-4 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.
In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, findings from 5 systematic reviews are reported.[23,7,32,24,25,] 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.

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 7-8).[23,] 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 ($p<0.00001$). The corticosteroid subgroup was not significantly different from platelet-rich plasma ($p=0.23$). Six studies comparing single versus multiple injections of platelet-rich plasma showed a significant difference in favor of 3 platelet-rich plasma injections ($p<0.00001$). Functional outcomes were reported via the Western Ontario and McMaster Osteoarthritis Index (WOMAC) scale for placebo (n=9), corticosteroids (n=1), and hyaluronic acid (n=15). Both pooled and subgroup analyses favored platelet-rich plasma ($p<0.00001$). In 5 studies assessing multiple versus single platelet-rich plasma injections, significant differences in favor of multiple injections were found ($p<0.00001$). 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 ($p=0.004$), no significant difference was found for placebo ($p=0.24$). 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 ($p=0.15$). 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), or placebo (2 trials, n=105), or no platelet-rich plasma (2 trials, n=123) or acetaminophen (1 trial, n=75), or a corticosteroid (1 trial, n=48).[7.] Meta-analysis of VAS pain scores showed that platelet-rich plasma was more effective than its comparators at 12 months (standard mean difference, –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 7-8).[32.] Risk of bias was assessed using Cochrane criteria. Four studies were assessed as having 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 Western Ontario and McMaster Universities Osteoarthritis Index or International Knee Documentation Committee (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 0-20; stiffness, scored from 0-8; and physical function, scored from 0-68. 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 7-8).[24.] Ten trials (total N =1110 patients) 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 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 (total N =1543 patients) (see Tables 7-8).[25.] 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
Trams et al (2020)[23.]	2005-2020	-10 PRP vs. placebo -23 PRP vs. HA -4 PRP vs. corticosteroid	Patients with knee OA	38 RCTs

		-2 PRP vs. acetaminophen -6 PRP, single vs. multiple injections		
Johal et al (2019)[7.]	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)[32.]	May 2016	-8 PRP vs. HA -2 PRP vs. placebo	Patients with knee OA	10 RCTs
Laudy et al (2015)[24.]	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)[25.]	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 - 2 Years	
Trams et al (2020)[23.]	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
Xu et al (2017)[32.]	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)[24.]	PRP vs. HA: -0.8 (-1.0 to -0.6)	PRP vs. HA: -1.3 (-1.8 to -0.9)
Chang et al (2014)[25.]	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.

Randomized Controlled Trials

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, 2 RCTs with follow-up durations of at least 12 months have been published subsequent to the above-described systematic reviews (Tables 9-12).[33.34.] All trials were conducted outside of the United States. Sample sizes ranged from 40 to 60 patients. Comparator treatments included corticosteroids or celecoxib. Both RCTs found statistically significantly greater 1-year reductions in pain and function scores with platelet-rich plasma versus the comparator treatments. However, these findings 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.[35.] 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.

Trueba Vasavilbaso et al (2017) conducted a controlled trial that randomized patients after knee arthroscopy to 5 injections of Suprahyal/Adant (n=10), 4 injections of Orthovisc (n=10), 3 injections of Synvisc (n=10), 1 injection of platelet-rich plasma (n=10), or standard of care (n=10).[36.] All patients received the same rehabilitation protocol. At 18-month follow-up, total WOMAC scores improved most from baseline with Suprahyal/Adant (65% reduction). The next best improvement was seen with platelet-rich plasma (55% reduction), then Synvisc (50% reduction), and Orthovisc (30% reduction). The control group experienced a 15% increase in the Western Ontario and McMaster Universities Osteoarthritis Index scores.

Table 9. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	**Comparator 1**	**Comparator 2**
Reyes-Sosa et al (2020)[33.]	Mexico	1	NR	Patients with knee OA, grade II-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)[34.]	Latvia	1	2016 - 2017	Patients with knee OA, grade II-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)[35.]	Italy	NR	2010 - 2011	Patients with hip OA	PRP (n=44)	PRP+HA (n=31)	HA (n=36)
Trueba Vasavilbaso et al (2017)[36.]	Mexico	1	2013 - 2014	Patients with meniscal pathology and knee OA, following knee arthroscopic debridement	PRP (n=10)	5 injections of Suprahyal/Adant (n=10)	4 injections of Orthovisc (n=10) OR Comparator 3=3 injections of Synvisc (n=10) OR Comparator 4=Standard Care (n =10)

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		
Reyes-Sosa et al (2020)[33.]	Change in VAS Score from Baseline at 12 mo, %	Change in WOMAC Score from Baseline at 12 mo
PRP	-68.69 (p<0.001)	-11.5[a]
Celecoxib	-40.94 (p<0.001)	-4[a]
***P*-value for Difference**	*p*<0.001	*p*<0.001
Elksnins-Finogejevs et al (2020)[34.]	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)
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)
Trueba Vasavilbaso et al (2017)[36.]	NR	Change in WOMAC Scores from Baseline at 18 mo, %
PRP		-55
Suprahyal/Adant		-65
Synvisc		-50
Orthovisc		-30
Standard care		+15
Hip OA		
Dallari et al (2016)[37.]	VAS Score at 6 mo	NR
PRP	21	
HA	35	
PRP + HA	44	

CI: confidence interval; CS: corticosteroids; IKDC: International Knee Documentation Score; NR: not reported; OA: osteoarthritis; VAS: visual analog scale.
[a] Calculated estimate.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Reyes-Sosa (2020)[33.]			4. Unclear adherence to treatment.	5. Clinically significant difference not defined.	
Elksnins-Finogejevs (2020)[34.]					
Dallari (2016)[35.]					
Trueba Vasavilbaso et al (2017)[36.]					

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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Binding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]

Reyes-Sosa (2020)[33]	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 (2020)[34]	2. Allocation not concealed from patients or health care providers.	1-3. Not double-blinded.				
Dallari (2016)[35]	2. Allocation not concealed from patients or health care providers	1. Only data collectors and outcome assessors blinded to treatment assignment				
Trueba Vasavilbaso et al (2017)[36]	3. Inadequate control for selection bias: Orthovisc® group older than Synvisc® group (71.1 y vs. 56.9 y; p=0.007)	1. Patients not blinded to treatment assignment	1. Not registered	6. Not intention to treat	1. Power not calculated	

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. The single systematic review evaluating hip osteoarthritis did not report any statistically or clinically significant differences in pain or functional outcomes compared to 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 patients with anterior cruciate ligament (ACL) reconstruction.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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
A Cochrane review by Moraes et al (2013) on platelet-rich therapies for musculoskeletal soft tissue injuries identified 2 RCTs and 2 quasi-randomized studies (total N =203 patients) specifically

on platelet-rich plasma used in conjunction with ACL reconstruction.[38] 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 (total N=740 patients).[23] Five studies showed no significant overall difference with respect to pain (p=0.43). In 4 studies reporting IKDC scores, no significant differences were noted (p=0.83). In 4 studies, no significant differences in functional outcomes as measured by the Lysholm score were reported (p=0.19). Pooled estimates for Tegner scale activity assessments in 5 studies showed no significant differences (p=0.38) in favor of the control. Twelve studies were deemed to be at high risk of bias in at least 1 domain.

A qualitative, systematic review by Figueroa et al (2015) included 11 RCTs or prospective cohort studies (total N=516 patients).[39] Four studies found significantly faster graft maturation while 3 found no significant difference. One study showed faster tunnel healing while 5 showed no benefit. One study showed better clinical outcomes while 5 showed no improvement in clinical outcomes when using platelet-rich plasma.

One of the largest RCTs, reported by Nin et al (2009), randomized 100 patients to arthroscopic ACL reconstruction with or without platelet-rich plasma.[40] 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.

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. Two systematic reviews conducted a meta-analysis, which showed that adjunctive platelet-rich plasma treatment did not result in a significant effect on function and activity outcomes, including IKDC score. Individual studies have shown mixed results.

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 patients with hip fracture.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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
One RCT was identified for 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.[41,] 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-labeled RCT has evaluated the efficacy of platelet-rich plasma injections in individuals with 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 patients with long bone nonunion.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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.

Review of Evidence
A Cochrane review by Griffin et al (2012) found only 1 small RCT (N =21) evaluating platelet-rich plasma for long bone healing.[42.] 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).[43.]

The trial study 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.[37.] 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).

Calori et al (2008) compared application of platelet-rich plasma with rhBMP-7 for the treatment of long bone nonunions in an RCT involving 120 patients and 10 surgeons.[43.] 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 (15-30 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).[44] 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 (2007)[37]	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 (2008)[43]	Italy	1	2005-2007	Patients undergoing treatment of long bone nonunions	PRP (n=60)	rhBMP-7 (n=60)	
Samuel (2017)[44]	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 Soceity Functional Score at 1 yr	Union Rate	Median Healing Time
Dallari (2007)[37]				
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 (2008)[43]				
PRP			41 (68.3%)	4 +/_ 0.61 months
rhBMP-7			52 (86.7%)	3.5 +/_ 0.48
P-value			0.016	
Samuel (2017)[44]				
PRP			18 (78%)	15.3 weeks
Control			10 (59%)	13.1 weeks
P-value			0.296	0.54

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 (2007)[37]	4. Only 33 patients included				
Calori (2008)[43]					
Samuel (2017)[44]					

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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 16. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Dallari (2007)[37]	3. Allocation concealment unclear	1,2,3. No blinding described			1,2. Study was underpowered and nonparametric statistical tests were performed	
Calori (2008)[43]	2. Allocation not concealed	1,2,3. No blinding described				
Samuel (2017)[44]	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 the 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, the results did not differ in the intention-to-treat analysis. An RCT which 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 a 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 patients with rotator cuff repair.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

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. The systematic reviews have varied in their outcomes of interest and findings (Tables 17 and 18).[45,7,38,46,47,48,49,]For pain outcomes, systematic reviews generally found significant reductions with platelet-rich plasma at 12 months.[48,45,7,] However, systematic review authors noted that the pain findings should be interpreted with caution due to significant residual statistical heterogeneity,[48,] lack of a clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically important

difference),[7.] and high risk of bias in study conduct.[7.]. Additionally, the 12-month pain reduction with platelet-rich plasma was not maintained in RCTs with longer-term follow-up of 24 months or longer.[45.] 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.[49.]No reviews have demonstrated a consistent statistical and clinical 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. Wang et al (2019)[45.] reported 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
Chen (2020)[49.]	2011-2017	17	Patients with rotator cuff tears	1116[a] (36-120)	RCT	NR
Johal (2019) [7.]	2011-2016	13	Patients undergoing surgery for rotator cuff repair	858 (25-120)	RCT	7w-24mo
Wang (2019)[45.]	2011-2017	8	Patients with full-thickness rotator cuff injury	566 (48-120)	RCT	12-42mo
Chen (201 8)[48.]	2011-2016	37	Patients with tendon and ligament injuries	1031[a] (NR)	RCT	NR
Fu (2017)[50.]	2011-2015	11	Patients with rotator cuff injury or tendinopathy	638 (NR)	RCT	NR
Zhao (2015)[46.]	2011-2013	8	Patients with rotator cuff injury	464 (28-88)	RCT	NR
Moraes (2013)[38.]	2008-2013	19	Patients undergoing rotator cuff repair	1088 (23-150	RCT and quasi-randomized trials	NR

NR: not reported; 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 at 1 Year	Difference in Retear Rate	Difference in Function at 1 Year
Chen (2020)[49.]	8 RCTs; N=469		UCLA Score: 6 RCTs; N=386
WMD	-0.34		1.39
95% CI	-0.76, 0.09		0.35, 2.43
I^2	87.5%		37.8%
Johal (2019)[7.]	7 RCTs, N=324		
SMD	-0.261		
95% CI	-0.46, -0.05		
I^2	0%		
Wang (2019)[45.]	5 RCTs; N=338	1-year results: 5 RCTs, N=215	UCLA Score: 5 RCTs, N=322

		≥2-year results: 5 RCTs, N=315	
SMD	-0.41	RR for 1-year: 0.29 RR ≥ 2-year: 0.96	0.38
95% CI	-0.62, -0.19	1-year: 0.13, 0.65 ≥ 2-year: 0.52, 1.78	0.16, 0.60
I^2	0%	1-year: 0% ≥2-year: 0%	0%
Chen (201 8)[48.]			
WMD	-0.84		
95% CI	-1.23 to -0.44		
P-value	<0.01		
Fu (2017)[50.]			
SMD	0.142[a]		
95% CI	-0.08 to 0.364		
P-value	0.209		
Zhao (2015)[46.]			
RR		0.94	
95% CI		0.70 to 1.25	
P-value		0.66	
Moraes (2013)[38.]			
SMD			0.25
95% CI			-0.07 to 0.57
P-value			0.12

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

Randomized Controlled Trials

Three small, single-center RCTs have been published subsequent to the systematic reviews described above.[51,52,53.] Walsh et al (2018) published a prospective, randomized, single-blinded study evaluating platelet-rich plasma in fibrin matrix as a means to augment rotator cuff repair[51.]. Malavolta et al (2018) published 5-year clinical and structural evaluations in follow-up to their 2014 publication of their 24-month results.[52.] In contrast to previous RCT s that have focused on administration of platelet-rich plasma at the time of rotator cuff repair surgery, the third RCT, published by Snow et al (2019),[53.] was unique in publishing a randomized double-blind trial of delayed delivery of platelet-rich plasma at 10-15 days post-surgery. Sample sizes ranged from 51 patients[52.] to 97 patients.[53.] Results of these 3 RCTs are consistent with the systematic reviews in finding no statistically or clinically significant benefit of platelet-rich plasma on multiple outcomes.

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 RCTs and systematic reviews with meta-analyses. 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. Additionally, the pain reductions with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on other outcomes. Findings of subsequently published small, single-center RCTs were consistent with the systematic reviews. The variability in platelet-rich plasma preparation techniques and platelet-rich plasma administration limit the generalizability of the studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 patients with spinal fusion.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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. 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

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.[54] 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.

Two prospective observational studies found no differences in fusion rates with use of a platelet gel or platelet glue compared with historical controls.[55,56]

Subsection Summary: 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). The evidence is insufficient to determine the effects of the technology on health outcomes.

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 patients with subacromial decompression surgery.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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
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.[57.] 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 patients with total knee arthroplasty.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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
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.[23] 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 mean difference, -0.29; 95% CI, -0.46 to -0.11), no significant differences in range of motion, functional outcomes, or long-term pain were observed.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Total Knee Arthroplasty
A single systematic review has evaluated the efficacy of intraoperative platelet-rich plasma in individuals undergoing total knee arthroplasty. There were no significant differences between the platelet-rich plasma and untreated control groups across several functional and pain outcomes.

Summary of Evidence
Primary Treatment for Tendinopathies
For individuals with tendinopathy who receive platelet-rich plasma injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews with meta-analyses. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that platelet-rich plasma did not have a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. Findings from subsequently published RCTs have also been mixed. In RCTs that have found significantly improved pain outcomes for platelet-rich plasma injections, important relevancy gaps and study conduct limitations preclude reaching strong conclusions based on their findings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Primary Treatment for Non-Tendon Soft Tissue Injury or Inflammation
For individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis) who receive platelet-rich plasma injections, the evidence includes several small RCTs, multiple prospective observational studies, and a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review, which identified 3 RCTs on platelet-rich plasma for plantar fasciitis, did not pool study findings. Results among the remaining RCTs were inconsistent. The largest RCT showed that treatment using platelet-rich plasma compared with corticosteroid injection resulted in statistically significant improvement in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Primary Treatment for Osteochondral Lesions
For individuals with osteochondral lesions who receive platelet-rich plasma injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the platelet-rich plasma group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Primary Treatment for Knee or Hip Osteoarthritis

For individuals with knee or hip osteoarthritis who receive platelet-rich plasma injections, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most trials have compared platelet-rich plasma with hyaluronic acid for knee 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 scores, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and limited or unclear blinding. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. The single systematic review evaluating hip osteoarthritis did not report any statistically or clinically significant differences in pain or functional outcomes compared to corticosteroids or placebo. Additional studies comparing platelet-rich plasma with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Studies are also needed to determine the optimal protocol for delivering platelet-rich plasma. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Adjunct to Surgery

For individuals with anterior cruciate ligament reconstruction who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes several systematic reviews of multiple RCTs and prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. In 2 systematic reviews that conducted a meta-analysis, adjunctive platelet-rich plasma treatment did not result in a significant effect on International Knee Documentation Committee scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. Individual trials have shown mixed results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hip fracture who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes an open-labeled RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The single open-labeled RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of platelet-rich plasma treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with long bone nonunion who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between those who received platelet-rich plasma plus allogenic bone graft and those who received only allogenic bone graft. While the trial showed a statistically significant increase 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. The second RCT, which compared platelet-rich plasma with recombinant human bone morphogenetic protein-7, also failed to show any clinical or radiologic benefits of platelet-rich plasma over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients receiving platelet-rich plasma injections versus no treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with rotator cuff repair who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are 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. Additionally, the pain reductions with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on other outcomes. Findings of subsequently published small, single-center RCTs were consistent with the systematic reviews. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals undergoing spinal fusion who receive platelet-rich plasma injections plus orthopedic surgery, 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). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with subacromial decompression surgery who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. A single small RCT failed to show a reduction in self-assessed or physician-assessed spinal instability scores with platelet-rich plasma injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with platelet-rich plasma. Larger trials are required to confirm these benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with total knee arthroplasty who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The review showed no significant differences between the platelet-rich plasma and untreated control groups in range of motion, functional outcomes, and long-term pain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 2013, the American Academy of Orthopaedic Surgeons (AAOS) guidelines did not recommend for or against growth factor injections and/or platelet-rich plasma for patients with symptomatic osteoarthritis of the knee.[58] A recommendation of inconclusive was based on a single low-quality study and conflicting findings. The AAOS recommendation was based on 3 studies published before May 2012.

In 2017, the AAOS issued evidence-based guidelines on the management of osteoarthritis of the hip.[59] In the section on intra-articular injectables, the guidelines stated there is strong evidence supporting the use of intra-articular corticosteroids to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was also strong evidence that the use of intra-articular hyaluronic acid does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines also noted that there were no high-quality studies comparing platelet-rich plasma with placebo for the treatment of osteoarthritis of the hip.

National Institute for Health and Care Excellence
In 2013, the National Institute for Health and Care Excellence (NICE) issued guidance on the use of autologous blood injection for tendinopathy.[60] 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.[61] 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.[62] 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 15.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02923700	Leukocyte-rich platelet-rich plasma (PRP) vs. Leukocyte-poor platelet-rich plasma (PRP) for the Treatment of Knee Cartilage Degeneration: a Randomized Controlled Trial	192	Dec 2020 (unknown)
NCT02872753	Intra-operative Platelet-rich Plasma (PRP) Injection Following Partial Meniscectomy	90	Mar 2021 (unknown)
NCT03734900	Comparison of Effectiveness Between PL and PRP on Knee Osteoarthritis: a Prospective,Randomized, Placebo-controlled Trial	150	Jul 2021 (recruiting)
NCT01668953[a]	Impact of Platelet Rich Plasma Over Alternative Therapies in Patients With Lateral Epicondylitis (IMPROVE)	100	Dec 2021 (ongoing)
NCT03300531	Autologous Pure Platelet-rich Plasma in the Treatment of Tendon Disease: A Randomized Controlled Trial	540	Dec 2021
NCT04241354	A Comparison of Platelet-rich Plasma Treatment to the Intra-articular vs. Intra- and Extra-articular Environments in Patients Diagnosed With Hip Osteoarthritis	84	Dec 2021 (recruiting)
NCT04521387	Evaluation of Clinical Efficacy of Different Injection Therapies for Treating Humeral Epicondylopathy	200	May 2022 (recruiting)

NCT04703998	Arthroscopic Rotator Cuff Repair Augmented With Platelet Rich Plasma	100	Sep 2022 (recruiting)
NCT04697667	Exercise and PRP vs. Exercise Alone in Patients With Knee Osteoarthritis	75	Dec 2022 (recruiting)
NCT03136965	Platelet-Rich Plasma Therapy for Patellar Tendinopathy: A Randomized Controlled Trial Correlating Clinical, Biomechanical and Novel Imaging Biomarkers	76	Aug 202 3 (recruiting)
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 2023 (recruiting)
NCT01843504	Platelet-Rich Plasma (PRP) Injection for the Treatment of Chronic Patellar Tendinopathy	44	Dec 2023
Unpublished			
NCT03138317	Evaluation of Platelet Rich Plasma (PRP) for Knee Osteoarthritis	60	May 2018 (unknown)
NCT03129971	Platelet-Rich Plasma Combined with Conventional Surgery in the Treatment of Atrophic Nonunion of Femoral Shaft Fractures	92	Dec 2018 (unknown)
NCT01915979	Role of Biological Therapy in Rotator Cuff Tendinopathy. Effectiveness of Plasma Rich in Growth Factors Regarding Functional Capacity and Pain Compared With the Conventional Treatment Using Steroids	92	Dec 201 8 (completed)

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
	20926	Tissue grafts, other (e.g., paratenon, fat, dermis)
	86999	Unlisted transfusion medicine procedure
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.

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 (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.

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:** Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations: • Primary use (injection) for the following conditions: o Achilles tendinopathy o Lateral epicondylitis o Osteoarthritis o Osteochondral lesions o Plantar fasciitis • Adjunctive use in the following surgical procedures: o Anterior cruciate ligament (ACL) reconstruction o Hip fracture o Long-bone nonunion o Patellar tendon repair o Rotator cuff repair o Spinal fusion o Subacromial decompression surgery o Total knee arthroplasty (TKA)	**Orthopedic Applications of Platelet-Rich Plasma 2.01.98** **Policy Statement:** Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations: I. Primary use (injection) for the following conditions: A. Achilles tendinopathy B. Lateral epicondylitis C. Osteoarthritis D. Osteochondral lesions E. Plantar fasciitis II. Adjunctive use in the following surgical procedures: A. Anterior cruciate ligament (ACL) reconstruction B. Hip fracture C. Long-bone nonunion D. Patellar tendon repair E. Rotator cuff repair F. Spinal fusion G. Subacromial decompression surgery H. Total knee arthroplasty (TKA)