Research Review Disposition of Comments Report

Research Review Title: *Platelet-Rich Plasma for Wound Care in the Medicare Population*

Draft report available for public comment from June 23, 2020 to July 14, 2020.

Citation: Qu W, Wang Z, Hunt C, Morrow AS, Urtecho M, Amin M, Shah S, Hasan B, Abd-Rabu R, Ashmore Z, Kubrova E, Prokop LJ, Murad MH. Platelet-Rich Plasma for Wound Care in the Medicare Population. Technology Assessment Program Project ID 040-353-492.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	General Comments	The report is very succinct, meaningful and defines the populations served. All key questions are well stated.	Thank you for the comments.
Peer reviewer #2	General Comments	Well written and interesting report. Presented in a meaningfully way with one exception. Diabetic foot ulcers are treated differently based on arterial flow. This should be clearer and if possible the RCTs should be separated based on arterial flow exclusion criteria	Thank you for the comments. We realized the importance to stratify by arterial flow status. However, there is not enough information on level of arterial flow in the included papers to include. We have added the need for studies to include vascular data this to KQ#4 results.
Peer reviewer #3	General Comments	This report is clinically meaningful in guiding evidence-based ulcer care, with target population and audience clearly defined and key questions appropriately and expressly stated.	Thank you for the comments.
Peer reviewer #4	General Comments	While there is clinical meaning to the report we do not know the dosing, frequency, or formulation of platelet rich plasma that is most effective. The target population and audience were not clearly	

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			populations and interventions across studies. This can be used as a guide for the setting in which applicability is the most.
Peer reviewer #6	General Comments	The key questions are appropriate and highly relevant for the older population and also younger persons with a long duration of diabetes. The report is clinically meaningful for treatment approach to chronic wounds. It was well done in literature search, analysis, description of the limitations and drawing of conclusions. The literature has progressed to the point where a few conclusions can be drawn in a limited indication. This report should be useful for clinicians and other decision makers.	Thank you for the comments.
Peer reviewer #7	General Comments	The report was well written with clearly defined key questions and target	

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		The key questions are clear and appropriate and clarify many of the studies' problems with patient cham	

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		the 108 pages of appendices eq. Table P.1.1	is much shorter and more focused. The risk of bias of the included studies has been included in the evaluation of strength of evidence (SOE). The repetition of the report (e.g. evidence summary, abstract, key points, main message) is necessary as some audiences may only read a part of the report.
Public reviewer #1 – Susan Foncannon (Retired RN)	General Comments	I only have general comments as I feel that this study is not only incomplete but also lacking in organization and basic clinical trial methods. I however do feel that with proper methods a viable conclusion could be submitted. This study needs to coordinate with a Home Health agency that cares for many wound care patients and wound care centers that also care for patients that are needed for this study. Like in any medical setting coordination of care must be maintained through various care givers so the group of patient's could be followed through any entity and appropriate conclusions could be made.	
Public reviewer #3 - Jassy	General Comments	Redacted	Commenter provided positive testimony about individual experience in contacting provider about

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		Leucopatch is not PRP as defined in this review where the definition is the fraction of blood plasma from a patient's peripheral blood that contains higher and cytokines, and is delivered as a preparation of aqueous suspension blood. Thus Leuocpatch which is a unique "patch" of platelets, leucocytes and fibrin, and is not an aqueous	

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(Reapplix Inc.)		*platelet-rich plasma (PRP) in lower extremity diabetic ulcers.* Comment: Due to the unclear patient benefit of surrogate markers of effect (e.g., wound area change) complete wound healing is the only United States Food and Drug Administration (FDA) recognized primary clinical trial end point (https://www.fda.gov/media/71278/download). Only 9 of 11 RCT studies had complete healing as an outcome (761 pts), including 269 pts (35%) from the study by Game 2018 (Reapplix is the manufacturer of the 3C Patch, the PRP technology also known as LeucoPatch evaluated in Game 2018). Of the studies that had complete healing as an outcome, the remaining study sizes ranged from 14 to 129 pts (Average 62). Beyond study size, study quality was highly variable. Of the 4 studies (n=488) assessed to have the least risk of bias which the authors characterized as moderate 55% of patients came from Game 2018. We believe the high impact of the Game 2018 study on the directionality and magnitude of the overall assessment should be emphasized in the final report.	in multiple parts of the report (Appendix Table P). We already included structure/form as an important characteristics in the report. The aforementioned product is produced from whole blood without anticoagulant by centrifugation. The content and mechanism of action of the product is not different from other PRP products. The gel structure is also one of the types discussed. In addition, it would be unfair to other products if we mention a product that is fundamentally not different. Heterogeneity of the products and the effect on generalizability has been discussed in Applicability and Limitations. Lastly, we do not see a reason to emphasize a certain study.

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		Although several PRP wound care technologies are currently available, the 3C Patch differs from other PRP products in several key respects, such as composition, structure and mechanism of action, production method, and positioning in clinical guidelines. Given the diversity of PRP technologies and treatment regimens, we encourage the authors to include wording that cautions against generalizing these data and conclusions to all Autologous platelet-rich plasma (PRP) [the fraction of blood plasma from a patient's peripheral blood that contains higher than baseline concentrations of platelets] based products. Re. KQ 2. The diversity of PRP preparations (see above) and the challenges in extrapolating clinical efficacy between	

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Peer reviewer #4	Introduction	P1 #2. current treatment modalities. First sentence does not make sense. Current treatment modalities focus on treatment of underlying disorders and good wound care to promote healthy granulation tissue. For diabetic foot ulcers, this involves restoring perfusion, offloading pressure, wound debridement, treating infection, optimal glycemic control and good wound care. For venous ulcers, compression, debridement, treatment of venous reflux, and good wound care are important. For pressure ulcers, management of pressure, friction, shear and moisture in addition to good wound care are critical. Unfortunately many studies of novel therapies do not address these standards of care adequately.	We appreciate the recommendation and have incorporated the text in our report. Thank you!
Peer reviewer #6	Introduction	The framework of the biology of non-healing	

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		PRP effectiveness in the past; i.e. some RCTs but no meta-analysis, overall effectiveness of PRP on wound healing outcomes has not been characterized. Also notably this introduction is very much "bench research" focused rather than clinically focused; depending on the intended audience it might be helpful to reduce the description of PRP acquisition (or move to methods)	actions. It is the nature of biologics therapy that understanding of the basic science is required in order to understand the potential effects. More clinical focus has been placed in the discussion Thank you for the comments. In this systematic review and meta-analyses, we summarized the findings for all relevant RCTs overall (the results section in the report) and individually (Appendix Table J). We felt it's unnecessary to discuss individual studies in the discussion.
Peer reviewer #9	Introduction	This report usefully applies strength of evidence criteria to the range of studies included here, which report a much higher efficacy and significance to PRP than is perhaps warranted (particularly in regard to rate of healing), based upon bias and control. This report is particularly useful in its analysis of the included studies shortcomings, including "inadequate description of offloading and wound care procedures, wound characteristics, platelet-rich plasma	Thank you for the comments. We graded the strength of evidence based on the methodological limitations of the studies; precision; directness of the evidence to the KQs; consistency of results; and the likelihood of reporting and publication bias. We agree that a statistically significant finding doesn't

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		formulation techniques, concentration and volume; inadequate length of follow-up; and lack of stratification by comorbidities and other patient characteristics.”	warrant a high strength of evidence.
Peer reviewer #10	**Introduction**	P20 “P” is thought to contain [illegible] weak description of the intervention. P20 Limited information on the different delivery methods is given.	[illegible] Application methods further explained in the text
Public reviewer #3 -			

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		findings based on specific PRP products to PRP products more broadly.	
Peer reviewer #1	Methods	I thought the search criteria was appropriate and well stated. The definitions or diagnostic criteria for outcomes measured was appropriate. The statistical methods used were appropriate.	Thank you for the comments.
Peer reviewer #2	Methods	Well done	Thank you for the comments.
Peer reviewer #3	Methods	The inclusion and exclusion criteria are sound, the search strategies plausible, outcome measures and statistical methods appropriate	Thank you for the comments.
Peer reviewer #4	Methods	Inclusion/exclusion criteria are justifiable Search strategies are explietus14 (ou)4 (t)2 (r)eg	

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		adverse effects are salient to patients and notable omissions in this field.	
Peer reviewer #7	Methods	The Methods section was very well written with appropriate inclusion criteria and assessment method. Further clarification of weight mean difference (WMD) in Methods section (page 8) vs weighted mean difference and it's use in Table 3 (pg 13) would have been helpful as it was stated that a meta-analysis was not possible, so uncertain what WMD vs. observed difference in healing time was meant to convey. There were 4 individuals studies, with individual WMD for time to completely heal wound.	Thank you for the comments. Weighted mean difference (WMD) means the mean difference between the intervention and the comparison when the same outcome scale was used. We clarified the meaning of WMD in the methods section.
Peer reviewer #8	Methods	-"Lower extremity diabetic ulcers" should be changed to "diabetic foot ulcers" in the methods and throughout the manuscript -Inclusions/exclusions are appropriate -For outcomes, "Time to complete wound closure" should be re-termed "Time to complete wound healing" -Amputation needs to be better defined - is this major amputation, minor amputation, or both?	Lower extremity diabetic ulcer was used because our search strategy included all locations in lower extremity. For terminology consistency, we changed 'time to complete wound healing' to "Time to complete wound closure". Studies did not specify amputation in terms of major or minor
Peer reviewer #9	Methods	The inclusion/exclusion criteria are well-justified, and encompass the most important parameters of high strength of evidence, including:	Thank you for the comments

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		adult patients (18 years and older) with lower extremity diabetic ulcers, lower extremity venous ulcers, pressure ulcers, or mixed of these three etiologies; 2) received autologous platelet-rich plasma or autologous platelet lysate; 3) compared with any other wound care without platelet-rich plasma or autologous platelet lysate; 4) reported outcomes of interest; 5) Randomized controlled trials (RCTs) and comparative observational studies; and 6) published in English. We excluded wounds of other etiologies, including traumatic wounds, peripheral arterial disease (PAD) related wounds in nondiabetics (i.e., diabetic wounds are to be included regardless of the presence of PAD, but PAD alone wounds without diabetes are a reason of exclusion), and acute wounds (<4 weeks). The inclusion of any other types of wounds would have muddied the findings, because the histopathology of other cutaneous wounds are fundamentally different. Search strategies are clear and exhaustive. The outcome measures are clearly defined and statistical measures well-conceived and appropriate.	

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		formation was enough for reconstructive plastic surgeries before the end of the 12th week) healing grade 1 was also defined. Despite this the study has been assigned a ROB like that of Game 2018. On this basis we question the weight assigned to the Li study in the appendix P fig P.1.1 forest plot.	encompasses all stages of wound, including the optimal outcome of complete closure or complete healing. The reason to assign moderate (i.e., some concerns) to Game 2018 is that “Participants, caregivers, and site investigators were not masked” and significant more patients in the PRP group reported protocol violation than those in the control group (20 vs. 9; OR=2.40; 95% CI: 1.05 to 5.48). With these issues, we rated moderate for “bias due to deviations from intended interventions”. Following the Cochrane’s guidance, the overall risk of bias was also rated as moderate as none other domains were rated high risk of bias.
Public reviewer #4 - Rasmus Lundquist (Reapplix Inc.)	Methods	Re. Key Question 2. What types of PRP preparations are currently being marketed in US medical practices (gel, liquid, etc.)?	The section was re-written in a way it more clearly describes the currently available products and the systems for manufacturing

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		P30 The wound sizes in Karimi 2016 also don't make sense clinically – 12.70 +/- 14.86 mm2 with a depth of 9 mm2. These would be very small almost puncture wounds. This study is not in PubMed. Given its prominent role in evaluating ROB, the numbers should be verified.	sensitivity analysis and found no significant changes on outcomes (Appendix Table O). We agree that the study (Karimi, 2016) reported conflicting and potentially anomalous results in different sections of the paper. We added a sensitivity analysis by excluding this study (Karimi

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			candidate for this therapy. This is already well acknowledged as a limitation.
Public reviewer #2 - Professor Fran Game (University Hospitals of Derby and Burton NHS Foundation Trust)	Results	Not withstanding that the literature search includes the leucopatch study which we feel is poorly defined as "PRP", we are extremely concerned about the assessment of bias. The Lueopatch study was assessed as overall "moderate risk of bias" . Whilst accepting that no study is perfect we cannot understand some of the ROB assessments, especially in comparison to other RCTs included in the review. We cannot understand how in the domain "deviations from intended interventions" which would usually imply a per protocol but no ITT analysis, or considerable cross-overs, that the Leucopatch RCT has been assessed as moderate ROB (and thus an overall moderate ROB). A pre-specified ITT analysis was presented in the paper, as well as a per-protocol analysis. We can only think that the 3 patients who withdrew immediately post randomisation, all of whom were in the usual care arm, have been misconstrued as meaning an ITT analysis was not	We used the Risk of Bias 2.0 tool by the Cochrane Collaboration to evaluate the risk of bias, which is the most common tool used for quality appraisal for RCTs. We follow the Cochrane's guidance to rate the overall risk of bias, which was added in this revision to clarify the approach. "Deviation from the intended interventions" is also referred to performance bias, which could rise due to failure to implement the protocol interventions as intended or non-adherence by participants to the interventions. The reason to assign moderate (i.e., some concerns) to Game 2018 is that "Participants, caregivers, and site investigators were not

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		includes important items such as assessment of arterial disease, usual care including offloading and whether the outcomes were those that would be expected from similar patients in cohort studies. This provides the granularity of risk of bias which is missing in this review. KQ4: what best practices in study design could be used to produce high quality evidence on PRP The IWGDF has produced and published a guide to this as above (Jeffcoate et al, Lancet Diabetes and Endocrinology) and this could be referenced here. However in terms of diabetic foot ulcers the major confounders are wound size and depth , the presence of arterial disease, site of ulcer (forefoot vs hind foot), infection and end stage renal disease. None of these are mentioned.	evaluated in bias from the randomization process. For observational studies, we

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Public reviewer #3 - Jassy	Results	Redacted	Commenter provided positive testimony about individual experience in contacting provider about successful treatment for personal medical problem
Peer reviewer #1	Discussion	Implications for major findings were clearly stated, The limitations of the studies reviewed were described adequately to include the lack of participants of color. No important literature was excluded.	Thank you for the comments.
Peer reviewer #2	Discussion	Well done. It is confusing that heal data was moderate but time to heal was low. It would be very hard for heal to be significant without time to heal also being significant. If one is low evidence then both should be low	To rate the strength of evid


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		The absence of a clear standard of care (i.e. a protocol) to use as a control is a clear problem in study design, and should be addressed in future clinical trials.	
Peer reviewer #10	Discussion	P8 Add lack of blinding for outcomes and small sample sizes. P39 Why are more prospective observational studies needed? They seem to add very little to understanding the efficacy of PRP. Trials also need clearly defined standard of care including off-loading and debridement. Glucose control is also a confounder.	Addressed in best practice in study design. Well stratified observational studies are of important value
Peer reviewer #10	Discussion	Little thought was given to the future research section besides listing standard problems with clinical trial design. Clearly one study (Game 2018) stood out as the best in design, execution, ROB, sample size and journal, but no effort was made to differentiate it from unblinded, poorly described studies with few participants.	We have described the limitations of the current literature and future research needs for better study design, including these listed features. It is expected that such recommended features would be congruent with generic standards of good clinical trial design and execution.
Public reviewer #2 - Professor Fran Game (University	Discussion	At the top of page 42 it is said that "unfortunately, complete healing is hard to accomplish in the majority of patients with standard care measures" and the cohort study used to support this	We changed the reference.

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		In contrast, the IWGDF guidelines do not support the use of autologous platelet gel (GRADE strength of recommendation: weak; quality of evidence: low): We suggest not using the following agents reported to improve wound healing by altering the wound biology: growth factors, autologous platelet gels, bioengineered skin products, ozone, topical carbon dioxide and nitric oxide, in preference to best standard of care.	The included studies used PRP as adjunctive treatment.
Public reviewer #4 - Rasmus Lundquist (Reapplix Inc.)	Discussion	Re.	


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Public reviewer #5 – Scott Haag, JD, MSPH (American Podiatric Medical Association)	Discussion	The efficacy and availability of this treatment for Medicare patients is extremely important to our members as many of them use it for treatment of ulcers in patients with diabetes, a group that is at high risk for other complications and ultimately for amputations. We have heard from a number of our members who are proponents of PRP and amnionic stem cell treatments, and feel this will eventually become a mainstay in the treatment of diabetic, venous stasis, and pressure ulcers in the future. Future peer-reviewed studies may well prove this out. The technical assessment is well written and reviewed. As the assessment indicates, there are still some concerns about the level of evidence for these treatments at this time, and more research needs to be done to support PRP therapy becoming the standard of care. Recognition and coverage of these treatments by Medicare and other payors may likely have the beneficial effect of stimulating the creation of additional quality studies. Naturally, there may need to be more standardization in the use of PRP for diabetic foot ulcers (DFU) before the treatment is more widely recognized and	Thank you for the comments.

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		accepted. In addition, the acceptance of PRP generally for DFUs may spur innovation in the development of additional techniques and products.	
Public reviewer #5- Scott Haag, JD, MSPH (American Podiatric Medical Association)	Discussion	This assessment determined, among other things, that the evidence is insufficient to estimate an effect of autologous PRP on wound healing in individuals with lower extremity venous ulcers. That is not unexpected as our members report that those wounds are particularly tough to heal, regardless of treatment. On the other hand, autologous PRP increases complete wound healing (moderate strength of evidence (SOE)), shortens healing time (low SOE), and reduces wound size (low SOE), in individuals with lower extremity diabetic ulcers. Our members that utilize PRP treatment report that this is consistent with their experience with the procedures. With respect to pressure ulcers, in which the assessment determined that the evidence is insufficient to estimate an effect of autologous PRP on wound healing, it may be too early to dismiss PRP. If adequate off-loading is not performed for these ulcer types, regardless of use of acellular dermal matrices, amnionic stem cells,	Thank you for the comments. We agree that future research needs to evaluate PRP in pressure ulcer (KQ 5).

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		hydrolyzed collagen, silver dressings, etc., the likelihood of healing is low. Consequently, it may likely be too soon to dismiss PRP for pressure ulcers until off-loading is effectively included as part of the treatment protocol. One aspect that may have been excluded from this assessment or that could be considered for future assessments is the musculoskeletal applications for PRP. Our members report that they also use PRP for athletic overuse injuries. That experience leads some to conclude that any opportunity to increase growth factor concentration in an ulcer wound bed would be generally beneficial, and likely assist in expediting wound healing. AHRQ may consider an additional technical assessment to consider the literature or efficacy regarding use with musculoskeletal conditions.	
Public reviewer #5 - Scott Haag, JD, MSPH (American Podiatric Medical Association)	Discussion	We agree that further studies are necessary, and APMA through its Clinical Practice Advisory Committee will continue to explore opportunities for us to collaborate with other stakeholders. Some APMA members have had preliminary discussions with their respective academic institutions about being involved 0.00out	

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Public reviewer #2 – Professor Fran Game (University Hospitals of Derby and Burton NHS Foundation Trust)	Appendix	ROB assessments As above: Game et al (2018) was assessed as overall "moderate risk of bias" . Whilst accepting that no study is perfect we cannot understand some of the ROB assessments, especially in comparison to other RCTs included in the review. We cannot understand how in the domain "deviations from intended interventions" which would usually imply a per protocol but no ITT analysis, or considerable cross-overs, that this RCT has been assessed as moderate ROB (and thus an overall moderate ROB). A pre-specified ITT analysis was presented in the paper, as well as a per-protocol analysis. We can only think that the 3 patients who withdrew immediately post randomisation, all of whom were in the usual care arm, have been misconstrued as meaning an ITT analysis was not performed. This was a pre-specified ITT and the protocol was published prior to trial completion. The effect of keeping the 3 patients in the ITT analysis would have meant they would all be marked as unhealed (also prespecified), which would have biased towards the intervention. It is acceptable practice in order to reduce bias to remove the	We used the Risk of Bias 2.0 tool by the Cochrane Collaboration to evaluate the risk of bias. We follow the Cochrane's guidance to rate the overall risk of bias, which was added in this revision to clarify the approach.

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		participants for analysis if they withdraw consent to data collection having	

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Peer reviewer #6	Quality of the Report	Superior	Thank you for the comments.
Peer reviewer #7	Quality of the Report	Good	Thank you for the comments.
Peer reviewer #8	Quality of the Report	Superior	Thank you for the comments.
Peer reviewer #9	Quality of the Report	Superior	Thank you for the comments.
Peer reviewer #10	Quality of the Report	Fair	Thank you for the comments.
Peer reviewer #1	Clarity and usability	I thought it was laid out clearly and the comparison report set perspective.	Thank you for the comments.
Peer reviewer #2	Clarity and usability	Well done	Thank you for the comments.
Peer reviewer #7	Clarity and usability	p. 18, line 48: Minor typo "response" vs. "respond"	Corrected.
Peer reviewer #8	Clarity and usability	There are a LOT of appendices to go through - it would be helpful to pare those down a bit so that readers can more easily find data of interest	It is difficult to reduce content without adequately addressing Key Questions.
Peer reviewer #10	Clarity and usability	Minimal footnotes. Data is dumped in poorly organized tables and text. Conclusions are stated with no explanations except for references to methods papers.	The report is organized in a standard way where we have key questions, summary of evidence and then conclusions, organized per wound type, as a second layer of subheadings. We understand that this doesn't

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