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SUMMARY WITH CRITICAL APPRAISAL

Platelet-Rich Plasma Injections for Wound Healing and Tissue Rejuvenation: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Context and Policy Issues

Platelet rich plasma (PRP) injections have been used in the context of musculoskeletal soft tissue injuries, bone fractures, orthopaedic surgery, osteoarthritis, bone defects, joint degeneration, wound care, and other indications.[1,2] Alternative treatment approaches in these contexts include physiotherapy, glucocorticoid injections, or non-steroidal anti-inflammatory medications. Administration of a supraphysiological concentration of platelets allows targeted delivery of a high "dose" of growth factors, cytokines, chemokines and other bioactive proteins to the target tissue. The use of autologous PRP has become popular due to its putative effects on tissue repair and regeneration.[3]

PRP has been defined as an autologous plasma derivative in which the concentration of platelets is above baseline.[4] Various classification methods have been proposed that provide more specific categories and are based on criteria such as platelet concentration, leukocyte content, red blood cell content, and the method of exogenous activation of platelets (e.g. by collagen, thrombin, or calcium). Standards for reporting these parameters have not been universally applied in PRP research studies and therefore may affect study interpretation.[4] In addition, there are many commercially available devices for PRP preparation.[1] There is also a wide variation of administration practices that vary by number of injections, volume of injection and location of injections.

Research Questions

1. What is the clinical effectiveness of platelet-rich plasma (PRP) injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?
2. What is the cost-effectiveness of PRP injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?
3. What are the evidence-based guidelines regarding the use of PRP injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

Key Findings

While there were some reports indicating modest improvements in some outcomes for PRP injections relative to comparators such as placebo, hyaluronic acid, or no PRP treatment, it is not possible to make definitive conclusions regarding the effectiveness of PRP in any of the clinical indications reviewed. The heterogeneity of clinical context, PRP intervention, and comparator agents, reduces certainty in the results. The interpretation of study investigators is also a source of heterogeneity, and in some cases, systematic review authors arrived at divergent conclusions in spite of the fact that they included similar studies in the systematic reviews. Assessing generalizability of the study results to the Canadian context is also difficult given the wide variety of PRP preparation methods used, the type of activator used, and variability in PRP treatment regimens.

While there have been no consistent signals of increased risk of harm for PRP relative to control groups in the data reviewed, none of the studies reviewed appears to have been rigorously designed to evaluate harms.

There was no relevant evidence identified to inform the cost-effectiveness of PRP injections for any indication.

Two good quality guidelines from the UK suggest that there are no significant risks of harm associated with PRP use, but the evidence on efficacy was inadequate to support the use of PRP for osteoarthritis of the knee or tendinopathy.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and May 15, 2017. Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (of any age) requiring treatment for wound healing or tissue rejuvenation (e.g., due to injury, trauma, or other orthopedic conditions)
Intervention	Platelet-rich plasma (PRP) injections
Comparator	Q1 and 2: Standard of care; Exercise and/or physiotherapy; Cortisone injections; Non-steroidal anti-inflammatory drugs (NSAIDS); Q3: No comparator required
Outcomes	Q1: Clinical benefit (e.g., wound healing, functional outcomes, pain, quality of life); Harms (e.g., re-injury rates, infection, injection-related harms, neurological outcomes) Q2: Cost-effectiveness outcomes (e.g., cost per quality adjusted life year or health benefit gained) Q3: Evidence-based guideline recommendations regarding the use of PRP injections (including HCP training requirements, indications, administration etc.)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), or meta-analyses (MA), randomized controlled studies, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Studies that administered PRP by routes other than injection were excluded. Studies without a control group (e.g. case

series) were excluded. Studies that focused on bone (e.g. long bone healing, bone defects, bone grafting) were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[5] randomized studies and non-randomized studies were critically appraised using the Downs and Black checklist,[6] and guidelines were assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 171 citations were identified in the literature search. Following screening of titles and abstracts, 129 citations were excluded and 42 potentially relevant reports from the electronic search were retrieved for full-text review. Twenty-nine potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 36 publications were excluded for various reasons, while 35 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Overlap between Systematic Reviews

There was substantial overlap in included studies between the systematic reviews, which is summarized in Appendix 2. There were also some differences, therefore no systematic reviews were excluded on the basis of study overlap.

Summary of Study Characteristics

Fifteen systematic reviews,[8-22]16 studies (reported in 18 publications)[23-40] and 2 clinical practice guidelines[41,42] met the inclusion criteria for this report. Detailed characteristics of the studies and a description of the guidelines can be found in Appendix 2.

Study Design

ACL Repair

Two systematic reviews which included 11 studies[8] and 15 studies,[9] and one RCT[37] on ACL repair were identified.

Total Knee Arthroplasty

Two systematic reviews were identified on total knee arthroplasty which included 11 studies[10] and 12 studies.[11]

Osteoarthritis of the Knee

Seven relevant systematic reviews which contained between 5 and 22 studies[12-18] one clinical practice guideline,[42] and one cross-sectional study were identified for osteoarthritis of the knee.[38]

Rotator Cuff Repair

Four RCTs were identified that were performed in the context of rotator cuff injury.[23-26]

Epicondylitis

Three RCTs were identified that were performed in patients with chronic tennis elbow.[27-29]

Hamstring Injury

Two RCTs were identified on the topic of acute hamstring injury.[30-33]

Other conditions

One systematic review was identified for each of the following categories/indications: general orthopaedic indications (containing 33 studies),[20] spinal fusion (containing 15 studies),[22] foot/ankle pathologies (containing 17 studies),[21] musculoskeletal soft tissue injuries (containing 19 studies).[19]

One relevant study was identified for each of the following categories/indications: Achilles tendinopathy (RCT),[34] patellar tendinopathy (RCT),[35] incision healing after ankle surgery (retrospective chart review with control group),[36] lumbar diskogenic pain (RCT),[40] and hip arthroplasty (retrospective chart review with control group).[39]

One clinical practice guideline was identified for tendinopathy.[41]

Country of Origin

ACL Repair

The systematic reviews were published from Chile[8] and Italy.[9] The RCT was published from Spain.[37]

Total Knee Arthroplasty

Both systematic reviews were published from China.[10,11]

Osteoarthritis of the Knee

The systematic reviews were published from the USA,[12,15] China,[13,18] Italy,[16] Taiwan,[17] and Canada.[14]

One retrospective study was published from Malaysia.[38]

One clinical practice guideline was published from the National Institute for Health and Care Excellence (NICE) in the UK.[42]

Rotator Cuff Repair

The four RCTs in rotator cuff injury were published from Korea,[23] Australia,[24] Brazil,[25] and Turkey.[26]

Epicondylitis

The three RCTs in tennis elbow were published from Iran,[27] Denmark,[28] and USA.[29]

Hamstring Injury

The two RCTs on hamstring injury were published from the Netherlands,[30-32] and Malaysia.[33]

Other conditions

The remaining systematic reviews in various conditions were published from Brazil,[19] Canada,[20] Italy,[21] and the USA.[22]

The remaining studies in various conditions were published from Denmark,[34] and the USA.[35,36,39,40]

The clinical practice guideline for tendinopathy were published from NICE in the UK.[41]

Patient Population

ACL Repair

The two systematic reviews included patients undergoing ACL reconstructive surgery and included 516 patients[8] and 817 patients.[9] The RCT included 150 patients undergoing ACL reconstruction.[37]

Total Knee Arthroplasty

The two systematic reviews included 1316 patients[10] and 1234 patients[11] undergoing total knee arthroplasty and included an almost identical list of studies.

Osteoarthritis of the Knee

The seven systematic reviews included between 577 to 1543 patients with osteoarthritis of the knee, though this was not clearly reported in all reviews.[12-18]

One retrospective study included 64 patients.[38]

The clinical practice guideline was intended for application to patients with osteoarthritis of the knee.[42]

Rotator Cuff Repair

The four RCTs enrolled between 40 and 74 patients with medium to large rotator cuff tears,[23] arthroscopic supraspinatus repair,[24,25] or rotator cuff tendinopathy or partial tendon rupture.[26]

Epicondylitis

Three RCTs included between 60 to 230 patients with chronic tennis elbow.[27-29]

Hamstring Injury

One RCT enrolled 80 athletes with acute hamstring injury.[30] Another RCT enrolled 28 patients with acute hamstring injury.

Other conditions

The systematic reviews in other conditions included patients with musculoskeletal soft tissue injuries,[19] various orthopaedic indications,[20] foot/ankle pathology,[21] and patients who underwent spinal fusion.[22]

The studies in various conditions included patients with chronic Achilles tendinopathy,[34] patellar tendinopathy,[35] patients who received Agility total ankle replacement,[36] hip replacement surgery,[39] and chronic lumbar diskogenic pain.[40]

The clinical practice guideline was intended to guide treatment of patients with tendinopathy (e.g. elbow, Achilles, patellar).[41]

Interventions and Comparators

The intervention in all studies was PRP, but there was considerable heterogeneity between the studies included in the systematic reviews and the individual studies. The PRP injections varied with respect to the preparation method, platelet concentration, presence/absence of an activator, number of centrifugations, concentration of leukocytes, volume of PRP injected, and the number and location of the PRP injections.

The included systematic reviews and individual studies used the following comparators:

- No PRP[8,9,12,20,23-25,33,36,37,39]
- Placebo (e.g. saline injection)[10-13,16-19,26,28,30,34]
- Autologous whole blood[19,27]
- Dry needling[19,35]
- Hyaluronic acid[13-18,38]
- Ozone[18]
- Glucocorticoid by injection[18,28]
- Bupivacaine/epinephrine by injection[29]
- Contrast agent[40]

Outcomes

ACL Repair

Outcomes in the systematic reviews included graft maturation, tunnel healing, clinical evaluation and harvest site healing.[8,9] The outcomes in one RCT[37] included pain score, swelling, inflammatory markers and the International Knee Documentation Committee scale.

Total Knee Arthroplasty

Outcomes in the two systematic reviews included haemoglobin level, range of motion, Knee Society Score, Western Ontario and McMaster Universities Arthritis Index (WOMAC), pain, length of hospital stay, and postoperative narcotic use.[10,11]

Osteoarthritis of the Knee

Outcomes in the seven systematic reviews included pain, functional changes, quality of life, adverse effects and patient satisfaction.[12-18]

The retrospective study included knee injury and osteoarthritis outcome score, International Knee Documentation Committee scale, and the WOMAC.[38]

The clinical practice guideline cited some of the above mentioned outcomes in the evidence base for the guideline and also stated the importance of the outcome of time to knee replacement surgery.[42]

Rotator Cuff Repair

Outcomes in the four RCTs included Constant score,[23,25] pain,[23-25] range of motion,[23] Sugaya classification,[24] Oxford Shoulder Score,[24] Quick Disability of the Arm, Shoulder and Hand,[24] Short Form 12 health survey,[24] Western Ontario Rotator Cuff Index,[26] the Neer test,[26] and the Shoulder Pain and Disability Index.[26]

Epicondylitis

Outcomes in the three RCTs included pain,[27,28] function,[27] Mayo score,[27] pressure pain threshold,[27] patient rated tennis elbow evaluation,[29] visual analog scale with resisted wrist extension.[29]

Hamstring Injury

Outcomes in the two RCTs included time to resuming sport, reinjury occurrence, patient satisfaction, hamstring outcome score.[30,33]

Other conditions

Outcomes in the other four systematic reviews included:

- Musculoskeletal soft tissue injuries: Function, pain, adverse effects, recovery time, return to activities, quality of life[19]
- Orthopaedic indications: function, pain[20]
- Foot/ankle pathology: pain, return to sport[21]
- Spinal fusion: bone regeneration[22]

Outcomes in the other studies included:

- Achilles tendinopathy RCT: Victorian institute of sports assessment Achilles[34]
- Patellar tendinopathy RCT: Victorian institute of sports assessment Achilles, Tegner activity score, Lysholm knee scale[35]
- Ankle replacement study: wound healing complications, return to surgery[36]
- Hip arthroplasty study: transfusion requirements[39]
- Diskogenic pain study: Functional rating index, numeric rating scale for pain, Short-Form 36 health survey[40]

The clinical practice guideline for tendinopathy stated the value of outcomes such as pain, quality of life, function and whether subsequent surgical intervention is needed.[41]

Summary of Critical Appraisal

Critical appraisal of the systematic reviews and clinical studies are summarized below and details are presented in Appendix 3.

ACL Repair

Two moderate quality systematic reviews were included.[8,9] No pooling of data was performed. Duplicate study selection was performed in both systematic reviews but it was not clear if duplicate data extraction was performed. Multiple databases were searched for relevant literature. There was significant overlap in the included studies as described in Appendix 2. One of the systematic reviews assessed the quality of the included studies and used this information when formulating conclusions.[8] A potential conflict of interest was reported in one of the systematic reviews.[8]

One low to moderate quality RCT was included.[37] The objectives and interventions used were clearly described. The study was not blinded and methods of allocation concealment

were not clear. Sample size estimation methods were not clearly described. No conflicts of interest were declared.

Total Knee Arthroplasty

Two moderate to high quality systematic reviews were included.[10,11] In both systematic reviews, a comprehensive literature search was performed, but grey literature searching was not mentioned. Both systematic reviews performed duplicate study selection and data extraction. Both systematic reviews reported pooled results that took into account statistical heterogeneity but pooling may not be appropriate given the existence of other sources of heterogeneity across studies (e.g. populations, intervention characteristics, different comparators, duration of studies, outcomes). There was significant overlap in the included studies as described in Appendix 2. No conflicts of interest were declared in either systematic review. Quality assessment of the included studies was performed and there was an attempt to incorporate this into the conclusions of the report.

Osteoarthritis of the Knee

Two moderate to high quality systematic reviews[12,18] and five low to moderate quality systematic reviews[13-17] were included for this indication. The objectives were clearly described in all systematic reviews[12-15,17,18] and a comprehensive literature search was performed in all seven systematic reviews, including a grey literature search in one systematic review.[12] Four systematic reviews performed duplicate study selection.[12,14,16,18] Three systematic reviews performed duplicate data extraction.[12,14,18] Pooling of data was performed in three studies.[12,17,18] Pooled analyses often took into account statistical heterogeneity but pooling may not be appropriate given the existence of other sources of heterogeneity across studies (e.g. populations, intervention characteristics, different comparators, duration of studies, outcomes). One systematic review provided pooled results based on inter-study differences (e.g. study design, PRP characteristics, patient characteristics).[17] Quality assessment was performed in three systematic reviews[12,17,18] with one systematic review clearly indicating that the quality assessment had bearing on the conclusions.[12]

One low quality retrospective study in knee osteoarthritis was subject to significant risk of bias due to lack of blinding and randomization and retrospective data collection.[38]

One high quality clinical practice guideline was included.[42] The guideline was developed by individuals with relevant professional backgrounds. Systematic methods were used to search for evidence. Strengths and limitations of the evidence were described and incorporated into the conclusions of the guidance.

Rotator Cuff Repair

Four moderate quality RCTs were included.[23-26] Two studies were single-blind[23,24] and two were double-blind.[25,26] All four studies provided sample size estimation methods for the primary outcomes based on outcomes such as the UCLA score,[25] Constant score,[23] Sugaya classification changes,[24] or WORC score.[26] Details of the assessment scales and their validity was not always provided.

Epicondylitis

Three moderate quality RCTs were included.[27-29] Patients and outcome assessors were blinded in all three RCTs. In two RCTs, the authors reported potential conflicts of interest.[28,29] Details of the assessment scales and their validity was not always provided.

Hamstring Injury

Two moderate quality RCTs were included.[30,33] Outcome assessors were blinded in both of the RCTs but patients were blinded in only one of the RCTs.[30] Both RCTs took into account patient follow-up times by analyzing the data using a Kaplan-Meier approach (for time to return to sport).

Other conditions

Two low quality systematic reviews (spinal fusion, soft tissue injuries)[21,22] were included that did not clearly describe methods of data selection and literature searching. Quality assessment of included studies was not performed in these systematic reviews. Two high quality systematic reviews (musculoskeletal soft tissue injuries, orthopaedic indications)[19,20] were also included which applied comprehensive literature searches including grey literature searches. The quality of the included studies was assessed and incorporated into the formation of conclusions.

Three moderate quality RCTs were included in which patients were blinded to their treatment assignment (Achilles tendinopathy, patellar tendinopathy, diskogenic pain).[34,35,40] In two of these RCTs, outcome assessors were also blinded to treatment status (patellar tendinopathy, diskogenic pain).[35,40] Details of the assessment scales and their validity was not always provided. Two low quality retrospective studies were included which had significant risk of bias(ankle replacement, hip arthroplasty).[36,39]

One high quality clinical practice guideline was included.[41] The guideline was developed by individuals with relevant professional backgrounds. Systematic methods were used to search for evidence. Strengths and limitations of the evidence were described and incorporated into the conclusions of the guidance.

Summary of Findings

Findings from the systematic reviews and RCTs are summarized below and details are available in Appendix 4.

What is the clinical effectiveness of PRP injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

ACL Repair

Two systematic reviews without meta-analyses reported conflicting results from individual trials.[8,9] Some studies indicated that there could be a benefit associated with PRP injections for the outcome of time to graft maturation, but not all studies showed a statistically significant benefit for PRP. In one systematic review, seven studies that reported clinical outcomes showed no difference in various clinical outcomes between PRP and no PRP.[9]

One RCT reported that the single spin (centrifugation during PRP preparation process) PRP group showed statistically significant improvement in swelling scores based on the perimeter at the kneecap (no specific data provided), relative to the group that did not receive PRP.[37] There were no statistically significant differences between PRP and no PRP

groups for range of motion, C-reactive protein and International Knee Documentation Committee scale.

Total Knee Arthroplasty

Pooled analyses from two systematic reviews found that PRP was associated with improvements in range of motion at day 3 and at 3 months postoperatively, relative to placebo or no PRP, with significant heterogeneity in the studies of the pooled analyses.[10,11] The clinical significance of the weighted mean difference estimates is not certain. One systematic review found a statistically significant difference in pain control for PRP relative to placebo,[11] but the other systematic review found no difference between PRP and control.[10] These two systematic reviews included an almost identical list of studies, but the conclusions of the authors are divergent, with one systematic review concluding a benefit for PRP based on WOMAC and pain[10] and the other systematic review asserting that there are no clinical advantages to PRP relative to placebo.[11]

Osteoarthritis of the Knee

Seven systematic reviews with significant study overlap had dissimilar conclusions regarding the efficacy of PRP injections in osteoarthritis of the knee.[12-18] One moderate to high quality systematic review suggested that PRP has a beneficial effect on medium term quality of life.[12] Another moderate to high quality systematic review concluded that PRP injections are more efficacious than saline placebo, hyaluronic acid, ozone, and corticosteroids, and found no difference in adverse events between treatment groups.[18] In contrast, another low to moderate quality systematic review reported an increase in non-specific adverse events with PRP relative to control based on pooled data.[14]

The following four systematic reviews were low to moderate quality. One of these systematic reviews observed potential benefits in some studies in the WOMAC and EQ VAS scores at early time points (e.g. 6 months), for PRP versus control but these were not maintained over longer time periods (e.g. 12 months and later).[13] One systematic review reported positive results in some trials for PRP, but commented that the improvement was limited over time and was seen mainly in younger patients not affected by advanced degeneration.[16] One systematic review suggested that PRP is superior to hyaluronic acid based on effect size comparisons for functional change.[17] One systematic review reported that PRP resulted in improvements to measures of function relative to hyaluronic acid and the differences were statistically significant.[15]

One low quality retrospective analysis found that PRP injections result in statistically significant improvements in International Knee Documentation Committee scale relative to hyaluronic acid.[38]

Rotator Cuff Repair

None of the four trials met their primary outcome. Three RCTs showed no clear advantages of PRP over comparators for measures of tendon-bone healing, re-tear rates, Constant score, visual analog scale (VAS) pain score, Western Ontario Rotator Cuff Index, Shoulder Pain and Disability Index, or functional recovery.[24-26] A fourth RCT found a lower re-tear rate for the PRP group, relative to the no-PRP group and suggested that PRP can increase quality of healing but not rate of healing.[23]

Epicondylitis

One RCT found that no statistically significant differences between PRP and autologous whole blood injections were observed for pain, functional scores, and treatment success rates.[27] A second RCT reported that glucocorticoid injections were associated with improved pain response, relative to PRP injections.[28] A third RCT found that there were statistically significant improvements in pain scores for PRP relative to bupivacaine/ epinephrine.[29]

Hamstring Injury

The two included RCTs for hamstring injury had divergent conclusions. One RCT reported no benefits of intramuscular PRP relative to placebo.[30] A second RCT observed a shorter time for return to sport and reduced pain, for PRP relative to the no-PRP group.[33]

Other conditions

A moderate to good quality systematic review and meta-analysis of general orthopaedic indications reported no clear indication of superior efficacy of PRP relative to placebo or no PRP.[20] One low to moderate quality systematic review reported that seven studies with control groups (most studies compared PRP to no PRP) showed no advantages for PRP over the control group for fusion rates.[22] One systematic review in musculoskeletal injuries showed no advantage of PRP over control (placebo, autologous whole blood, dry needling or no PRP) for short or medium or long term function.[19] There was a statistically significant benefit in the pain scores for PRP relative to control but the result may not be clinically significant.[19] One systematic review concluded that there is no overall benefit to using PRP in the context of foot and ankle surgery.[21]

One RCT showed no statistically significant benefit for PRP relative to saline in patients with Achilles tendinopathy.[34] One RCT showed that PRP accelerates the recovery from patellar tendinopathy relative to dry needling.[35] A retrospective study found no advantage of using PRP for incision healing after total ankle replacement.[36] A retrospective study in hip arthroplasty found no benefit to using PRP.[39] One RCT in diskogenic pain found improvements in pain, function and satisfaction with PRP relative to contrast agent.[40]

What is the cost-effectiveness of PRP injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

There were no relevant studies identified that could address this question.

What are the evidence-based guidelines regarding the use of PRP injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

Recommendations from the guidelines are summarized below and details are presented in Appendix 4.

The NICE 2014 Interventional Procedure Guidance for platelet-rich plasma injections for osteoarthritis of the knee states that the evidence on efficacy is inadequate in quality, and that there are no major safety concerns.[42] They recommend that the procedure should only be used with special administrative and clinical arrangements in the UK health system. The guidance states that the evidence base contains heterogeneous populations, variations in treatment techniques and inconsistencies in the findings of the studies. Therefore confidence in the efficacy of PRP injections is lacking.

The NICE 2013 Interventional Procedure Guidance for autologous blood injection for tendinopathy states that there is no major safety concerns but the evidence for efficacy is

inadequate.[41] They recommend that the procedure should only be used with special administrative and clinical arrangements in the UK health system. The committee noted that patients treated for Achilles tendinopathy with PRP may respond differently compared to PRP use at other sites, and it may not be possible to extrapolate findings across indications within the broader category of tendinopathy.

Limitations

There was significant heterogeneity in the PRP studies, including within individual indications. The sources of heterogeneity include the PRP, the method and dose of PRP administration and the existence of many different comparator agents across studies. Given the numerous indications for PRP and the differences in underlying pathology, it may not be possible to extrapolate the results of a study in a given clinical condition to another clinical condition. The quality of the studies within the systematic reviews also varied. Some systematic reviews included case series without control groups.

Conclusions and Implications for Decision or Policy Making

A total of 35 relevant publications, including 15 systematic reviews,[8-22] 16 studies (reported in 18 publications)[23-40] and 2 clinical practice guidelines[41,42] were identified. The indications included ACL repair,[8,9,37] total knee arthroplasty,[10,11] osteoarthritis of the knee, [12-18,38,42] rotator cuff injury,[23-26] chronic tennis elbow,[27-29] hamstring injury,[30-33] general orthopaedic indications,[20] spinal fusion,[22] foot/ankle pathologies,[21] musculoskeletal soft tissue injuries,[19] Achilles tendinopathy,[34] patellar tendinopathy,[35] incision healing after ankle surgery,[36] lumbar diskogenic pain,[40] tendinopathy,[41] and hip arthroplasty.[39]

While there were some reports indicating modest improvements in some outcomes for PRP injections relative to comparators such as placebo, hyaluronic acid, or no PRP treatment, it is not possible to make definitive conclusions regarding the effectiveness of PRP in any of the clinical indications reviewed. The heterogeneity of clinical context, PRP intervention, and comparator agents reduces certainty in the results. The interpretation of study investigators is also a source of heterogeneity, and in some cases, systematic review authors arrived at divergent conclusions in spite of the fact that they included similar studies in the systematic reviews. Assessing generalizability of the study results to the Canadian context is also difficult given the wide variety of PRP preparation methods used, the type of activator used, and variability in PRP treatment regimens.

While there have been no consistent signals of increased risk of harm for PRP relative to control groups in the data reviewed, none of the studies reviewed appears to have been rigorously designed to evaluate harms.

There was no relevant evidence identified to inform the cost-effectiveness of PRP injections for any indication.

Two good quality guidelines from the UK suggest that there are no significant risks of harm associated with PRP use, but the evidence on efficacy was inadequate to support the use of PRP for osteoarthritis of the knee or tendinopathy.

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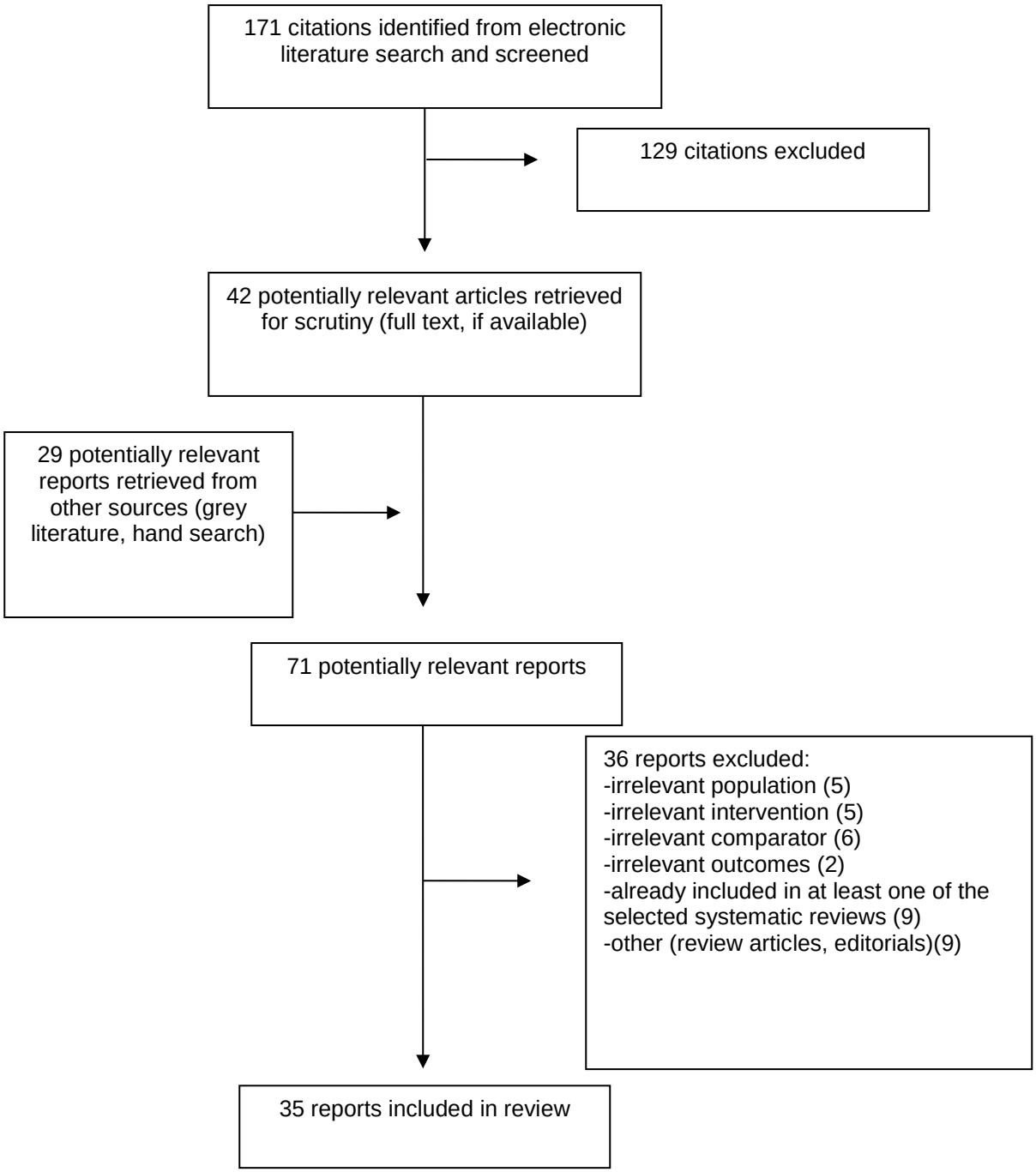
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, year, country	Number and type included studies; Focus of Review	Population Characteristics, Total N	PRP Description	Comparator Description	Main outcomes of interest
ACL repair					
Figueroa (2015)[8] Chile	11 controlled studies (including 9 RCTs, 2 cohort studies); utility of PRP in treatment of ACL ruptures	Patients with ACL injuries; N=516	PRP concentration ranged from 3-12 x normal, injected into graft and/or tibial and/or femoral tunnels	Control groups received standard procedure without PRP.	Graft maturation, tunnel healing, clinical evaluation
Andriolo (2015)[9] Italy	15 controlled clinical studies (including 11 RCTs, 3 non-RCTs and 1 retrospective study); utility of PRP during ACL surgery	Patients undergoing ACL reconstructive surgery; N=817	Variability across trials reported for: preparation methods, PRP concentration, application method	Control groups received standard procedure without PRP. One study used thrombin to activate PRP.	Harvest site healing, tendon graft maturation and bony tunnel/graft integration, clinical results
Total Knee Arthoplasty					
Li(2016)[10] China	11 controlled studies (including 7 RCTs, 4 non-RCTs); effect of PRP on ROM and pain after TKA	Patients receiving unilateral TKA and intraoperative PRP; N=1316	PRP dose ranged from 5-12 ml	Placebo or no PRP (control groups not well described)	ROM at day 3 and month 3 post-op, WOMAC at month 3, pain, infection rate
Kuang (2016)[11] China	12 controlled studies (including 5 RCTs, 7 non-RCTs); utility of PRP in post-op bleeding and functional recovery after TKA	Patients with intraoperative PRP during TKA; N=1234	PRP dose ranged from 5-12 ml	Placebo or no PRP (control groups not well described)	Haemoglobin, ROM, Knee Society Score, WOMAC, pain, length of stay, post-op narcotic use,
Orthopaedic Injury					
Sheth(2012)[20] Canada	33 controlled studies (including 23 RCTs, 10 cohort studies); PRP impact on pain, healing and function in bone and soft tissue injuries	Patients with orthopaedic injury; N= NR	Variability across trials reported for: preparation methods, PRP concentration, application method,	Placebo or no PRP (control groups not well described)	Functional outcomes, pain
Spinal Fusion Surgery					
Elder(2015)[22] USA	15 studies (including 2 RCTs,	Patients who underwent spinal	PRP concentration ranged from 3.3x	Control groups not well described	Bone regeneration

Author, year, country	Number and type included studies; Focus of Review	Population Characteristics, Total N	PRP Description	Comparator Description	Main outcomes of interest
	prospective and retrospective controlled and uncontrolled studies); role of PRP in spinal fusion	fusion surgery; N=692	to 10x normal, one study used allogenic blood, preparation methods varied between studies		
Foot/Ankle Pathologies					
Vannini(2014)[21] Italy	17 studies (including 7 controlled and 10 uncontrolled studies); utility of PRP in foot/ankle pathologies	Achilles tendon, plantar fasciitis, talar osteochondral lesions, total ankle replacement, foot/ankle fusion; N= 674	Intraoperative PRP in surgical studies, single or multiple PRP injections in injury studies, activation and preparation methods varied	No control (10 studies), historical control (3 studies), control groups not well described	Pain, recovery from surgery, return to sport, fusion rate
Rotator Cuff Injury					
Moraes (2014)[19] Brazil	19 studies (including 17 RCTs and 2 quasi-randomized studies); PRP for treating musculoskeletal soft tissue injuries	Rotator cuff tears (arthroscopic repair), shoulder impingement syndrome surgery, elbow epicondylitis, ACL reconstruction, patellar tendinopathy, achilles tendinopathy, Achilles rupture repair; N=1088	PRP by injection	Placebo, autologous whole blood, dry needling or no PRP	Function, pain, adverse effects, recovery time, return to activities, quality of life, condition recurrence, need for subsequent procedure, patient satisfaction
Osteoarthritis of the Knee					
AHRQ(2017)[12] USA	5 RCTs; effect of PRP on pain and function in osteoarthritis of the knee	Osteoarthritis of the knee, N= NR	PRP injections	No PRP, different number of PRP doses, saline, paracetamol	Pain, function
Shen(2017)[18] China	14 RCTs; treatment of knee osteoarthritis	Osteoarthritis of the knee; N=1423	PRP injections	Saline, placebo, ozone, hyaluronic acid, corticosteroids	Pain, physical function, adverse effects
Lai(2015)[13] USA	8 studies (including 2 RCTs, 4 studies without a control and 2 observational	Osteoarthritis of the knee; N= NR	PRP injections given 1, 2 or 3 times, every week, every 2 weeks or every 3 weeks,	Hyaluronic acid, saline injection	Function, pain, quality of life

Author, year, country	Number and type included studies; Focus of Review	Population Characteristics, Total N	PRP Description	Comparator Description	Main outcomes of interest
	studies); treatment of knee osteoarthritis		PRP methods and characteristics varied between studies		
Filardo(2015)[16] Italy	22 clinical studies (including 13 case series, 4 comparative studies and 5 RCTs); 19/22 studies focused on knee osteoarthritis	Osteoarthritis of the knee, 2 studies included hip osteoarthritis and one in osteochondral talar lesions N=NR	Single or multiple PRP injections, PRP methods and characteristics varied between studies	Hyaluronic acid, saline injection	Function, pain
Chang(2014)[17] Taiwan	16 studies (including 8 single-arm studies, 3 quasi-experimental studies and 5 RCTs; PRP for treating knee joint cartilage degeneration	Patients with knee OA of severity less than grade III on Kellgren Lawrence scale; N=1543	Dose (4-8ml), dosing interval (1-4 weeks), number of doses (1-4) and activation agents varied between studies	Saline injection, hyaluronic acid, PRP with different preparation method, no comparator	Functional changes
Tietze(2014)[15] USA	13 studies (including 4 controlled studies and 9 case series); Large-joint osteoarthritis	Knee (12 studies) or hip (1 study) osteoarthritis; N=1147	Dosing interval (1-4 weeks), number of doses (1-4) and activation agents varied between studies	Hyaluronic acid, PRP with different concentrations of growth factors	Function, pain
Khoshbin(2013)[14] Canada	6 studies (including 4 RCTs and 2 controlled studies); Level 1 and 2 evidence for PRP in knee osteoarthritis	Knee osteoarthritis; N=577	Dosing interval (1-4 weeks), number of doses (1-4) and location of injection varied between studies	Hyaluronic acid, saline	Function, pain, patient satisfaction, adverse events

ACL=anterior cruciate ligament; NR= not reported; RCT = randomized controlled trial; PRP= platelet rich plasma; ROM=range of motion; TKA= total knee arthroplasty;

Table 3: Characteristics of Included Primary Studies

Author, year, country	Study Design, N	Population Characteristics	Comparisons	Outcomes of Interest
Rotator Cuff Injury				
Jo 2015[23] Korea	RCT (evaluators blinded for some outcome measures) N=74	Patients undergoing arthroscopic repair for medium to large rotator cuff tears	PRP versus no PRP	Constant score at 3 months after surgery, pain, ROM, satisfaction, function
Wang 2015[24]	RCT (evaluators	Patients	PRP (2 doses, at	Sugaya

Author, year, country	Study Design, N	Population Characteristics	Comparisons	Outcomes of Interest
Australia	blinded for some outcome measures) N=60	undergoing arthroscopic double row supraspinatus tendon repair	day 7 and 14 post-op) versus no PRP	classification at week 16, Oxford Shoulder Score, Quick Disability of the Arm, Shoulder and Hand, pain, Short-Form 12 QOL
Malavolta 2014[25] Brazil	DB RCT (patients and evaluators blinded) N=54	Patients undergoing complete supraspinatus tear repair	PRP at end of procedure versus no PRP	Constant score, UCLA score, pain, MRI
Kesikburun 2013[26] Turkey	DB RCT (patients, clinicians and evaluators blinded) N=40	Patients with rotator cuff tendinopathy	PRP (one dose) versus saline	WORC, SPADI, Neer test, VAS, ROM
Tennis Elbow				
Raeissadat 2014[27] Iran	DB RCT (patients and some evaluators were blinded) N=76	Patients with chronic lateral humeral epicondylitis >3 months	1 dose leukocyte rich PRP versus autologous whole blood	Pain, function, Mayo score, pressure pain threshold
Krogh 2013[28] Denmark	DB RCT (patients and outcome assessors were blinded) N=60	Patients with chronic lateral epicondylitis	One dose of PRP or saline or glucorticoid	Pain, ultrasonographic change in tendon thickness
Mishra 2013[29] USA	DB RCT (patients and outcome assessors were blinded) N=230	Chronic lateral epicondylar tendinopathy	One dose of PRP or bupivacaine+ epinephrine	Pain using VASRWE, PRTEE
Hamstring Injury				
Reurink 2015[30-32]	DB RCT N=80	Athletes with acute hamstring injury	Rehabilitation program plus , either 2 doses of PRP or placebo	Time to resuming sport, re-injury, satisfaction, Hamstring outcome score
Hamid 2014[33] Malaysia	RCT (only assessors were blinded) N=28	Patients with acute hamstring injury	Rehabilitation program plus 1 dose of PRP or no PRP (no placebo used)	Time to return to play (sport), pain
Achilles Tendinopathy				
Krogh 2016[34] Denmark	RCT (only patients were blinded) N=24	Patients with chronic Achilles tendinopathy	One dose of PRP or saline	VISA-A score, pain

Author, year, country	Study Design, N	Population Characteristics	Comparisons	Outcomes of Interest
Patellar Tendinopathy				
Dragoo 2014[35] USA	DB RCT (patients and clinicians were blinded) N=23	Patients with patellar tendinopathy	One dose of leukocyte rich PRP or dry needling	VISA score, pain, Tegner activity score, Lysholm knee scale, Short Form 12,
Total Ankle Replacement				
Kane 2016[36] USA	Retrospective review N=133	Patients who received Agility total ankle replacement	PRP to augment incisional closure versus no PRP	Healing complications, prolonged wound care, return to surgery
ACL Repair				
Azcarte 2014[37] Spain	RCT N=150	Patients undergoing arthroscopic ACL reconstruction	Double spinning PRP with leukocytes versus no PRP versus single spinning PRP	Inflammation, pain, IKDC
Osteoarthritis of the Knee				
Saturveithan 2016[38] Malaysia	Retrospective cross sectional study N=64 (101 knees)	Patients with grade 3 or 4 knee osteoarthritis	PRP versus PRP plus hyaluronic acid	IKDC, VAS, WOMAC, KOOS
Hip Arthroplasty				
Safdar 2015[39] USA	Retrospective comparative study N=60	Patients undergoing hip replacement surgery	PRP versus no PRP	Hemoglobin level, transfusion requirements, hospitalization rates
Lumbar Diskogenic Pain				
Tuakali-Wosornu 2016[40] USA	DB RCT (physicians and patients were blinded) N=47	Patients with chronic lumbar diskogenic pain	One dose of intradiskal PRP or contrast agent after provocative diskography	Functional rating index, numeric rating scale for pain, Short-Form 36, NASS

DB= double blind; IKDC= international knee documentation committee scale; KOOS= Knee injury and osteoarthritis outcome score; NASS=North American Spine Society Outcome Questionnaire; PRTEE=patient rated tennis elbow evaluation; PRP=platelet rich plasma; QOL= quality of life; RCT = randomized controlled trial; SPADI= Shoulder Pain and Disability Index; UCLA= University of California at Los Angeles; VAS=visual analog scale; VASRWE= visual analog scale with resisted wrist extension; VISA= Victorian institute of sports assessment; VISA-A= Victorian institute of sports assessment Achilles; WOMAC= Western Ontario and McMaster Universities Arthritis Index; WORC=Western Ontario Rotator Cuff Index

Table 4: Characteristics of Included Clinical Practice Guidelines

Intended users/ target population	Interventions and practice considered	Outcomes considered	Evidence Collection, Selection, Synthesis	Recommendations development and evaluation	Guideline validation
NICE 2013[41] - Tendinopathy					
Clinicians in the UK	Autologous blood injection for tendinopathy	Pain, weakness, stiffness, return to sport, function	Literature search, submissions from stakeholders	Quality of evidence was reviewed in an attached technical report	Feedback solicited
NICE 2014[42] – Osteoarthritis of the knee					
Clinicians in the UK	Platelet rich plasma injections for osteoarthritis of the knee	Function, need for other interventions, cartilage repair, radiographic imaging, pain, stiffness	Literature search, submissions from stakeholders	Quality of evidence was reviewed in an attached technical report	Feedback solicited

NICE=National Institute of Clinical Excellence; RCT = randomized controlled trial

Table 5: Overlap in Included Studies between Systematic Reviews

Study author (year of publication)	ACL Reconstruction		Study author (year of publication)	Total Knee Arthroplasty	
	Figueroa (2015)[8]	Andriolo (2015)[9]		Li (2017)[10]	Kuang (2016)[11]
Ventura (2005)		x	Peerbooms (2009)	x	x
Orrego (2008)	x	x	Morishita (2014)	x	x
Nin (2009)		x	Aggarwal (2014)	x	x
Silva (2010)		x	Dong(2014)	x	x
Vogrin (2010)	x	x	Horstmann(2011)	x	x
Vogrin (2010) B		x	Guerreiro(2015)	x	x
Figueroa (2010)	x	x	Mochizuki(2016)	x	
Sanchez (2010)	x	x	Floryan(2004)		x
Radice (2010)	x	x	Pace(2013)	x	x
Vadala (2013)	x	x	Tingstad(2015)	x	x
Mirzatolooei (2013)	x	x	Berghoff(2006)	x	x
Rupreht (2013)		x	Gardner(2007)		x
Siejas (2013)		x	Diiorio(2012)	x	x
Magnussen (2013)		x			
Rupreht (2013) B		x			
de Almeida(2012)		x			
Cervellin (2012)		x			
Valenti Nin(2009)		x			
Silva (2009)		x			

Table 6: Overlap in Included Studies between Systematic Reviews

Study author (year of publication)	Knee Osteoarthritis						
	AHRQ(2017)[12]	Chang(2014)[17]	Filardo(2015)[16]	Tietze(2014)[15]	Lai(2015)[13]	Khoshbin(2013)[14]	Shen(2017)[18]
Patel(2013)	x	x	x		X	x	x
Gormeli(2015)	x						x
Rayegani(2014)	x						
Acosta-Olivio(2014)	x						
Simental-Mendia(2016)	x						
Halpern(2013)		x					
Jang(2013)		x					
Gobbi(2012)		x	x	x	x		
Napolitano(2012)		x	x	x			
Filardo(2011)		x		x	x		
Sampson(2010)		x	x	x	x		
Wang-Saegusa(2011)		x	x	x			
Kon(2010)		x	x	x	x		
Filardo(2012)		x	x				
Spakova(2012)		x	x	x	x	x	x
Kon(2011)		x	x	x	x	x	
Cerza(2012)		x	x			x	x
Filardo(2012 RCT)		x	x		x	x	
Sanchez(2012)		x	x				x
Li(2011)		x				x	x
Koh(2012)			x				
Koh(2013)			x				
Jang(2013)			x				
Hart(2013)			x				

Study author (year of publication)	Knee Osteoarthritis						
Torrero(2012)			x				
Sanchez(2008)			x	x			
Sanchez(2012 Rheumatology)			x	x			
Battaglia(2011)							
Mei-Dan(2012)			x				
Gobbi(2011)				x			
Jang/Kim(2012)				x			
Filardo (2015)							X
Forogh(2016)							X
Montanez(2016)							X
Paterson (2016)							X
Raeissadat(2015)							X
Smith (2016)							X
Vaquerizo							x

Appendix 3: Critical Appraisal of Included Publications

Table 7: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

		ACL Repair		Knee Arthroplasty		General Orthopedic Indications	Spinal Fusion	Foot/ Ankle Pathology	Soft Tissue Injury
AMSTAR Item		Figueroa (2015)[8]	Andriolo (2015)[9]	Li(2016)[10]	Kuang (2016)[11]	Sheth(2012)[20]	Elder(2015)[22]	Vannini(2014)[21]	Moraes (2014)[19]
Was an a priori design provided?		⊕	⊕	⊕	⊕	⊕	X	X	⊕
Was there duplicate study selection and data extraction?	Selection	⊕	⊕	⊕	⊕	⊕	?	?	⊕
	Extraction	?	?	⊕	⊕	⊕	?	?	⊕
Was a comprehensive literature search performed?		⊕	⊕	⊕	⊕	⊕	X	X	⊕
Was the status of publication (i.e., grey literature) used as an inclusion criterion?		?	?	?	?	⊕	X	X	⊕
Was a list of studies (included and excluded) provided?	Included	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Excluded	X	X	X	X	?	X	X	⊕
Were the characteristics of the included studies provided		⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Was the scientific quality of the included studies assessed and documented?		⊕	X	⊕	⊕	⊕	X	X	⊕
Was the scientific quality of the included studies used appropriately in formulating conclusion?		⊕	X	⊕	⊕	⊕	X	X	⊕
Were the methods used to combine the findings of studies appropriate?		NA	NA	?	?	⊕	NA	NA	⊕
Was the likelihood of publication bias assessed?		X	X	⊕	⊕	⊕	X	X	X
Was the conflict of interest included?		⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕

Legend: ⊕ = Yes, X = No, ? = Unclear, NA=not applicable

Table 8: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

		Osteoarthritis (these publications focused on knee)						
AMSTAR Item		AHRQ(2017)[12]	Shen(2017)[18]	Lai(2015)[13]	Filardo(2013)[16]	Chang(2014)[17]	Tietze(2014)[15]	Khosbin (2013)[14]
Was an a priori design provided?		⊕	⊕	⊕	⊕	⊕	⊕	⊕
Was there duplicate study selection and data extraction?	Selection	⊕	⊕	?	⊕	?	?	⊕
	Extraction	⊕	⊕	?	?	?	?	⊕
Was a comprehensive literature search performed?		⊕	⊕	⊕	X	⊕	⊕	⊕
Was the status of publication (i.e., grey literature) used as an inclusion criterion?		⊕	?	?	?	X	?	?
Was a list of studies (included and excluded) provided?	Included	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Excluded	⊕	⊕	X	X	X	X	X
Were the characteristics of the included studies provided		⊕	⊕	⊕	⊕	⊕	X	⊕
Was the scientific quality of the included studies assessed and documented?		⊕	⊕	X	X	⊕	X	?
Was the scientific quality of the included studies used appropriately in formulating conclusion?		⊕	?	X	X	?	X	?
Were the methods used to combine the findings of studies appropriate?		⊕	?	N/A	N/A	⊕	N/A	⊕
Was the likelihood of publication bias assessed?		?	⊕	X	X	⊕	X	X
Was the conflict of interest included?		⊕	⊕	⊕	X	X	⊕	⊕

Table 9: Strengths and Limitations of Primary Clinical Studies using Downs and Black[6]

	Rotator Cuff				Epicondylitis			Hamstring		Other indications						
Downs and Black Item	Jo 2015[23]	Wang 2015[24]	Malavolta 2014[25]	Kesikburun 2013[26]	Raeissadat 2014[27]	Krogh 2013[28]	Mishra 2013[29]	Reurink 2015[30-32]	Hamid 2014[33]	Krogh 2016[34]	Dragoo 2014[35]	Kane 2016[36]	Azcarte 2014[37]	Saturveithan 2016[38]	Safdar 2015[39]	Tuakali 2016[40]
Reporting																
Is the hypothesis/aim/objective of the study clearly described?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	X	⊕	⊕
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	⊕	⊕	X	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	X	X	⊕	⊕

Downs and Black Item	Rotator Cuff				Epicondylitis			Hamstring		Other indications						
	Jo 2015[23]	Wang 2015[24]	Malavolta 2014[25]	Kesikburun 2013[26]	Raeissadat 2014[27]	Krogh 2013[28]	Mishra 2013[29]	Reurink 2015[30-32]	Hamid 2014[33]	Krogh 2016[34]	Dragoo 2014[35]	Kane 2016[36]	Azcarte 2014[37]	Saturveithan 2016[38]	Safdar 2015[39]	Tuakali 2016[40]
Are the characteristics of the patients included in the study clearly described?	⊕	x	⊕	⊕	x	⊕	⊕	⊕	⊕	⊕	⊕	x	x	x	x	x
Are the interventions of interest clearly described?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	⊕	x	⊕	⊕	x	⊕	x	⊕	⊕	⊕	⊕	x	x	x	x	x
Are the main findings of the study clearly described?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	X	⊕	⊕
Does the study provide estimates of the random variability in the data for the main outcomes?	⊕	x	⊕	⊕	⊕	⊕	x	⊕	⊕	⊕	⊕	x	x	⊕	X	⊕
Have all important adverse events that may be a consequence of the intervention been reported?	x	x	⊕	⊕	x	⊕	⊕	⊕	⊕	⊕	x	x	?	?	x	⊕
Have the characteristics of patients lost to follow-up been described?	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Have actual probability values been reported for the main outcomes?	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
External Validity																
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Were the staff, place, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Internal Validity – Bias																
Was an attempt made to blind study subjects to the intervention they have	x	x	⊕	⊕	⊕	⊕	⊕	⊕	x	⊕	⊕	x	x	x	x	⊕

Downs and Black Item	Rotator Cuff				Epicondylitis			Hamstring		Other indications						
	Jo 2015[23]	Wang 2015[24]	Malavolta 2014[25]	Kesikburun 2013[26]	Raeissadat 2014[27]	Krogh 2013[28]	Mishra 2013[29]	Reurink 2015[30-32]	Hamid 2014[33]	Krogh 2016[34]	Dragoo 2014[35]	Kane 2016[36]	Azcarte 2014[37]	Saturveithan 2016[38]	Safdar 2015[39]	Tuakali 2016[40]
received?																
Was an attempt made to blind those measuring the main outcomes of the intervention?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	x	⊕	x	x	x	x	⊕
In trials and cohort studies do the analyses adjust for different lengths of follow-up of patients or in case-control studies is the time period between the intervention and outcome the same for cases and controls?	x	x	x	x	x	x	x	⊕	⊕	x	x	x	x	x	x	x
Were the statistical tests used to assess the main outcomes appropriate?	⊕	⊕	⊕	⊕	?	⊕	⊕	⊕	⊕	⊕	⊕	?	⊕	?	⊕	⊕
Was compliance with the intervention/s reliable?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	?	⊕	⊕
Were the main outcome measures used accurate (valid and reliable)?	?	?	?	?	?	?	?	⊕	⊕	?	?	?	?	?	⊕	?
Internal Validity – Confounding																
Were the patients in different intervention groups or were the cases and controls recruited from the same population?	?	?	?	?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	?	?	?	?	⊕
Were study subjects in different intervention groups or were the cases and controls recruited over the same period of time?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	x	?	?	⊕	⊕
Were study subjects randomized to intervention groups?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	x	⊕	x	X	⊕
Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	?	⊕	⊕	⊕	?	⊕	?	⊕	⊕	⊕	⊕	N/A	?	N/A	N/A	⊕
Was there adequate adjustment for confounding in the analyses from which	?	?	?	?	?	?	?	⊕	⊕	?	?	x	?	x	?	?

Downs and Black Item	Rotator Cuff				Epicondylitis			Hamstring		Other indications						
	Jo 2015[23]	Wang 2015[24]	Malavolta 2014[25]	Kesikburun 2013[26]	Raeissadat 2014[27]	Krogh 2013[28]	Mishra 2013[29]	Reurink 2015[30-32]	Hamid 2014[33]	Krogh 2016[34]	Dragoo 2014[35]	Kane 2016[36]	Azcarte 2014[37]	Saturveithan 2016[38]	Safdar 2015[39]	Tuakali 2016[40]
the main findings were drawn?																
Were losses of patients to follow-up taken into account?	?	?	?	?	?	?	?	⊕	⊕	?	?	X	?	N/A	?	?
Power																
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	⊕	⊕	⊕	⊕	?	⊕	⊕	⊕	⊕	⊕	⊕	?	?	?	?	⊕
Additional Critical Appraisal Points																
Was conflict of interest mentioned?	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	X	⊕	⊕

Legend: ⊕ = Yes, **X** = No, **?** = Unclear

Table 10: Strengths and Limitations of Guidelines using AGREE II[7]

Strengths	Limitations
NICE 2013[41] - Tendinopathy	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. Stakeholder Involvement • The guideline was developed by individuals with relevant professional backgrounds. • Target users were described. • NICE solicits user feedback and patient feedback. Rigour of development • Systematic methods were used to search for evidence. • Strengths and limitations of the evidence were described. • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • NICE has policies that address updates to guidance. • The link between recommendations and the supporting evidence was explicit. Clarity of Presentation • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable. Applicability • The guideline provides advice on how the recommendations can be put into practice. • The potential resource implications of applying the recommendations were considered. Editorial Independence • This guideline was funded by the NICE.	Rigour of development • Criteria for selecting the evidence were not fully described in the guideline but are available in the attached technical document. • Methods for formulating the recommendations were not clearly described, but there are detailed descriptions of these processes available. Applicability • The guideline did not describe facilitators of and barriers to its application.
NICE 2014[42] – Osteoarthritis of the knee	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. Stakeholder Involvement • The guideline was developed by individuals with relevant professional backgrounds. • Target users were described. • NICE solicits user feedback and patient feedback. Rigour of development • Systematic methods were used to search for evidence.	Rigour of development • Criteria for selecting the evidence were not fully described in the guideline but are available in the attached technical document. • Methods for formulating the recommendations were not clearly described, but there are detailed descriptions of these processes available. Applicability • The guideline did not describe facilitators of and barriers to its application.

Strengths	Limitations
• Strengths and limitations of the evidence were described. • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • NICE has policies that address updates to guidance. • The link between recommendations and the supporting evidence was explicit. Clarity of Presentation • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable. Applicability • The guideline provides advice on how the recommendations can be put into practice. • The potential resource implications of applying the recommendations were considered. Editorial Independence • This guideline was funded by the NICE.	

Appendix 4: Main Study Findings and Author's Conclusions

Table 11: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
ACL Reconstruction	
Figueroa (2015)[8]	
• No pooling of data was performed. • Six studies reported a statistically significant difference (4 studies) or tendency toward faster graft maturation in the platelet group (2 studies). One study found no differences. • Tunnel healing/widening: 1 study showed faster healing in the PRP group and 5 studies showed no differences between the 2 groups. • Clinical outcomes, 1 study showed better clinical outcomes with PRP use and 5 studies showed no benefits with the use of PRP.	• "Concerning ACL graft maturation, there is promising evidence that the addition of PRP could be a synergic factor in acquiring maturity more quickly than grafts with no PRP, with the clinical implication of this remaining unclear. Regarding tunnel healing, it appears that there is not an improvement with the addition of PRP. There is no proof that clinical outcomes of ACL surgery are enhanced by the use of PRP."(p981)
Andriolo (2015)[9]	
• No pooling of data was performed • 7 studies reported "clinical outcome…between 6 months and 2 years" with no difference between PRP and control groups. • Among the 6 studies reporting data about graft maturation, 4 of them reported results in favour of PRP augmentation relative to control, and 2 studies reported no difference between treatment groups. 9 studies reported data on graft integration in the bone tunnels and 7 of these reported no advantage with PRP administration. 3 trials focused on the bony tunnel widening and none of these demonstrated that PRP was able to prevent tunnels' enlargement over time.	• "Clinical results on PRP use for ACL augmentation are controversial. The intraoperative use of PRP proved to be safe, and PRP actually showed to even reduce the surgical morbidity promoting graft harvest site healing. Based on current evidence, PRP seems to play a positive role in the healing mechanisms after ACL surgery for what regards graft maturation, whereas the majority of the studies showed no benefit in terms of graft integration, especially in preventing bone tunnel widening. Finally, PRP did not provide a superior clinical outcome at short-term followup, whereas data at longer followup are lacking to address the overall clinical benefit of PRP augmentation."(p13)
Total Knee Arthroplasty	
Li(2016)[10]	
• Statistically significant increases in ROM relative to control (6 studies, N=655) were observed at day 3 (WMD= 4.72, 95%CI 2.74-6.69) and 3 months postoperatively (WMD= 7.55, 95%CI 5.91-9.19) with large heterogeneity (I^2 = 87.4%, P = 0.000). • No statistically significant differences in WOMAC (3 studies, N-163) at month 3 (WMD=-4.88, 95%CI -12.12, 2.41; p=0.20) • Three studies (217 patients) reported pain intensity and meta-analysis indicated that there was no statistically significant difference between the two groups in pain intensity at 24 hours (WMD=0.54, 95%CI -1.14, 0.06; P=0.077, , 48 hours (WMD=0.78, 95%CI -2.64, 1.08; P= 0.760) and 7 days (WMD= 0.01, 95% CI -1.11, 1.12; P=0.988,) postoperatively. • Six studies (511 patients) reported the occurrence of infection, pooled results indicated that there was no statistically significant difference between the PRP and	• "PRP is associated with increasing the ROM after TKA in short term and long term. What's more, PRP can also decrease the WOMAC score and pain intensity without increasing the occurrence of infection."(p109)

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>control in the occurrence of infection (RR= 0.64, 95%CI: 0.19, 2.14; P=0.464,</td><td></td></tr>
<tr><td colspan="2">Kuang (2016)[11]</td></tr>
<tr><td>• The authors reported no statistically significant differences for mean change in haemoglobin post operatively in their pooled analysis of RCTs (mean difference -0.47mg/dL, 95%CI 0.94,-0.01; p=0.05) and non-RCTs (mean difference -0.20, 95%CI -0.50,0.10; p=0.19)
ROM Pooled results
<table>
<tr><td></td><td>Standardized mean difference(95%CI) PRP vs control (negative values favour PRP)</td></tr>
<tr><td>Perioperative</td><td>RCTs: 0.24(-0.20,0.69)
Non-RCTs: 0.20(-0.13,0.33)</td></tr>
<tr><td>Short term</td><td>RCTs: 2.85(-1.80,7.51)
Non-RCTs: 4.90(1.20,8.60)</td></tr>
<tr><td>Long term</td><td>RCTs: 0.38(0.08,0.68)
Non-RCTs: 0.24(0.03,0.46)</td></tr>
</table>
Pain VAS Pooled results
<table>
<tr><td></td><td>Standardized mean difference(95%CI) PRP vs control (negative values favour PRP)</td></tr>
<tr><td>Perioperative</td><td>RCTs: -0.32(-0.59,-0.05)
Non-RCTs: -0.90(-1.22,-0.59)</td></tr>
<tr><td>Short term post-operative</td><td>RCTs: -0.89(-1.45,-0.33)</td></tr>
<tr><td>Long term post-operative</td><td>RCTs: -1.02(-1.56,-0.49)</td></tr>
</table></td><td>• "Compared with placebo, APG offers superior pain control after TKA. However, APG has no advantage in blood loss, functional recovery,postoperative narcotics and length of stay. Considering theproduction of APG is complicated and larger volumes of whole blood should be prepared during TKA, the use of APG is not worthy of being recommended as a bioactive autologous material to improve the clinical outcomes in TKA patients."(p64)</td></tr>
<tr><td colspan="2">Miscellaneous Usages</td></tr>
<tr><td colspan="2">Sheth(2012)[20]</td></tr>
<tr><td>• 6 RCTs showed that PRP provided a significant functional benefit, fifteen demonstrated no difference between platelet-rich plasma and the control, and one showed that the control provided a significant functional benefit; the authors of the remaining study did not evaluate functional outcomes Of the ten prospective cohort studies, three showed that PRP provided a significant functional benefit, six demonstrated no difference between PRP and the control, and one study showed that the control provided a significant functional benefit.
• No significant difference in VAS scores between PRP and control groups across RCTs (standardized mean difference, –0.34; 95% CI, –0.75 to 0.06; p = 0.10; and I2 = 70%) or prospective cohort studies (standardized mean difference, –0.20; 95% CI, –0.64 to 0.23; p = 0.36; and I2 = 0%)</td><td>• "Current evidence is insufficient to discern whether autologous blood concentrates provide a clinical benefit in the treatment of orthopaedic conditions. Large and carefully designed randomized clinical trials are needed to draw definitive conclusions on the potential risks and benefits of autologous blood concentrates, such as platelet-rich plasma, in orthopaedics."(p306)</td></tr>
<tr><td colspan="2">Elder(2015)[22]</td></tr>
<tr><td>• No pooling of data was performed
• 7 studies with control groups reported no differences in</td><td>• "PRP may be a promising strategy to augment spinal fusion in the future, particularly due to its low cost,</td></tr>
</table>

Main Study Findings	Author's Conclusion
fusion rates between PRP and control. 2 studies with control groups reported numerically higher fusion rates in the control group versus PRP (statistical analyses not provided)	low risk profile, and reportedly low complication rates. However, further work must be undertaken to optimize the many aforementioned variables in order to more accurately determine the effects of PRP on spinal fusion." (p. 1067)
Vannini(2014)[21]	
• No pooling of data was performed • 1 or 2 RCTs in Achilles tendinopathy/tendon rupture showed no difference in clinical outcome or return to sport between PRP and control. Clinical outcome was better in the control group in one RCT. • 1 RCT comparing PRP to corticosteroids for planta fasciitis showed no difference in pain or function between treatment groups. • 1 RCT comparing PRP to hyaluronic acid found statistically significant improvements for PRP relative to hyaluronic acid for "controlling pain and re-establishing function."	• "Considering the literature currently available, no clear indications for using PRP in the foot and ankle district emerged."(p. 2)
Moraes (2014)[19]	
• Short term function: No statistically significant difference between PRP and control (4 trials, 3 conditions, SMD 0.26; 95%CI -0.19 to 0.71; P=0.26; I^2 = 51%; N=162; positive values favour PRP • Medium-term function No statistically significant difference between groups (5 trials, 5 conditions, SMD -0.09, 95%CI -0.56 to 0.39; P=0.72; I^2 = 50%; N=151). • Long-term function: No statistically significant difference between groups (10 trials, 5 conditions, SMD 0.25, 95%CI -0.07 to 0.57; P=0.12; I^2 = 66%; N=484). • Short-term pain: Statistically significant benefit in favour of PRP on a 10-point scale (4 trials, 3 conditions, MD -0.95, 95% CI -1.41 to -0.48; I^2 = 0%; N=175). The clinical significance of this result is marginal. • Four trials reported adverse events; another seven trials reported an absence of adverse events. There was no difference between treatment groups in the numbers of participants with adverse effects (7/241 versus 5/245; RR 1.31, 95% CI 0.48 to 3.59; I^2 = 0%; N=486).	• "Overall, and for the individual clinical conditions, there is currently insufficient evidence to support the use of PRT for treating musculoskeletal soft tissue injuries. Researchers contemplating RCTs should consider the coverage of currently ongoing trials when assessing the need for future RCTs on specific conditions. There is need for standardization of PRP preparation methods."(p. 2)
Osteoarthritis of the Knee	
AHRQ(2017)[12]	
• No pooling of data was performed. • Short term pain score (<4 months): 2 RCTs showed no significant difference between PRP and control. 1 RCT showed significantly greater improvement in the PRP group compared to control. • Medium term effects on pain: 5 RCTs reported statistically significant improvements in pain for PRP versus control (e.g. saline, paracetamol) on the WOMAC, VAS or KOOS pain scores. • Medium term effects on function: WOMAC function scores were significantly decreased (improved) for PRP compared	• "A low strength of evidence based on four RCTs supports a beneficial effect of PRP on medium-term pain and quality of life." • "A low strength of evidence based on three RCTs supports a beneficial effect of PRP on medium-term quality of life." • "Evidence was insufficient to draw conclusions regarding the effects of PRP on medium-term function." • "Evidence was insufficient to draw conclusions regarding outcomes at shorter or longer times." (pES-8)

Main Study Findings	Author's Conclusion
to control in 1 RCT. Another RCT showed no difference in WOMAC function scores for PRP compared to control.	
Shen(2017)[18]	
• WOMAC pain subscores (negative values favour PRP): Month 3, three studies; MD, −3.69 [95% CI, −6.87 to −0.51], I2 = 94%, p = 0.02). At 6 months, 5 studies,MD, −3.82 [95% CI, −6.40 to −1.25], I2 = 96%, p = 0.004. At 12 months, 4 studies (MD, −3.76 [95% CI, −5.36 to −2.16], I2 = 86%, p < 0.001) • WOMAC physical function (negative values favour PRP): at 3 months, 3 studies, MD, -14.24, 95%CI -23.43 to -5.05; p=0.002. • Total WOMAC scores (negative values favour PRP): at 3 months, 6 studies, MD, -14.53 95%CI, -21.97 to -7.09; p<0.001. • Adverse events: no statistically significant difference in the number of patients with adverse events between PRP and control in 9 studies (RR, 1.40 [95% CI, 0.80 to 2.45], I2 = 59%, p = 0.24)	• "Intra-articular PRP injections probably are more efficacious in the treatment of knee OA in terms of pain relief and self-reported function improvement at 3, 6, and 12 months follow-up, compared with other injections, including saline placebo, hyaluronic acid, ozone, and corticosteroids."(p11)
Lai(2015)[13]	
• No pooling of data was performed • Several studies indicated that potential benefits observed in the WOMAC and EQ VAS scores at earlier time points (e.g. 6 months), were not maintained over longer time periods (e.g. 12 months and later), but remained better than baseline. • One placebo controlled study indicated superior efficacy for PRP for improving pain, stiffness, and physical function over 6 months and that frequency of PRP administration may not affect outcomes. • One RCT showed no difference between PRP and hyaluronic acid for pain and function measures.	• "PRP … may be an effective alternative treatment for knee OA for patients who do not adequately symptomatically respond to more traditional treatments. However, current studies are, at best, inconclusive regarding the efficacy of PRP treatment. Significant variations in administration schedule likely make it difficult to draw definitive conclusions about PRP in general."(p647)
Filardo(2015)[16]	
• No pooling of data was performed • Of the 9 studies that utilized a comparator, four studies reported superior results for PRP versus comparator for "short term evaluation", "clinical outcome", "functional improvement", or "pain control" (no clear definitions of these outcomes were provided). No clear advantages of PRP over the comparator were reported for the other 5 studies and one study reported higher post-injection pain in the leukocyte rich PRP group compared to control.	• "A few high-quality trials have been published, which showed the clinical usefulness of PRP but only with an improvement limited over time and mainly in younger patients not affected by advanced degeneration. Many biological variables might influence the clinical outcome and have to be studied to optimize PRP injective treatment in case of cartilage degeneration and OA."(p2471)
Chang(2014)[17]	
• Authors used pooled analysis to calculate the effect size of change in function comparing pre-treatment to post treatment values and using variance to estimate an effect size. The authors pooled data from single arm and	• "The present meta-analysis demonstrates a significant functional improvement after PRP intervention in patients with knee cartilage degenerative pathology, compared with their pretreatment baseline, although this finding should be

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>comparative studies. The authors did not perform direct statistical comparisons with PRP groups versus control. Positive values for effect size indicate improvement.
• PRP groups pooled data: compared with baseline, the pooled effect size was 2.31 (95% CI, 1.53-3.09) at 2 months, 2.52 (95%CI, 1.94-3.09) at 6 months, and 2.88 (95% CI, 0.97-4.79) at 12 months,
• Hyaluronic acid groups pooled data: compared with baseline, the pooled effect size was 1.15 (95% CI, 0.78-1.52) at 2 months, 0.75 (95% CI, 0.62-0.88) at 6 months, and 0.85 (95% CI, 0.46-1.24) at 12 months.</td><td>interpreted with caution because of the low methodological quality of the included trials. The effectiveness of PRP is likely superior to that of HA, with a longer effective duration. Discrepancy in the degenerative severity modified the treatment response, leading the participants with a lower degree of knee degenerative lesions to benefit more from PRP injections. We suggest that future studies target the population with mild to moderate knee OA based on the consideration of clinical utility."(p574)</td></tr>
<tr><td colspan="2">Tietze(2014)[15]</td></tr>
<tr><td>• Three studies compared PRP to hyaluronic acid. In these studies, PRP resulted in improvements to measures of function relative to hyaluronic acid and the differences were statistically significant (e.g. IKDC, WOMAC)
• There were no statistically significant differences in WOMAC, IKDC, EQ VAS or Tegner scores in a single trial that compared PRP to PRGF.
• Nine case series publications reported improvements at 6 months in patients receiving PRP relative to baseline, for IKDC, VAS, KOOS, Marx, and Tegner scores. Some studies reported worsening in scores after the 6 month time point.</td><td>• "Platelet-rich plasma may improve short-term patient outcomes in knee OA. Younger patients with less of a disease burden tend to have the most improvement. In the studies that compared PRP to HA, a statistically significant improvement was noted in the PRP group. Platelet-rich plasma appears to have the greatest benefit in knee OA between 6 and 12 months. Given the variance in volume and scheduling of PRP used, no conclusions can be reached about the standardization of its use. No conclusions can be reached regarding the use of PRP in large joints other than the knee, as our review yielded only 1 study on hip OA. None of the studies reviewed showed that PRP can reverse the articular damage caused by OA." (p36)</td></tr>
<tr><td colspan="2">Khoshbin(2013)[14]</td></tr>
<tr><td><table><tr><th></th><th>Weighted mean difference (95%CI) PRP vs hyaluronic acid or saline</th></tr><tr><td>WOMAC</td><td>4 studies N=366
-18.03(-27.75,-8.30), favours PRP</td></tr><tr><td>IKDC</td><td>3 studies, N=239
8.28(2.58,13.98), favours PRP</td></tr><tr><td>VAS</td><td>2 studies, N=196
0.46(-0.52,1.43)</td></tr><tr><td>Patient Satisfaction</td><td>2 studies, N=108
8.97(0.54,149.25)</td></tr></table>• Reported adverse events included pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia, post-injection pain, swelling of the injection site, and activity limitations. A pooled analysis of adverse events showed that PRP treatment had a higher incidence of adverse events compared with control treatments (8.4% v 3.8%, P=0.002).</td><td>• "As compared with HA or NS injection, multiple sequential intra-articular PRP injections may have beneficial effects in the treatment of adult patients with mild to moderate knee OA at approximately 6 months. There appears to be an increased incidence of nonspecific AEs among patients treated with PRP."(p2045)</td></tr>
</table>

EQ VAS= Euroqol visual analog scale; IKDC= International Knee Documentation Committee score; KOOS= knee injury and osteoarthritis outcome score; MD=mean difference; OA=osteoarthritis; PRDF= preparation rich in growth factors; PRP=platelet rich plasma; PRT= plasma rich therapy; SMD= standardized mean difference; TKA= total knee arthroplasty; VAS=visual analog score; WOMAC=Western Ontario McMaster University Osteoarthritis Index

Table 12: Summary of Findings of Included Individual Studies

Main Study Findings	Author's Conclusion
Rotator Cuff	
Jo 2015[23]	
• There were not statistically significant differences between PRP and no treatment for the Constant score (primary outcome), pain, ROM, muscle strength, overall satisfaction and function. • Retear rate for the PRP group was 3% versus 20% in the no-PRP group (p=0.032).	• "Compared with repairs without PRP augmentation, the current PRP preparation and application methods for medium to large rotator cuff repairs significantly improved the quality, as evidenced by a decreased retear rate and increased CSA of the supraspinatus, but not the speed of healing. However, further studies may be needed to investigate the effects of PRP on the speed of healing without risking the quality."(p2102)
Wang 2015[24]	
• There were no differences between PRP and the control group in early functional recovery, range of motion, or strength or influence pain scores at any time point after arthroscopic supraspinatus repair. • There was no difference in structural integrity of the supraspinatus repair on MRI between the PRP group (0% full-thickness retear; 23% partial tear; 77% intact) and the control group (7% full-thickness retear; 23% partial tear; 70% intact) at 16 weeks postoperatively (P =0.35).	• "After arthroscopic supraspinatus tendon repair, image-guided PRP treatment on 2 occasions does not improve early tendon-bone healing or functional recovery."(p1430)
Malavolta 2014[25]	
• There was no statistically significant difference in mean UCLA score, mean Constant score, or VAS pain score for PRP versus control. • There were 2 partial retears in the PRP group and in the non-PRP group there were 4 partial retears and 1 complete retear (p=0.42).	• "Platelet-rich plasma prepared by apheresis and applied in the liquid state with thrombin did not promote better clinical results at 24-month follow-up. Given the numbers available for analysis, the retear rate also did not change."(p2446)
Kesikburun 2013[26]	
• There were no statistically significant differences between PRP and the control group for WORC, SPADI and VAS scores at 1 year follow up.	• "…PRP injection was found to be no more effective in improving quality of life, pain, disability, and shoulder range of motion than placebo in patients with chronic RCT who were treated with an exercise program during a 1-year follow-up study. These findings do not support the use of PRP injections in chronic RCT." (p2615)
Epicondylitis	
Raeissadat 2014[27]	
• No statistically significant differences between PRP and autologous whole blood injections were observed for pain, functional scores and treatment success rates.	• "The efficacy of PRP was similar to whole blood injection at 12 month follow up in relieving pain and improving function. It can be concluded from our study that there might be no need to platelets in higher concentration than whole blood to get therapeutic effects. Because PRP and whole blood are autologous and are prepared at the point of care, they have an excellent safety profile."(p9)

Main Study Findings	Author's Conclusion
Krogh 2013[28]	
• No statistically significant differences between PRP and saline or between PRP and glucorticoid in pain at 3 months. • At 1 month, there were statistically significant differences favouring glucocorticoid relative to PRP (mean difference between groups: -9.3, 95%CI -15.4 to -3.2), PRTEE.	• "Neither injection of PRP nor glucocorticoid was superior to saline with regard to pain reduction in LE at the primary end point at 3 months. However, injection of glucocorticoid had a short-term pain-reducing effect at 1 month in contrast to the other therapies."(p625)
Mishra 2013[29]	

• Pain improvement of at least 25% compared to baseline:
  ○ 12 weeks (N=192)
  ▪ PRP: 75.2%
  ▪ Bupivicaine: 65.9% (p=not reported)
  ○ 24 weeks (N=119)
  ▪ PRP 83.9%
  ▪ Bupivicaine: 68.3% (P=0.037)
	• "No significant differences were found at 12 weeks in this study. At 24 weeks, however, clinically meaningful improvements were found in patients treated with leukocyte-enriched PRP compared with an active control group."(p463)

Hamstring Injury	
Reurink 2015[30-32]	
• No statistically significant difference between PRP and placebo for time to return to play (primary outcome). The median time until the resumption of sports activity was 42 days (interquartile range, 30 to 58) in the PRP group and 42 days (interquartile range, 37 to 56) in the placebo group (hazard ratio in the PRP group 0.96; 95% confidence interval [CI], 0.61 to 1.51; P = 0.66). The reinjury rate was 16% in the PRP group and 14% in the placebo group (odds ratio, 1.17; 95% CI, 0.33 to 4.18; P = 0.81).	• "Although the 95% confidence interval still allows for a small chance that there was a clinically relevant between-group difference, our study demonstrated no benefit for intramuscular PRP injections, as compared with placebo injections, in patients with acute hamstring injuries."(p 2547)
Hamid 2014[33]	
• Mean time to return to play with the PRP group was 26.7 +/- 7.0 days versus 42.5+/-20.6 days in the control group (p=0.02). • Patients in the PRP group had significantly lower pain severity scores than controls at all time points (linear mixed model analysis P = 0.007).	• "This study showed that a single 3-mL injection of autologous PRP (P4-x-A classification) combined with a … rehabilitation program was significantly more effective than a control in reducing the severity of pain and allowing a significantly shorter time to return to play after an acute grade 2a hamstring injury."(p2417)
Other Indications	
Krogh 2016[34] – Achilles tendinopathy	
• There was no statistically significant difference in the primary outcome (VISA-A score) at 3 months between PRP and saline: mean difference, –1.3; 95% CI, 217.8 to 15.2; P=0.868.	• "1 injection of PRP did not result in improvement in the primary outcome, the VISA-A score after 3 months, compared with a placebo injection. These findings match the results from a very similar study by de Vos et al and the conclusion drawn in a recent Cochrane review by Moraes et al. Regarding safety, over a 3-month period, no adverse events were reported."(p1996)
Dragoo 2014[35] - Patellar tendinopathy	
• There were statistically significant improvements in the primary outcome (VISA score at week 12) favouring PRP over dry needling (mean difference from baseline: PRP 25.4, 95%CI 10.3 to 40.6; dry needling 5.2, 95%CI -2.2 to 12.6;	• "A therapeutic regimen of standardized eccentric exercise and ultrasound-guided leukocyte-rich PRP injection with DN accelerates the recovery from patellar tendinopathy relative to exercise and ultrasound-guided DN alone, but

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>p=0.02). The difference between PRP and dry needling was not statistically significant at week 26.</td><td>the apparent benefit of PRP dissipates over time."(p610)</td></tr>
<tr><td colspan="2">Kane 2016[36] – Wound healing ankle replacement</td></tr>
<tr><td>• 10.3% of patients receiving PRP underwent operative treatment of an incisional complication versus 5.5% of patients without PRP (P=0.52).</td><td>• "We were unable to find a statistically significant reduction in incision-related complications in patients who had their incisions augmented with PRP."(p1)</td></tr>
<tr><td colspan="2">Azcarate 2014[37] – ACL reconstruction</td></tr>
<tr><td>• The single spin PRP group showed statistically significant improvement in swelling scores based on the perimeter at the kneecap (no specific data provided), relative to both the double spin PRP group and the group that did not receive PRP.
• No statistically significant differences between treatment groups for ROM, CRP, IKDC.</td><td>• "PRGF used in ACL allograft reconstruction was associated with reduced swelling; however, the intensity and uniformity of the graft on MRI were similar in the three groups, and there was no clinical or pain improvement compared with the control group."(pS36)</td></tr>
<tr><td colspan="2">Saturveithan 2016[38] – Knee osteoarthritis</td></tr>
<tr><td>Mean(standard deviation) IKDC score
<table><tr><th></th><th>HA</th><th>HA+PRP</th><th>Mean diff (95%CI)</th></tr><tr><td>2 months</td><td>7.0(7.8)</td><td>16.3(11.9)</td><td>-9.3(-13.2,-5.4); p<0.05</td></tr><tr><td>6 months</td><td>12.1(8.2)</td><td>24.3(13.7)</td><td>-12.1(-16.6,-7.7); p<0.05</td></tr></table></td><td>• "We propose intra-articular HA and PRP injections as an optional treatment modality in Grade III and IV knee osteoarthritis in terms of functional outcome and pain control for up to six months when arthroplasty is not an option."(p35)</td></tr>
<tr><td colspan="2">Safdar 2015[39] – Hip arthroplasty</td></tr>
<tr><td>• There was no statistically significant difference between PRP and no PRP for hemoglobin pre to post operative changes, transfusion requirements, analgesic use, length of hospitalization.</td><td>• "We concluded that there is no clinical efficacy in using PRP in hip replacement surgeries."(p49)</td></tr>
<tr><td colspan="2">Tuakli-Worsornu 2016[40] – Lumbar diskogenic pain</td></tr>
<tr><td>• There were no statistically significant differences between PRP and placebo for SF-36 pain, SF-36 physical function, current pain or worst pain, up to 8 weeks after injection.
• There were statistically significant differences favouring PRP over placebo for the Functional Rating Index (p=0.03), best pain (p=0.015)
• Patients taking PRP were more likely to report being satisfied with their treatment (56%) compared to placebo (18%), p=0.01.</td><td>• "Participants who received intradiskal PRP showed significant improvements in FRI, NRS Best Pain, and NASS patient satisfaction scores over 8 weeks compared with controls. Those who received PRP maintained significant improvements in FRI scores through at least 1 year of follow-up."(p1)</td></tr>
</table>

ACL= anterior cruciate ligament; CRP= C Reactive Protein; FRI= Functional rating index; HA= hyaluronic acid; IKDC= International Knee Documentation Committee scale; NASS= North America Spine Society Outcome Questionnaire; NRS= numerical rating scale; PRP=platelet rich plasma; PRTEE= patient related tennis elbow evaluation questionnaire; QOL= quality of life; RCT = randomized controlled trial; ROM=range of motion; SF-36= Short Form 36; SPADI= Shoulder Pain and Disability Index; UCLA= University of California at Los Angeles; VAS=visual analog scale; WORC=Western Ontario Rotator Cuff Index

Table 13: Summary of Evidence-based Guidelines

Guideline	Selected Recommendations
NICE 2013[41] - Tendinopathy	"The evidence on autologous blood injection for tendinopathy raises no major safety concerns. The evidence on efficacy remains inadequate, with few studies available that use appropriate comparators. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research."(p1)
NICE 2014[42] – Osteoarthritis of the knee	"Current evidence on platelet-rich plasma injections for osteoarthritis of the knee raises no major safety concerns; however, the evidence on efficacy is inadequate in quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research."(p1)

Appendix 5: Additional References of Potential Interest

The following references provide additional relevant information but did not meet the inclusion criteria for this report.

CADTH. Platelet rich plasma lumbar disc injections for lower back pain: clinical effectiveness, safety, and guidelines [Internet]. Ottawa (ON): CADTH; 2014 [cited 2017 Jun 12]. Available from: https://www.cadth.ca/media/pdf/htis/mar-2014/RB0649%20Platelet%20Rich%20Plasma%20Final.pdf

Hsu WK, Mishra A, Rodeo SR, Fu F, Terry MA, Randelli P, et al. Platelet rich plasma in orthopaedic applications: evidence based recommendations for treatment. J Am Acad Orthop Surg 2013;21(12):739-48

Mautner K, Malanga GA, Smith J, Shiple B, Ibrahim V, Sampson S, et al. A call for a standard classification system for future biologic research: the rationale for the new PRP nomenclature. Pm r 2015;7(4 Suppl):S53-S59

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