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:**
  - Achilles tendinopathy
  - Lateral epicondylitis
  - Osteoarthritis
  - Osteochondral lesions
  - Plantar fasciitis

- **Adjunctive use in the following surgical procedures:**
  - Anterior cruciate ligament (ACL) reconstruction
  - Hip fracture
  - Long-bone nonunion
  - Patellar tendon repair
  - Rotator cuff repair
  - Spinal fusion
  - Subacromial decompression surgery
  - Total knee arthroplasty (TKA)

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, demis)

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
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 considered off-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 SmartPRePO [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 (QOL), 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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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. RCTs 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 (PRP) consists of several RCTs comparing PRP 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 PRP, 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 PRP or PRP 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

PRP as a Primary Treatment for Tendinopathy
Clinical Context and Therapy Purpose
The purpose of PRP 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 tendinopathy.

The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures? The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with tendinopathy.

Interventions
The therapy being considered is PRP injections. The use of 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.

Comparators
Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, and anti-inflammatory agents. These treatments are managed by primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity.

Timing
The existing literature evaluating PRP injections as a treatment for tendinopathy has varying lengths of follow-up, ranging from six months to two years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients with tendinopathy are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.
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.

Several systematic reviews have evaluated PRP 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.

Miller et al (2017) conducted a systematic review and meta-analysis on PRP for symptomatic tendinopathy and included only RCTs with injection controls.7 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 PRP differed across trials as did the number of injections, with most studies administering one injection and a few administering two injections. Eight of the 18 groups reported statistically significant lower pain scores using PRP compared with control and the other ten reported no differences in pain scores between trial arms. A meta-analysis reported a standard mean difference (SMD) in pain scores favoring PRP over control (0.47; 95% confidence interval [CI], 0.21 to 0.72; I²=67%).

Tsikopoulos et al (2016) published a meta-analysis of RCTs that compared PRP with placebo or dry needling in patients who had tendinopathy lasting at least 6 weeks.8 Minimum length of follow-up was six months. The primary outcome was pain intensity; the secondary outcome was functional disability. Five RCTs met reviewers’ eligibility criteria. Two RCTs addressed lateral epicondylitis, two rotator cuff tendinopathy, and two patellar tendinopathy. Three RCT studies had a saline control group, and two compared PRP 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 PRP and placebo/dry needling (SMD = -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 (SMD = -0.48; 95% CI, -0.86 to -0.10). While statistically significant, reviewers noted that the difference between groups in pain intensity at six 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 PRP group (SMD = -0.47; 95% CI, -0.85 to -0.09). Functional disability six months postintervention was not addressed.

A systematic review by Balasubramaniam et al (2015) included RCTs on PRP for tendinopathy.9 Unlike the Tsikopoulos et al (2016) review, these reviewers did not limit inclusion criteria by type of control intervention or postintervention 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, two rotator cuff tendinopathy, two patellar tendinopathy, and one 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 one trial on PRP 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 PRP 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 PRP in the treatment of painful tendinopathies.\textsuperscript{10} 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 seven on chronic elbow, two on rotator cuff, three on patellar, and one study on Achilles. Control interventions included physical therapy (one trial), extracorporal shock wave therapy (one trial), corticosteroid (three trials), autologous blood (three trials), saline (three trials), and dry needling (two trials). Risk of bias was considered to be low in four studies, unclear in three, and high in six. The meta-analysis found that PRP was no better than control interventions in reducing pain at one or two 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 PRP 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 Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (2017)</td>
<td>2006-2015</td>
<td>16</td>
<td>Patients with symptomatic tendinopathy</td>
<td>median 35 (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Tsikopoulos (2016)</td>
<td>2013-2014</td>
<td>5</td>
<td>Patients with tendinopathy</td>
<td>170 (23-40)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Andia (2014)</td>
<td>2010-2014</td>
<td>13</td>
<td>Patients with tendinopathy</td>
<td>636</td>
<td>Prospective</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial.

### Table 2. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD in Pain for PRP</th>
<th>SMD in functional disability for PRP</th>
<th>WMD in Pain Reduction at 3 Months</th>
<th>Year (WMD between PRP and Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (2017)</td>
<td>0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.22-0.72</td>
<td></td>
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<td></td>
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<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tsikopoulos (2016)</td>
<td>-0.48</td>
<td>-0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.86 to -0.1</td>
<td>-0.85 to -0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andia (2014)</td>
<td>-0.61</td>
<td>-1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.97 to -0.25</td>
<td>-2.29 to -0.83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### Section Summary: PRP as a Primary Treatment of Tendinopathy

Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of PRP injections in individuals who have tendinopathy. 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.

### PRP as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation

#### Clinical Context and Therapy Purpose

The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest are individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

Interventions
The therapy being considered is PRP injections. The use of 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.

Comparators
Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, and anti-inflammatory agents. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity.

Timing
The existing literature evaluating PRP 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 one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, two years of follow-up is considered necessary to demonstrate efficacy.

Setting
Patients with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

Franceschi et al (2014) published a qualitative systematic review of the literature on PRP for chronic plantar fasciitis. 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 PRP. The 3 single-blinded RCTs (n=90 patients) compared PRP treatment with corticosteroids (n=60) or prolotherapy (n=30). Two trials reported statistically significant improvements with PRP and one trial reported no difference. The largest RCT (n=40) by Monto (2014) compared PRP with corticosteroid injection and had a follow-up to 24 months. There was an apparent difference in age and baseline scores between the PRP 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 PRP 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 PRP in plantar fasciitis.

**Section Summary: PRP as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation**

Three small RCTs and multiple prospective observational studies have evaluated the efficacy of PRP injections in individuals with chronic plantar fasciitis. Preparation of PRP and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the three RCTs showed that treatment using PRP compared with corticosteroid resulted in statistically significant but temporary improvements in AOFAS Ankle-Hindfoot Scale scores, indicating improved outcomes. Larger RCTs would be required to confirm these findings.

**PRP as a Primary Treatment of Osteochondral Lesions**

**Clinical Context and Therapy Purpose**

The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are individuals with osteochondral lesions.

**Interventions**

The therapy being considered is PRP injections.

The use of 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.

**Comparators**

Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

**Outcomes**

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity.

**Timing**

The existing literature evaluating PRP injections as a treatment for osteochondral lesions has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 28 weeks of follow-up is considered necessary to demonstrate efficacy.

**Setting**

Patients with osteochondral lesions are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.
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. Studies with duplicative or overlapping populations were excluded

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 PRP. At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale score improved to a greater extent in the PRP 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 PRP 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: PRP as a Primary Treatment of Osteochondral Lesions
A single quasi-randomized study has evaluated the efficacy of PRP injections in individuals who have osteochondral lesions. Compared with hyaluronic acid, treatment with PRP 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.

PRP as a Primary Treatment of Knee or Hip Osteoarthritis
Clinical Context and Therapy Purpose
The purpose of PRP 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 knee or hip OA. The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with knee or hip OA.

Interventions
The therapy being considered is PRP injections. The use of 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.

Comparators
Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

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

Setting
Patients with knee or hip OA are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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. Studies with duplicative or overlapping populations were excluded.

A number of RCTs and several systematic reviews of RCTs evaluating the use of PRP for knee OA have been published. Protocols used in PRP interventions for knee OA varied widely. For example, in the studies identified in the Laudy et al (2015) systematic review, PRP was prepared using single, double, or triple spinning techniques and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.

Systematic Reviews
Xu et al (2017) conducted a systematic review and meta-analysis of RCTs comparing PRP with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee OA (see Table 3). Risk of bias was assessed using Cochrane criteria. Four studies were assessed as having low-quality, three as moderate-quality, and three as high-quality. Meta-analyses including seven of the trials comparing PRP with hyaluronic acid showed that PRP significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or International Knee Documentation Committee (IKDC) scores compared with hyaluronic acid at six-month follow-up; however, when meta-analyses included only the two high-quality RCTs, there was not a significant difference between PRP and hyaluronic acid (see Table 4). Also, note that 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 PRP with placebo, a third trial was included, which had four treatment groups, two of which were PRP and placebo. This analysis showed that PRP significantly improved WOMAC or IKDC scores compared with placebo; however, only one of the trials was considered high-quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials ($I^2 \geq 90\%$).

Laudy et al (2015) conducted a systematic review of RCTs and nonrandomized clinical trials to evaluate the effect of PRP on patients with knee OA (see Table 3). Ten trials (total n=1110 patients) were selected. Cochrane criteria for risk of bias were used to assess study quality, with one trial rated as having a moderate-risk of bias and the remaining nine trials as high-risk of bias. While meta-analyses showed that PRP was more effective than placebo or hyaluronic acid in reducing pain and improving function (see Table 4), 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 Table 3). 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 PRP (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 PRP (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 three injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. PRP 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 3. Systematic Review Characteristics for Knee or Hip OA

<table>
<thead>
<tr>
<th>Study</th>
<th>Search Date</th>
<th>Trials</th>
<th>Participants</th>
<th>Design</th>
</tr>
</thead>
</table>
| Xu et al (2017)
| May 2016      | e. 8 PRP vs HA f. 2 PRP vs placebo | Patients with knee OA | g. 10 RCTs |
|                |             |                 |                  |              |
| Jun 2014      | h. 8 PRP vs HA i. 1 PRP vs placebo j. 1 PRP, different preparations | Patients with knee OA | k. 6 RCTs l. 4 nonrandomized |
| Chang et al (2014)
| Sep 2013      | m. 6 PRP vs HA n. 1 PRP vs placebo o. 1 PRP, different preparations p. 8 single-arm PRP | Patients with knee OA | q. 5 RCTs r. 3 quasi-randomized s. 8 single-arm |

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

### Table 4. Systematic Review Results for Knee or Hip OA

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in Functional Scores (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Months</td>
</tr>
</tbody>
</table>
| Xu et al (2017)
| PRP vs HA:     | -0.9 (-1.4 to -0.3)                 | NR        |
|                | All trials:                         | 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) |

| PRP vs HA:     | -0.8 (-1.0 to -0.6)                 | PRP vs HA: -1.3 (-1.8 to -0.9) |
| PRP, baseline vs post-treatment: | All studies: 2.5 (1.9 to 3.1) | All studies: 2.9 (1.0 to 4.8) |
|                | Single-arm: 3.1 (2.0 to 4.1)        | Single-arm: 2.6 (-0.4 to 5.7) |
|                | Quasi-randomized: 3.1 (1.4 to 3.8)  | Quasi-randomized: 4.5 (4.1 to 5.0) |
|                | RCT: 1.5 (1.0 to 2.1)               | RCT: 0.9 (0.5 to 1.3) |

CI: confidence interval; HA: hyaluronic acid; NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; OA: osteoarthritis.

* Functional outcomes were measured by the International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Score, or Western Ontario McMaster Osteoarthritis Index.

### Randomized Controlled Trials

The systematic review by Chang et al (2014) identified a single placebo-controlled trial, Patel et al (2013). This RCT included 78 patients with bilateral knee OA. Patients were randomized to a single injection of PRP, two injections of PRP, or a single saline placebo injection. There was significantly greater improvement in the WOMAC scores at one, three, and six months in the active treatment groups combined, compared with the placebo group (p < 0.01) as well as in VAS scores (p < 0.01). WOMAC scores in the PRP arm decreased by...
approximately 50% of their baseline values at 6 months (from 50 to 27 in the group receiving 1 PRP injection, from 53 to 31 in the group receiving 2 PRP injections). Based on a study by Tubach et al (2005), which determined minimal clinically important differences for WOMAC scores, the reductions experienced by the PRP groups met the clinically meaningful criteria. However, no responder analysis was reported. The difference in WOMAC scores between patients who received one or two PRP injections did not differ significantly. Multiple limitations of this trial were recognized. While powered to detect a difference of 1.5 points in VAS scores, the primary endpoint was deemed to be WOMAC scores. More importantly, methods to control for type I error for multiple comparisons were not described and possibly not used. Further, the process of randomization and randomized allocation was not described. Lastly, though the trial was described as double-blind, the number of injections between the active arm receiving two PRP injections differed from that for placebo and that for PRP patients who received only one injection; as such, maintenance of blinding through the trial period is questionable.

Smith et al (2016) conducted a double-blind, placebo-controlled trial (n=30) in patients with knee OA, which showed that treatment with PRP resulted in statistically and clinically significant improvements in WOMAC scores compared with placebo, beginning at week 2 (p=0.016) and continuing through the trial duration at 1 year. A similar trend was seen in all three domains of the WOMAC (pain, stiffness, physical function). Overall WOMAC mean scores in the PRP and placebo-treated arms at baseline were 47 and 46, respectively. Post-1 year, the respective overall mean scores were 10 and 43 (p<0.05). Patients answered the questions and then received a cumulative score for each of the three domains.

Dallari et al (2016) reported on results of an RCT that compared PRP with hyaluronic acid alone or with a combination PRP plus hyaluronic acid in 111 patients with hip OA. Although this well-conducted RCT reported positive results, with statistically significant reductions in VAS scores (lower scores imply less pain) at 6 months in the PRP arm (21; 95% CI, 15 to 28) vs the hyaluronic acid arm (35; 95% CI, 26 to 45) or the PRP 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 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 PRP (n=10), or standard of care (n=10). 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 PRP (55% reduction), then Synvisc (50% reduction), and Orthovisc (30% reduction). The control group experienced a 15% increase in WOMAC scores.

### Table 5. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel (2013)</td>
<td>India</td>
<td>1</td>
<td>NR</td>
<td>Patients with bilateral knee OA</td>
<td>Single PRP injection (n=52 knees)</td>
<td>2 PRP injections 3 weeks apart (n=50 knees)</td>
<td>Single injection of normal saline (n=46 knees)</td>
</tr>
<tr>
<td>Smith (2016)</td>
<td>US</td>
<td>1</td>
<td>NR</td>
<td>Patients with knee OA</td>
<td>Treatment with PRP (n=15)</td>
<td>Placebo (n=15)</td>
<td></td>
</tr>
<tr>
<td>Dallari (2016)</td>
<td>Italy</td>
<td>NR</td>
<td>2010-2011</td>
<td>Patients with hip OA</td>
<td>PRP (n=44)</td>
<td>PRP+HA (n=31)</td>
<td>HA (n=36)</td>
</tr>
</tbody>
</table>

HA: hyaluronic acid; RCT: randomized controlled trial; OA: osteoarthritis; PRP: platelet-rich plasma; NR: not reported.
Table 6. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Score from at 6 mo.</th>
<th>Change in WOMAC Scores from Baseline to 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel (2013)21.</td>
<td>Single PRP 2.16</td>
<td>47 to 10 (78% decrease)</td>
</tr>
<tr>
<td></td>
<td>Double PRP 2.54</td>
<td>46 to 43 (7% decrease)</td>
</tr>
<tr>
<td>Smith (2016)23.</td>
<td>Placebo 4.61</td>
<td></td>
</tr>
<tr>
<td>Dallari (2016)24.</td>
<td>PRP 21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRP+HA 35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HA 44</td>
<td></td>
</tr>
</tbody>
</table>

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PRP: platelet-rich plasma; HA: hyaluronic acid; VAS: visual analog scale; RCT: randomized controlled trial.

Table 7. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow.Upa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel (2013)21.</td>
<td>1. Possible cartilage regeneration not evaluated</td>
<td>1.2. Only 6 months follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith (2016)23.</td>
<td>4. Only 30 patients included</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- 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.
- Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
- Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

Table 8. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective.Reportingc</th>
<th>Follow.Upd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel (2013)21.</td>
<td>Patients were randomized instead of knees</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith (2016)23.</td>
<td>2. Allocation not concealed from patients or health care providers</td>
<td>1. Only data collectors and outcome assessors blinded to treatment assignment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dallari (2016)24.</td>
<td>2. Allocation not concealed from patients or health care providers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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: PRP as a Primary Treatment of Knee or Hip OA
Multiple RCTs and systematic reviews with meta-analysis have evaluated the efficacy of PRP injections in individuals with knee or hip OA. Three RCTs have compared PRP with placebo while most trials have compared PRP with hyaluronic acid for knee OA. A single RCT compared PRP with hyaluronic acid alone or combination PRP plus hyaluronic acid in hip OA. A meta-analysis of three trials comparing PRP with placebo showed a significant improvement in functional scores; however, only one of the trials was considered high-quality. Comparisons between PRP and hyaluronic acid have found inconsistent results, with a meta-analysis including only low-risk of bias studies showing no difference between the two treatments. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust. The single RCT evaluating hip OA reported statistically significant reductions in VAS scores but no significant differences in Harris Hip Score and WOMAC scores. Additional larger controlled studies comparing PRP with placebo and alternatives other than hyaluronic acid are needed to determine the efficacy of PRP for knee and hip OA. Further studies are also needed to determine the optimal protocol for delivering PRP.

PRP as an Adjunct to Surgery
Anterior Cruciate Ligament Reconstruction

Clinical Context and Therapy Purpose
The purpose of PRP 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 ACL reconstruction.

The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with ACL reconstruction.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of 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.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

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

Setting
Patients with ACL reconstruction are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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.

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 PRP used in conjunction with ACL reconstruction.27 Pooled data found no significant difference in IKDC scores between the PRP and control groups.

A qualitative, systematic review by Figueroa et al. (2015) included 11 RCTs or prospective cohort studies (total n=516 patients).28 Four studies found significantly faster graft maturation while three found no significant difference. One study showed faster tunnel healing while five showed no benefit. One study showed better clinical outcomes while five showed no improvement in clinical outcomes when using PRP.

The largest RCT, reported by Nin et al. (2009), randomized 100 patients to arthroscopic ACL reconstruction with or without PRP.29 The use of PRP 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 two-year follow-up.

Subsection Summary: PRP as Adjunctive Treatment of ACL Reconstruction
Two systematic reviews that included multiple RCTs, quasi-randomized studies, and prospective studies have evaluated the efficacy of PRP injections in individuals undergoing ACL reconstruction. Only one of the two systematic reviews conducted a meta-analysis, which showed that adjunctive PRP treatment did not result in a significant effect on IKDC score. Individual studies have shown mixed results.

Hip Fracture
Clinical Context and Therapy Purpose
The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest are individuals with hip fracture.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of 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.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity.

Timing
The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for hip fracture has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients with hip fracture are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

One RCT was identified for treatment of a hip fracture with PRP. Griffin et al (2013) reported on a single-blind randomized trial assessing the use of PRP for the treatment of hip fractures in patients ages 65 years and older. 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 PRP 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% PRP; 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 PRP group. The length of stay was significantly reduced in the PRP-treated group (median difference, eight days). For this measure, there is a potential for bias from the nonblinded treating physician.

Subsection Summary: PRP as Adjunctive Treatment for Hip Fracture
A single open-labeled RCT has evaluated the efficacy of PRP injections in individuals with hip fracture. This trial failed to show any statistically significant reductions in the need for revision surgery after PRP treatment.
Long Bone Nonunion
Clinical Context and Therapy Purpose
The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with long bone nonunion.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of 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.

Comparators
Comparators of interest include rhBMP-7 plus orthopedic surgery. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity.

Timing
The existing literature evaluating PRP 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 one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients with long bone nonunion are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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.

A Cochrane review by Griffin et al (2012) found only 1 small RCT (n=21) evaluating PRP for long bone healing. However, because only studies comparing PRP with no additional treatment or placebo were eligible for inclusion, reviewers did not select a larger RCT by Calori et al (2008; discussed below).

The trial study by Dallari et al (2007), which was included in the Cochrane review, compared PRP plus allogenic bone graft with allogenic bone graft alone in patients undergoing corrective osteotomy for medial compartment osteoarthrosis of the knee. 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 one year. However, the proportion of bones united at 1 year was statistically significantly higher in the PRP 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 PRP with rhBMP-7 for the treatment of long bone nonunions in an RCT involving 120 patients and 10 surgeons. Inclusion criteria were posttraumatic atrophic nonunion for at least nine months, with no signs of healing over the last three 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 PRP group. Computer-generated randomization created two homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the two 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 PRP patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the PRP 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 PRP.

Samuel et al (2017) conducted a controlled trial in which patients with delayed unions (15-30 weeks old) were randomized to 2 PRP injections at the fracture site at baseline and 3 weeks (n=23) or no treatment (n=17). 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 three 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 PRP group vs 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the PRP group vs 13.1 weeks for the control group).

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>Italy</td>
<td>NR</td>
<td>NR</td>
<td>Patients undergoing high tibial osteotomy to treat genu varum</td>
<td>Implantation of lyophilized bone chips with platelet gel (n=11)</td>
<td>Implantation of lyophilized bone chips with platelet gel and bone marrow stromal cells (n=12)</td>
</tr>
<tr>
<td>Calori (2008)</td>
<td>Italy</td>
<td>1</td>
<td>2005-2007</td>
<td>Patients undergoing treatment of long bone nonunions</td>
<td>PRP (n=60)</td>
<td>rhBMP-7 (n=60)</td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td>India</td>
<td>1</td>
<td>2010-2014</td>
<td>Patients with delayed unions</td>
<td>PRP (n=23)</td>
<td>No treatment (n=17)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Knee Society Score at 1 yr</th>
<th>Knee Society Functional Score at 1 yr</th>
<th>Union Rate</th>
<th>Median Healing Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>91.3 +/- 2</td>
<td>99.0 +/- 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Knee Society Score at 1 yr</td>
<td>Knee Society Functional Score at 1 yr</td>
<td>Union Rate</td>
<td>Median Healing Time</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------</td>
<td>---------------------------------------</td>
<td>------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>PRP+bone marrow</td>
<td>89.9 +/- 4</td>
<td>99.2 +/- 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PRP</td>
<td>90.3 +/- 4</td>
<td>98.8 +/- 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td>41 (68.3%)</td>
<td>4 +/- 0.61 months</td>
</tr>
<tr>
<td>rhBMP-7</td>
<td></td>
<td></td>
<td>52 (86.7%)</td>
<td>3.5 +/- 0.48</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td>18 (78%)</td>
<td>15.3 weeks</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td>10 (59%)</td>
<td>13.1 weeks</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td>0.296</td>
<td>0.54</td>
</tr>
</tbody>
</table>

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

Table 11. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>4. Only 33 patients included</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps 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.


Table 12. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective.Reporting</th>
<th>Follow-Up</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>3. Allocation concealment unclear</td>
<td>1,2,3. No binding described</td>
<td>1,2. Study was underpowered and nonparametric statistical tests were performed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008)</td>
<td>2. Allocation not concealed</td>
<td>1,2,3. No binding described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td>1. Randomization procedure not described, 3. Allocation concealment unclear</td>
<td>1,2,3. No binding described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps 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...
Subsection Summary: PRP as Adjunctive Treatment for Long Bone Nonunion

Three RCTs have evaluated the efficacy of PRP 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 PRP plus allogenic bone graft vs 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 PRP in a modified intention-to-treat, the results did not differ in the intention-to-treat analysis. An RCT which compared PRP with rhBMP-7 also failed to show any clinical and radiologic benefits of PRP over rhBMP-7. The third RCT found no difference in a number of unions or time to union in patients receiving PRP injections or no treatment.

Rotator Cuff Repair
Clinical Context and Therapy Purpose

The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with rotator cuff repair.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of 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.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity.

Timing
The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for rotator cuff repair has varying lengths of follow-up, ranging from six months to 3.5 years. While studies...
described below all reported at least one 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.

**Setting**

Patients with rotator cuff repair are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

**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.

The literature on PRP for rotator cuff repair consists of RCTs that have evaluated the efficacy of PRP membrane or matrix combined with surgical repair of the rotator cuff. Also, several systematic reviews of the literature, which pooled analysis of data, generally did not show a statistically or clinically significant benefit of PRP.

**Systematic Reviews**

Chen et al (2017) conducted a systematic review and meta-analysis on the efficacy of PRP for tendon and ligament healing. The literature search, conducted through April 2017, identified 37 articles for qualitative synthesis, 21 of which reported VAS outcomes and were used in a meta-analysis. Of the 21 studies, 8 enrolled patients undergoing rotator cuff repair. Patients in the PRP group experienced significant reductions in VAS pain compared with the control group at both short-term (6 months) follow-up (-0.5; 95% CI, -0.7 to -0.1) and long-term (≥1 year) follow-up (-0.5; 95% CI, -1.0 to -0.1). While findings were encouraging, reviewers warned that there was extensive variability in both the way PRP was prepared and how the PRP injections were administered.

Fu et al (2017) reported on the results of a meta-analysis that only included RCTs comparing the efficacy of PRP with platelet-rich fibrin matrix for improving healing of rotator cuff injuries. Eleven RCTs were included; they enrolled 320 patients with active treatment and 318 patients as controls. Results for the primary outcome (functional score change from pre- to posttreatment) were similar between patients administered PRP plus fibrin matrix and patients in the control group (SMD for functional scores, 0.029; 95% CI, -0.132 to 0.190; p=0.725). The SMD was also similar for patients administered PRP and the controls (SMD=0.142; 95% CI, -0.080 to 0.364; p=0.209). Reviewers concluded that meta-analytic results did not support the use of PRP plus platelet-rich fibrin matrix in patients with rotator cuff injuries.

Saltzman et al (2016) published a systematic review of meta-analyses on PRP at the time of surgery and clinical outcomes for patients undergoing rotator cuff repair. Reviewers identified 7 meta-analyses, all published after 2012, that pooled analyses of trial data. Systematic reviews varied in their outcomes of interest, but all pooled data on the overall re-tear rate, and none reported a statistically significant difference in the re-tear rate among patients who received PRP compared with a control intervention; the RR ranged from 0.55 to 0.94 and the odds ratio reported in 1 study was 1.11. However, one of the meta-analyses included in the Saltzman et al (2016) review found a significantly lower risk of re-tear with PRP use when an outlier study was excluded from the analysis.

The 2013 Cochrane review by Moraes et al (2013), which pooled data for long-term function from 6 RCTs of PRP applied with rotator cuff repair, showed no statistically or clinically significant
differences between the PRP groups and control groups. Moreover, a meta-analysis by Zhao et al (2015) included 8 RCTs with sample sizes ranging from 28 to 88 (total n=464 patients). Meta-analysis showed no significant differences between the PRP groups and control groups in re-tear rate (RR=0.94; 95% CI, 0.70 to 1.25; p=0.66), Constant score (mean difference, 1.12; 95% CI, -1.38 to 3.61; p=0.38), or University of California at Los Angeles Shoulder Score (mean difference, -0.68; 95% CI, -2.00 to 0.65; p=0.32). The strength of the evidence based on GRADE was considered to be low for re-tear, moderate for Constant score, and low for University of California at Los Angeles Shoulder Score.

Table 13. Systematic Reviews & Meta-Analysis Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2017)</td>
<td>2011-2016</td>
<td>37</td>
<td>Patients with tendon and ligament injuries</td>
<td>1031a (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Fu (2017)</td>
<td>2011-2015</td>
<td>11</td>
<td>Patients with rotator cuff injury or tendinopathy</td>
<td>638 (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Zhao (2015)</td>
<td>2011-2013</td>
<td>8</td>
<td>Patients with rotator cuff injury or tendinopathy</td>
<td>464 (28-88)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Moraes (2013)</td>
<td>2008-2013</td>
<td>19</td>
<td>Patients undergoing rotator cuff repair</td>
<td>1088 (23-150)</td>
<td>RCT and quasi-randomized trials</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial.
aNumber of participants from the 21 articles which could be included in the quantitative analysis.

Table 14. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Reduction at 1 Year</th>
<th>VAS Change from Pre to Posttreatment</th>
<th>Difference in Retear Rate</th>
<th>Difference in function at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2017)</td>
<td>-0.84</td>
<td>-1.23 to -0.44</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Fu (2017)</td>
<td>0.142</td>
<td>-0.08 to 0.364</td>
<td>0.209</td>
<td></td>
</tr>
<tr>
<td>Zhao (2015)</td>
<td>0.94</td>
<td>0.70 to 1.25</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Moraes (2013)</td>
<td>0.25</td>
<td>-0.07 to 0.57</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

RR: risk ratio; SMD: standard mean difference; WMD: weighted mean difference; VAS: visual analog scale; CI: confidence interval.

Randomized Controlled Trials

Walsh et al (2018) published a prospective, randomized, single-blinded study evaluating PRP in fibrin matrix as a means to augment rotator cuff repair. Seventy-six patients were randomized to either the PRP (n=32) or control group (n=44) between 2011 and 2013. At 24 months, Western Ontario Rotator Cuff scores had changed from 1106 to 94 for PRP and from 1257 to 139 for control. Rate of retear at 6 months was 7.4% for the PRP group and 19% for control. Strength of supraspinatus and infraspinatus were 96.6% and 103%, respectively, for PRP and 99.8% and 104%, respectively, for control. No results reached statistical significance. The study was limited by the following: (1) the study was single- rather than double-blinded, (2) no attempt was made...
to quantify the concentration of platelets used in the repairs, (3) follow-up was relatively short (two years), and (4) magnetic resonance imaging scans were only made at six-month follow-up.

Ebert et al (2017) published an RCT after the systematic reviews discussed above comparing rotator cuff repair alone with rotator cuff repair plus PRP treatment. Patients were randomized to 2 ultrasound-guided injections of PRP to the tendon repair site at 7 and 14 days after arthroscopic supraspinatus repair (n=27) or not (n=28). Outcomes of interest included Oxford Shoulder Score, Quick Disabilities of the Arm, Shoulder and Hand questionnaire, and VAS score for pain. At a mean follow-up of 3.5 years, there were no statistically significant differences in any of the outcomes of interest. There was also no difference in re-tear rates, with two patients in each trial group experiencing symptomatic re-tears.

Subsection Summary: PRP as Adjunctive Treatment for Rotator Cuff Repair
Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of PRP injections in individuals undergoing rotator cuff repair. The systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. The variability in PRP preparation techniques and PRP administration limit the generalizability of the studies.

Spinal Fusion
Clinical Context and Therapy Purpose
The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with spinal fusion.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery.

The use of 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.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity.

Timing
The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for spinal fusion has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.
Setting
Patients with spinal fusion are actively managed pre- and postoperatively by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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.

No RCTs on use of PRP for spinal fusion were identified. Two prospective observational studies found no differences in fusion rates with use of a platelet gel or platelet glue compared with historical controls.\textsuperscript{39,40}

Subacromial Decompression Surgery

Clinical Context and Therapy Purpose
The purpose of PRP 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 PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with subacromial decompression surgery.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of 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.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity.

Timing
The existing literature evaluating PRP 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 one outcome of interest, longer follow-up was necessary to fully observe outcomes.
Setting
Patients with subacromial decompression surgery are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

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

One small RCT evaluated the use of PRP 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 (PLRP) gel following open subacromial decompression surgery in a carefully selected patient population. Neither self-assessed nor physician-assessed instability improved. Both subjective pain and use of pain medication were lower in the PLRP group across the six weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the PLRP group (close to 4 in the control group, close to 2 in the PLRP group), and only 1 (5%) patient in the PLRP group was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvements in the PLRP group across the six-week assessment period, with patients reporting improvements in activities of daily living, such as the ability to sleep on the operated shoulder at four weeks after surgery and earlier return to work.

Subsection Summary: PRP as Adjunctive Treatment for Subacromial Decompression Surgery
A single small RCT has evaluated the efficacy of PRP injections in individuals undergoing subacromial decompression surgery. Compared with controls, PRP 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 PRP. Larger RCTs would be required to confirm these benefits.

Total Knee Arthroplasty
Clinical Context and Therapy Purpose
The purpose of PRP 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 TKA.

The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with TKA.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of 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.
Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity.

Timing
The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for TKA has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients with TKA are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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.

Morishita et al (2014) reported on the results of a controlled trial of 40 patients, scheduled for unilateral TKA, who were randomized to intraoperative PRP (n=20) or no additional intraoperative treatment (n=20). There were no significant differences between the PRP and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, Knee Society Scores, or Knee Injury and Osteoarthritis Outcome Score.

Subsection Summary: PRP as Adjunctive Treatment for TKA
A single small RCT has evaluated the efficacy of PRP injections in individuals undergoing TKA. There were no significant differences between the PRP and untreated control groups across several functional and pain outcomes.

Summary of Evidence
Primary Treatment for Tendinopathies
For individuals with tendinopathy who receive PRP injections, the evidence includes multiple RCTs and systematic reviews with meta-analyses. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that PRP did not have a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Non-Tendon Soft Tissue Injury or Inflammation
For individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) who receive PRP injections, the evidence includes three small RCTs, multiple prospective observational studies, and a systematic review. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The systematic review, which identified three RCTs on PRP for plantar fasciitis, did not pool study findings. Results among the three RCTs were inconsistent. The largest RCT showed that treatment using PRP compared with corticosteroid injection resulted in statistically significant but temporary
improvements in AOFAS Ankle-Hindfoot Scale scores, indicating improved outcomes. Confirmation of these results in larger double-blind RCTs would be needed to permit greater certainty on the efficacy of PRP in plantar fasciitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Primary Treatment for Osteochondral Lesions**

For individuals with osteochondral lesions who receive PRP injections, the evidence includes an open-labeled quasi-randomized study. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the PRP 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 the effects of the technology on health outcomes.

**Primary Treatment for Knee or Hip OA**

For individuals with knee or hip OA who receive PRP injections, the evidence includes multiple RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. Three RCTs have compared PRP with placebo while most trials have compared PRP with hyaluronic acid for knee OA. A meta-analysis of three trials comparing PRP with placebo showed a significant improvement in functional scores. However, only one of the trials was considered at low-risk of bias. Comparisons between PRP and hyaluronic acid have shown inconsistent results. A meta-analysis including only low-risk of bias trials showed no difference between the two treatments in functional scores. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust. The single RCT evaluating hip OA reported statistically significant reductions in VAS scores for pain, with no difference in functional scores. Additional studies comparing PRP with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of PRP for knee and hip OA. Studies are also needed to determine the optimal protocol for delivering PRP. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Adjunct to Surgery**

For individuals with ACL reconstruction who receive PRP injections plus orthopedic surgery, the evidence includes two systematic reviews of multiple RCTs and prospective studies. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. Only one of the two systematic reviews conducted a meta-analysis; it showed that adjunctive PRP treatment did not result in a significant effect on IKDC 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 the effects of the technology on health outcomes.

For individuals with hip fracture who receive PRP injections plus orthopedic surgery, the evidence includes an open-labeled RCT. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, 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 PRP treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with long bone nonunion who receive PRP injections plus orthopedic surgery, the evidence includes three RCTs. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, 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 PRP 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 PRP in
a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. The second RCT, which compared PRP with rhBMP-7, also failed to show any clinical or radiologic benefits of PRP over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients receiving PRP injections versus no treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with rotator cuff repair who receive PRP injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes. For individuals with spinal fusion who receive PRP injections plus orthopedic surgery, the evidence includes two controlled prospective studies. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The two studies failed to show any statistically significant differences in fusion rates between the PRP arm and the control arm. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with subacromial decompression surgery who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, 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 PRP injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with PRP. Larger trials are required to confirm these benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with TKA who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The RCT showed no significant differences between the PRP and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, or Knee Society Score and Knee Injury and Osteoarthritis Outcome Score. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION
Practice Guidelines and Position Statements

American Academy of Orthopaedic Surgeons
The AAOS guidelines (2013) did not recommend for or against growth factor injections and/or platelet-rich plasma (PRP) for patients with symptomatic osteoarthritis (OA) of the knee.43 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.

The AAOS issued evidence-based guidelines (2017) on the management of OA of the hip.44 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 OA 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 OA. The guidelines also noted that there were no high-quality studies comparing PRP with placebo for the treatment of OA of the hip.
National Institute for Health and Care Excellence
The NICE issued guidance (2013) on the use of autologous blood injection for tendinopathy.45 The NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy was “inadequate” in quantity and quality. The NICE also issued guidance (2013) on the use of autologous blood injection (with or without techniques for producing PRP) for plantar fasciitis.46 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.

The NICE issued guidance (2014) on the use of PRP for OA of the knee.47 The NICE concluded that current evidence on PRP injections for OA of the knee raised “no major safety concerns”; however, the “evidence on efficacy is inadequate in quality.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01843504</td>
<td>Platelet-Rich Plasma (PRP) Injection for the Treatment of Chronic Patellar Tendinopathy</td>
<td>44</td>
<td>Mar 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT03138317</td>
<td>Evaluation of Platelet Rich Plasma (PRP) for Knee Osteoarthritis</td>
<td>60</td>
<td>May 2018</td>
</tr>
<tr>
<td>NCT01668953a</td>
<td>Impact of Platelet Rich Plasma Over Alternative Therapies in Patients With Lateral Epicondylitis (IMPROVE)</td>
<td>100</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT01923909</td>
<td>Intraarticular Platelet-rich Plasma Injections Versus Intraarticular Corticosteroid Injections in Primary Knee Osteoarthritis</td>
<td>100</td>
<td>Dec 2019 (ongoing)</td>
</tr>
<tr>
<td>NCT01945528</td>
<td>Platelet Rich Plasma (PRP) in Chronic Epicondylitis</td>
<td>86</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT02920177</td>
<td>Platelet-rich Plasma Versus Corticosteroid Injection for the Treatment of Femoracetabular Impingement</td>
<td>40</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>NCT02694146</td>
<td>Clinical Trial to Evaluate the Use of Platelet Rich Plasma in Front Hyaluronic Acid in Coxarthrosis</td>
<td>74</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT03129971</td>
<td>Platelet-Rich Plasma Combined with Conventional Surgery in the Treatment of Atrophic Nonunion of Femoral Shaft Fractures</td>
<td>92</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01833598</td>
<td>Percutaneous Needle Tenotomy (PNT) Versus Platelet Rich Plasma (PRP) with PNT in the Treatment of Chronic Tendinosis</td>
<td>40</td>
<td>Jun 2019</td>
</tr>
<tr>
<td>NCT02984228</td>
<td>Platelet-rich Plasma vs. Hyaluronic Acid for Glenohumeral Osteoarthritis</td>
<td>70</td>
<td>Aug 2019</td>
</tr>
<tr>
<td>NCT02923700</td>
<td>Leukocyte-rich PRP vs Leukocyte-poor PRP for the Treatment of Knee Cartilage Degeneration: a Randomized Controlled Trial</td>
<td>192</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT03133416</td>
<td>Platelet-Rich Plasma Injections and Physiotherapy in the Treatment of Chronic Rotator Cuff Tendinopathy</td>
<td>165</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT01406832</td>
<td>Treatment of Acute and Chronic Ligament and Tendon Injuries with Platelet Rich Plasma</td>
<td>100</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02872753</td>
<td>Intra-operative PRP Injection Following Partial Meniscectomy</td>
<td>90</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>NCT03300531</td>
<td>Autologous Pure Platelet-rich Plasma in the Treatment of Tendon Disease: A Randomized Controlled Trial</td>
<td>540</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
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<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
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<tr>
<td>NCT03136965</td>
<td>Platelet-Rich Plasma Therapy for Patellar Tendinopathy (PRP)</td>
<td>66</td>
<td>Aug 2022</td>
</tr>
<tr>
<td>NCT01915979</td>
<td>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</td>
<td>84</td>
<td>Dec 2016 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

References


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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

### IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed</td>
</tr>
<tr>
<td></td>
<td>20926</td>
<td>Tissue grafts, other (e.g., paratenon, fat, dermis)</td>
</tr>
<tr>
<td></td>
<td>86999</td>
<td>Unlisted transfusion medicine procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>P9020</td>
<td>Platelet rich plasma, each unit</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

## Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/04/2015</td>
<td>BCBSA medical policy adaptation</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

## Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.