National Institute for Health and Care Excellence

IP1097/2 Platelet-rich plasma injections for osteoarthritis of the knee

IPAC date: 11th October 2018

Comm. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments

1	Consultee 1 Clinician	**1, 3**	As part of the future NICE recommendations related to the PRP (platelet-rich-plasma) I bring to your attention our recent research and international publications. I sent you by mail a French study with a long-term follow-up (4 years) of the therapeutic interest of a combination treatment PRP and HA (hyaluronic acid) in knee osteoarthritis after failure of HA alone: Cellular Matrix Regenlab laboratory, Mont-sur-Lausanne, Switzerland. Publication in International Journal of Clinical Rheumatology 08-2018. **1758-4272-13-230.pdf** We will publish in the same journal, in October 2018, a special issue devoted to regenerative medicine in osteoarthritis three other articles related to the PRP HA combination: - an article of pure research carried out with the CNRS of Marseille (French country) demonstrating by MRI high field 3Tesla and specific sequences dgemric Siemens a positive structural effect on the proteoglycan content of the articular cartilage of the knee. - An article demonstrating by ultrasound a quantitative gain in articular cartilage of knee osteoarthritis. - A positive medico-economic study in favor of savings in medical and surgical care after use of PRP-HA in osteoarthritis of the knee. We will keep at your disposal the planned and already published publications of these various studies. Thanking you for your attention and interest.	Thank you for your comments and sharing information about your upcoming publications. The focus of current guidance is to evaluate the efficacy and safety of PRP alone. The French study (**Renevier JL, Marc JF, Adam P et al (2018)** Cellular matrix™ PRP-HA": A new treatment option with platelet-rich plasma and hyaluronic acid for patients with osteoarthritis having had an unsatisfactory clinical response to hyaluronic acid alone: Results of a pilot, multicenter French study with long-term follow-up. ***Int. J. Clin. Rheumatol.*** 13(4), 226-229) assesses a combination of PRP and hyaluronic acid (HA) and is out of the scope of this assessment. Any data that have not yet been published or accepted for publication by peer-reviewed journals are not normally selected for presentation to the Committee. IPAC may review the guidance upon publication of new evidence in peer-reviewed journals.

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2	Consultee 2 Regen Lab SA	**1.2**	The audit tool should include information regarding the PRP preparation process (volume of blood required, volume of PRP produced, technology used for PRP preparation), PRP composition (platelet concentration factor, level of white blood cell contamination) and PRP treatment protocol (number of injections, injected volume, interval between two injections, concomitant procedures e.g. effusion aspiration). This would allow to determine which type of PRP and which injection protocols give optimal results. For example the Riboh meta-analysis (Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. Am J Sports Med. 2016;44(3):792-800.) shows that only leukocyte poor PRP give significantly better WOMAC score than control treatment.	Thank you for your comments. NICE prepares an audit tool with advice from specialist advisers and committee members to help and encourage good auditing practice for the procedure. The team will share this information with the appropriate team to inform this audit tool production. Section 1.2 has been amended as follows: *Audit and review details of different PRP preparations used and clinical outcomes of all patients having platelet-rich plasma injections for knee osteoarthritis. NICE has identified relevant audit criteria and is developing an audit tool (which is for use at local discretion), which will be available when the guidance is published.*

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3	Consultee 3 Regen Lab SA	**2.3**	The sentence *'It can be prepared by carrying out 2-spin cycles using a standard bench-top centrifuge'* is not precise enough and might lead to preparations that are not in conformity with UK and EU regulations. Laboratory 2-spin cycle methods for PRP preparation are open systems and thus can be performed only in Good Manufacturing Practice-licensed facility in order to ensure that PRP is prepared in condition suitable for its use as an autologous biological tissue intended for therapeutic use. All products that are in contact with blood or PRP should be bio-compatible and non-pyrogenic. The anticoagulant should be pharmaceutical grade, suitable for injection and with no ancillary effect on patient. The facility is responsible for the traceability, sterility and safety of the resulting PRP.	Thank you for your comments. 2.3 has been amended as follows; *'Platelet-rich plasma is prepared by a clinician or a technician. Blood is taken from the patient and centrifuged to obtain a concentrated suspension of platelets in plasma. Different preparation methods may affect the concentrations of platelets. Different agents such as calcium chloride or thrombin may be added '.*

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4	Consultee 3 Regen Lab SA	**2.3**	The statement *"Agents such as calcium chloride may be added to activate the platelets."* is inaccurate. Addition of agents such as calcium chloride or calcium gluconate, which is less irritant than calcium chloride, counterbalances the effect of citrate based anticoagulant, thus induce coagulation of the PRP. Calcium is involved in platelet activation, however platelet activation is mainly induced by the contact with extracellular matrix proteins such as collagen.	Thank you for your comments. 2.3 has been amended as follows: *'Platelet-rich plasma is prepared by a clinician or a technician. Blood is taken from the patient and centrifuged to obtain a concentrated suspension of platelets in plasma. Different preparation methods may affect the concentrations of platelets. Different agents such as calcium chloride or thrombin may be added '.*
5	Consultee 4 Private Sector Professional	**1**	We are very attentive to NICE recommendation on the PRP since the publication 2014. We respect all items including recommendation 1, publishing in an Anglo-Saxon review.	Thank you for your comments.

6	Consultee 5 Arthrex Ltd		Since 2014 interventional procedure consultation on PRP for OsteoArthritis 17 additional level I/II studies (to our knowledge) were published. (According to study 1, 6 RCTs were published before 2014). 13 out of these 17 new studies showed superiority vs. the control group. 3 out of the 4 non-superiority studies used a leukocyte-rich PRP. The committee came to the conclusion that there was high heterogeneity across studies in terms of PRP treatment protocols (page 31). The review by Milants C (not considered in the consultation but listed in the appendix) addressed this issue and aimed at identifying features of PRP recommended for knee OA treatment. The authors came to the conclusion that for knee OA treatment the use of a single spinning technique, a platelet concentration lower than 5 times the baseline, and avoidance of leukocytes should be preferred. RCTs published after 2014 and considered in the evaluation: Duymus (cited in study 1) superior Filardo (cited in study 1) not superior (leukocyte-rich) Forogh (cited in study 1) superior GÃrmeli (cited in study 1) superior Montanez Hereda (cited in study 1) superior Paterson (cited in study 1) not superior (leukocyte-rich) Raeissadat (cited in study 1) superior Smith (cited in study 1) superior Angoorani (Study 4) moderately superior (double spin, probably leukocyte-rich) Simental-Mendia (Study 5) superior Rahimzadeh (Study 6) superior Jubert (Study 7) not superior (leukocyte-poor)	Thank you, the committee notes the comments made about individual papers included in the overview. The Committee is also grateful for the comprehensive list of additional papers suggested (and not listed in the appendix).

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6	Consultee 5 Arthrex Ltd		**RCTs published after 2014 and not listed in the appendix:** 2015 Duif (RCT) superior to arthroscopy alone (Arch Orthop Trauma Surg. 2015 Jul;135(7):971-7. doi: 10.1007/s00402-015-2227-5. Epub 2015 May 10) Study Type: randomized controlled clinical trial with reduced power Country: Germany Recruitment method: During January 2010 and December 2011 all patients presenting with non-traumatic knee pain, image-proven OA and intended arthroscopic surgery after failed conservative treatment of at least 12 weeks. Study population and number: n=58 ; OA stages II to IV according to Kellgrenâ€“Lawrence Classification; LP-PRP injection (n=24) in arthroscopy compared to arthroscopy alone (n=34) Age and sex: Mean age LP-PRP 64.1 years, Arthroscopy 64.3 years . Patient selection criteria: Inclusion criteria were OA stages II to IV according to Kellgrenâ€“Lawrence Classification for plain radiographs or modified Outerbridge grading for MR imaging with or without concomitant meniscal lesions. Due to our study protocol, we only included patients favouring general anesthesia. Exlusion criteria patients incapable of providing informed	The focus of current guidance is to evaluate the efficacy and safety of PRP alone. This study (Duif 2015 Does intraoperative application of leukocyte-poor platelet-rich plasma during arthroscopy for knee degeneration affect postoperative pain, function and quality of life? A 12-month randomized controlled double-blind trial; Arch Orthop Trauma Surg DOI 10.1007/s00402-015-2227-5) compared PRP during arthroscopy with arthroscopy alone and is out of the scope of this assessment.

			consent due to age or mental status, circumscribed chondral damage with surgical option for regenerative procedures (microfracture, autologous chondrocyte implantation), local or systemic infection, corticosteroid injection within the last 3 months, rheumatological disorders, OA with collateral ligament instability [grade II,] immunosuppression, cancer or other severe disorders contradicting autologous transfusion of blood products or resulting in a probable loss to follow-up. Technique: Knee arthroscopy was performed according to an internal standard operating procedure (SOP) with the patient in a supine position, using an inflatable tourniquet and approaching the joint through anterolateral and anteromedial standard portals. The knee joint and its cartilage surface was completely inspected with a 30 scope and the anterior cruciate ligament (ACL) and both menisci were manually tested for integrity and fixation using a hook. After completing arthroscopic interventions (cartilage debridement, partial meniscectomy), the irrigation fluid was evacuated. In cases of random allocation to the interventional group, 15 ml of blood were obtained from a peripheral cubital vein and preparation of LP-PRP was made using the ACP technique. Blood was centrifuged for 5 min with 1.500 rpm and separated into three fractions, with the thrombocyte phase being isolated in a second sterile syringe for direct application via the anterolateral portal. Wound closure without any kind of drainage was performed and full-weight bearing was allowed immediately. Follow-up: 12 months Conflict of interest/source of funding: none	

6	Consultee 5 Arthrex Ltd	**3**	**2015 Forogh (RCT)** superior to corticosteroid (J Sports Med Phys Fitness. 2016 Jul-Aug;56 (7-8):901-8. Epub 2015 Jul 14); cited in study 1 but not cited/listed in the PRP vs. CS comparison Study Type: Double-blind Randomized Clinical Trial Country: Iran Recruitment method: not reported Study population and number: n=48; OA stages II to III according to Kellgren-Lawrence Classification; single PRP injection (n=24) compared to single corticosteroid injection (n=24) Age and sex: 66.7% were women with an average age of 61.1 yrs Â± 7.0. No significant statistical difference in age and sex between groups. Patient selection criteria: INCLUSION " VAS score (100mm VAS scale) of at least 60 at time of admission, knee pain for at least 3 months, residing in Tehran and its suburbs, symptoms not managed from at least two OA treatments (including lifestyle changes, weight loss, oral medications, physiotherapy, acupuncture, laser, using insoles, cane, or orthotic devise). EXCLUSION " patients with a history of collagen vascular or severe cardiovascular and hematopoietic diseases, diabetes mellitus, history or presence of cancer, malignant disorders	This study (Forogh 2016) has been included in study 1 in table 2. Outcomes from this study has been added to efficacy section as follows: *One RCT (Forogh 2016, included in the systematic review by Shen 2017) reported decreased joint pain, more symptom relief and enhanced quality of life for patients who had 1 injection of LR-PRP compared with corticosteroids[1].* .

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			or immunosuppression, hepatitis B or C, HIV infection, any active infection or wound of the knee, history of any knee articular infections, infection, arthroscopy, or surgery during the past 6 months, active lumbosacral radiculopathy and/or drug abuse. Patients that had received physiotherapy, laser, or acupuncture on their knees in the previous 6 months were also excluded from the study. Technique: PRP was prepared by harvesting 20ml of autologous blood and adding 2ml of anticoagulant (ACD-A). The samples went through two centrifugation procedures: 1 at 1600 RPM for 6 mins and a second at 2000 RPM also for 6mins. This produced 5ml of PRP. 0.5ml of calcium gluconate solution was added to the PRP to activate it, which was then injected into each patients knee. For the control group, patients were injected with 1ml of Depo-medrol (40mg methylprednisolone acetate). Follow-up: 6 months Conflict of interest/source of funding: none	

6	Consultee 5 Arthrex Ltd		2017 Lisi (RCT) superior to HA (Clin Rehabil. 2018 Mar;32(3):330-339. doi: 10.1177/0269215517724193. Epub 2017 Aug 8) Study Type: Double-blind Randomized Controlled Clinical Trial Country: Italy Recruitment method: Patients presenting with knee to an Outpatient rehabilitation service; years 2011-2013 Study population and number: Patients with knee osteoarthritis grades -3 at magnetic resonance imaging (MRI) were included after consent and randomized. 30 patients randomized to PRP group and 28 to HA group. Age and sex: PRP: 67% were males with average age of 53.5 yrs. HA : 57% were males with average age of 57.1yrs. No significant statistical difference Patient selection criteria: Grade II/III osteoarthritis of the knee demonstrated at MRI, according to Shahriaree Classification System; Age >18 years; No previous osteoarthritis treatment with local hyaluronic acid or steroid injections; Life expectancy >1 year (i.e. no cancer, no end stage liver disease, no-end-stage kidney disease, no heart failure New York Heart Association (NYHA) class III or IV); No ongoing pregnancy; Ability to understand and complete clinical and functional scales; No known allergy to hyaluronic acid; No	*(Lisi, C., Perotti, C., Scudeller, L., Sammarchi, L., Dametti, F., Musella, V., & Natali, G. D. (2018). Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clinical Rehabilitation, 32(3), 330-339. DOI: 10.1177/0269215517724193 [doi])* This study (Lisi C 2018) was not been identified in our update search. The team checked and added this to appendix in the overview as similar studies have already been included in systematic reviews added to table 2.

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			acute bacterial skin and soft structure infection of the knee; Written consent. Technique: Patients in the intervention group received three autologous platelet-rich plasma plus calcium gluconate (as activator) intra-articular injections at four-week intervals. Briefly, at the Immunohaematology and Transfusion Service, on each scheduled visit, 20 mL of autologous whole blood was sampled from each patient and 2 mL Anticoagulant Citrate Dextrose Solution, Solution A was added directly through the syringe as anticoagulant; finally, the vial was gently centrifuged at 900 r/min for seven minutes. Platelet-rich plasma was collected. The platelet-rich plasma vial plus activator was immediately shipped to the rehabilitation unit, where intra-articular injection was performed by an experienced physiatrist. Patients in the control group received three intra-articular hyaluronic acid (20 mg/2 mL; Hyalgan; Fidia, Abano Terme, Italy) injections at the same intervals by the same study staff. It was not possible to blind injectors for the different look of the treatments being compared. The infiltration technique used for both groups was the superolateral approach into the suprapatellar pouch. Follow-up: 12 months Conflict of interest/source of funding: none	

6	Consultee 5 Arthrex Ltd		2018 Ahmad (RCT) superior to HA (Int J Rheum Dis. 2018 May;21(5):960-966. doi: 10.1111/1756-185X.13315) Study Type: A single-blinded randomized controlled trial was conducted on parallel treatment groups Country: Egypt Recruitment method: One hundred consecutive patients with primary KOA were enrolled for the study from March 2016 to February 2017. Study population and number: Patients with primary knee OA, Kellgren-Lawrence grade I-III. n=89 (45 in the PRP group and 44 in the HA group). Age and sex: PRP = 68.9% Female with an average age of 56.2 yrs Â± 6.8. HA = 68.2% Female with an average age of 56.8 yrs Â± 7.4. No significant statistical difference. Patient selection criteria: To be eligible for inclusion, the patients had to meet the European League Against Rheumatism 2010 criteria for the diagnosis of primary KOA and had to have radiographic evidence of mild to moderate OA as per the Kellgren-Lawrence classification. The exclusion criteria included age < 40 years, coagulopathies, diabetes mellitus, intake of antithrombotic and antiplatelet drugs and NSAIDs, thrombocytopenia, and history of previous knee surgery or knee disorder other than the current primary OA. Technique: For PRP-IAI preparation, 8 mL of peripheral	This study (Ahmad 2018) identified in our update search is to appendix in the overview as similar studies have already been included in systematic reviews added to table 2.

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			blood was extracted and centrifuged for 9 min at 3500 rpm. The protocol that was used in this study did not include a second centrifugation step. Subsequently, 4 mL of PRP were obtained from each patient and were used for the intra-articular injection. PRP used in this study was not leucocytes-free. For the HA-IAI injection, 2.0 mL (20 mg of HA) of high molecular weight HA were given to patients in the HA group. Post-injection, patients were instructed to an apply icepack on the injected area for 30 min three times a day during the first 2 days, and switch to hot packs on the third and fourth days post-injection. Follow-up: 6 months Conflict of interest/source of funding: The researchers acknowledge that there are no conflicts of interests	

6	Consultee 5 Arthrex Ltd		2018 Buendia Lopez (RCT) superior to HA / to NSAID (J Orthop Traumatol. 2018 Aug 20;19(1):3. doi: 10.1186/s10195-018-0501-3) Study Type: Prospective, randomized clinical trial. Country: Spain Recruitment method: From April 2013 to November 2013, 124 patients were screened and finally 106 were randomized for this study, being the starting point of the groups of treatment from December 2013 through May 2014. Patients were followed up at 6 and 12 months, until May 2015. Study population and number: Patients with symptomatic knee OA Kellgren-Lawrence grade I-II. N= 98 (PRP=33, HA=32, NSAID=33) Age and sex: PRP= 17/33 Female, average age of 56.15yrs Â± 3.00. HA = 17/32 Female, average age of 56.63yrs Â± 2.90. NSAID = 17/33 Female, average age of 57.42yrs Â± 3.10 Patient selection criteria: Eligibility criteria were: symptomatic knee osteoarthritis as defined by the Spanish Society of Rheumatology (based on the Altman osteoarthritis for the knee criteria, combining both clinical and radiographic criteria with a 91% sensitivity and 86% specificity) and Kellgren-Lawrence grade of 1 or 2. Patients were excluded if they had a varus deformity of > 4.2Â° (moderate varus) [17] or a valgus deformity, recent trauma, inflammatory arthritis, history of gastrointestinal or	Thank you for your comments. This study (Buendia Lopez 2018) identified in our update search is added to table 2 in the overview.

			cardiovascular disease, concomitant medications of potent analgesics, corticosteroid, NSAID, anticoagulant or antiplatelet therapy within 12 months of study enrolment; previous surgery to the limb or spine; previous injection to study joint or any active local or systemic infection; systemic disorders with restrictions for the use of NSAID, (diabetes) or potential effect on the knee (rheumatic, metabolic, musculoskeletal or neuropathic disorders). Technique: The PRP group received a 5-ml PRP injection. Each patient had 60 ml of peripheral blood extracted by venepuncture of the antecubital vein. A double centrifugation process was carried out. The first spin step was 1050 rpm for 15 min and for the second spin step, an acceleration of 2000 rpm for 10 min was applied. A total 5 ml of an LP-PRP preparation was obtained, being activated by 1 ml of calcium chloride. Five patients of the PRP group were selected by lot to get a double preparation in order to find out the platelet concentration. The platelet concentration was 1,095,000 Â± 23,200/mm3, which was 3.87 times greater than the baseline concentration. In the HA group, patients were treated with a single high molecular weight preparation (60 mg/2 ml, DurolaneÂ©). The control group received a daily NSAID dose (60 mg etoricoxib, AcoxxelÂ©) for 52 weeks. We coprescribed a proton pump inhibitor (20 mg omeprazole a day). Follow-up: 6 and 12 months	

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			Conflict of interest/source of funding: The authors declare that they have no competing interests.	
7	Consultee 6 Patient	**General**	I have not had the pleasure of receiving platelet-rich plasma injections for osteoarthritis of the knee but I have had Prolotherapy in both of my knees that was administered by a Doctor in [redacted]. Both of my knees are shot and the immediate response was of absolute joy because I could bend and straighten up without any pain or discomfort whatsoever. The dramatic turnaround was unbelievable but was sadly so short lived I felt that I had being conned for it seems it was the Novocaine that did the trick. I did return a couple of weeks later and the result was exactly the same but as soon as I had returned to Dorset so had my discomfort. I have read a number of cases where suffers have had PRP injections and they had gone on to enjoy long term benefits something that I would like to enjoy. My last visit to a specialist was 6 ½ years ago and the specialist just took one look at my knees and said “knee replacements” I asked what the alternative was as I wanted to retain my own knees and his reply was nothing. Consequently I left there and then and keep hoping for a miracle that one day my knees will be cured.	Thank you for your comments and comprehensive account of your clinical experience.