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. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. HHSA290201500013I.) Rockville, MD: Agency for Healthcare Research and Quality. September 2020. Available at: http://www.ahrq.gov/research/findings/ta/index.html.

Comments to Draft Report

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This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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 stated. The key questions were appropriate and explicit	Thank you for the comments. Due to the poor reporting of the included studies, we were not able to evaluate dosing, frequency, and formulation. We presented these issues as the limitations. In the revised report, we added a statement to the applicability section that describes the average description of

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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 audience, though somewhat broadly defined as healthcare providers, insurers, and healthcare networks. Overall, with minor clarifying edits, this document will be of value to the target audience. Through no fault of the authors, there is significance risk of bias with these studies and with the variability in application of this therapy, which the authors did a very good job of describing.	Thank you for the comments.

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Peer reviewer #8	General Comments	Overall very thorough and well written. As mentioned below the introduction is a bit too basic science focused compared to the rest of the article, which appears to be more clinically focused.	Thank you for the comments. As a new therapy, we felt that the mechanism of action needs to be presented in some detail.
Peer reviewer #9	General Comments	This systematic review is clinically meaningful and will provide assistance to clinicians, health system leaders, policy makers, and patients (particularly those with diabetes) in making well-informed decisions about the enormous promise and potential of autologous platelet-rich plasma as a treatment option By evaluating the overall effectiveness of platelet-rich plasma as a treatment of lower extremity diabetic ulcers, lower extremity venous ulcers, and pressure ulcers, while also evaluating the platelet-rich plasma content, carriers, concentration and dosage, frequency and duration of applications (e.g. centrifuge type, centrifuge speed, centrifuge time, radius of rotor), this review offers a much-needed insight into the strength of evidence of the existing randomized controlled clinical trials and comparative observational studies on the topic.	Thank you for the comments. We have added standardized wound classification to KQ#4

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		The key questions are clear and appropriate and clarify many of the studies' problems with patient characteristics; types of PRP preparations, formulations, and applications; the risk of bias; and best practices for study design to produce highest quality evidence. Key Question 1.c.i. is of particular interest (regarding standard of care in the comparator groups); the absence of any protocol to create a meaningful standard against which to measure the effectiveness of an experimental therapy like PRP is vitally important and is a key finding of this review. There is a pressing need for a clear, standardized protocol for treating these types of wounds.	
Peer reviewer #10	General Comments	My comments for the entire review will focus on diabetic foot ulcers and the main paper using the pdf page numbers. The key questions are appropriate and stated. The target audience is not clear and does not appear to be clinicians, but policy analysts. The overall quality of the studies is poor so combining them to draw conclusions is problematic. Overall, repetitious report that is hard to read. The main findings are buried in	The report was commissioned by CMS but the target audience can also include clinicians. It is true that the studies have many limitations which we have highlighted. We agree that the large report may not be user friendly for individuals with limited time or for clinicians; hence, the evidence summary section

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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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			successful treatment for personal medical problem
Public reviewer #6 – American Geriatrics Society	General Comments	Based on low or moderate strength of evidence in individuals with lower extremity diabetic ulcers, autologous platelet-rich plasma increases complete wound healing, shortens healing time and reduces wound size. The evidence is insufficient to estimate an effect of autologous platelet- rich plasma on wound healing in individuals with lower extremity venous ulcers or pressure ulcers. The American Geriatrics Society believes that there is a need for more high powered randomized controlled trials that predominantly include older adults are needed before this mode of treatment can be endorsed as a standard of care among Medicare patients who are seeking advanced and safe wound care therapy. For those trials, efforts to homogenize the production method variables are necessary to better evaluate the efficiency and adverse effects of the products. Trials should look at other outcomes, including whether or not lower extremity amputation was prevented in	Thank you for the comments. We agree that high quality randomized controlled trials, including older adults, are needed to further evaluate PRP, which we presented in KQ4 (page 21) and in the discussion applicability section.

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		diabetics; was wound healing faster than using existing modalities.	
Public reviewer #6 – American Geriatrics Society	General Comments	There is a need for more comparative effectiveness research that is focused on whether this newer, more expensive therapy is more effective than existing therapies. The language of the conclusion regarding use of autologous platelet-rich plasma for patients with venous ulcers of pressure ulcers should be modified to explicitly recommend that there is not sufficient evidence to warrant using this new therapy to treat these conditions.	Thank you for the comments. We agree that high quality randomized controlled trials are needed to further evaluate PRP, which were presented in KQ4 (page 21). The language of the conclusions and main points have been revised accordingly.
Peer reviewer #1	Key Messages	Key messages were explicit and applicable.	Thank you for the comments.
Public reviewer #2 – Professor Fran Game (University Hospital of Derby and Burton NHS Foundation Trus)	Evidence summary	Statement 1. Autologous platelet-rich plasma increases complete wound healing (moderate strength of evidence, SOE), shortens healing time and reduces wound size (low SOE), in individuals with lower extremity diabetic ulcers. Conclusions about other important outcomes such as hospitalization, amputations and wound recurrence, are not possible. On behalf of the co-authors of the RCT of Leucopatch on DFUs (Game et al 2018) we are concerned that this RCT is even included in this review of PRP.	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.

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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 than baseline concentrations of platelets including concentrated growth factors and cytokines, and is delivered as a preparation of aqueous suspension obtained by centrifugation of whole blood. Thus Leuocpatch which is a unique "patch" of platelets, leucocytes and fibrin, and is not an aqueous suspension, is fundamentally different from the other included study. As it contributed more participants than any other single study is of some concern in drawing these conclusions. We suggest a sensitivity analysis without this study to ensure the conclusions remain the same.	Therefore, no sensitivity study is justified.
Public reviewer #3 - Jassy	Evidence summary	Redacted	Commenter provided positive testimony about individual experience in contacting provider about successful treatment for personal medical problem
Public reviewer #4 – Rasmus Lundquist	Evidence summary	*Re.* *Lower extremity diabetic ulcers* *Twelve RCTs8, 9, 12, 14-22 and 1 comparative observational study26 with 1,010 patients evaluated autologous*	We appreciate your comment. Diversity of different types of PRP in preparation method and content has been discussed

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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 PRP types with such disparate characteristics should be mentioned. Re. KQ 4 Suggest adding structure or form to the sentence:	

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		Future studies should focus on the characterization of the PRP products, with clear description of structure/form, platelet concentration, key growth factor content, and leukocyte count.	
Public reviewer #6 - American Geriatrics Society	Evidence summary	There are significant limitations in how to apply the evidence when caring for older adults given the lack of inclusion of older adults in the trials. In general, the section would benefit from an explicit discussion of the lack of inclusion in older adults in the clinical trials that were reviewed in the development of this report.	Age range including older adults were reported. The fact that the mean age were not at the older adult age range does not mean older aged adults were excluded the study population. We recognize that older adults are relatively underrepresented in trials and have included the recommendation of this subpopulation in future studies.
Peer reviewer #1	Introduction	The introduction was well done however, I thought after reading it that more pressure ulcer patients were included in studies.	Thank you for the comments. Pressure ulcer was intended to be analyzed to full extent, but only two trials were found and included.
Peer reviewer #2	Introduction	Well done	Thank you for the comments.
Peer reviewer #3	Introduction	The introduction is concise, informative, and well-written.	Thank you for the comments.

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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 wound might be helpful for this section. Around p. 20, line 18. The interruption of orderly healing, and the role of cells and molecules might then be introduced. Otherwise it is quite a nice introduction that covers the bases needed for the rest of the report.	Biology of non-healing wound is summarized in background
Peer reviewer #7	Introduction	The introduction was very clear.	Thank you for the comments.
Peer reviewer #8	Introduction	Overall well written but could perhaps use a couple of sentence putting into context what has been published on	Introduction of a new treatment needs description of the mechanism of

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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 "PRP is thought to contain . . ." is a weak description of the intervention. P20 Limited information on the different delivery methods is given.	'is thought to' is removed. Application methods further explained in the text
Public reviewer #3 - Jassy	Introduction	Redacted	Commenter provided positive testimony about individual experience in contacting provider about successful treatment for personal medical problem
Public reviewer #4 - Rasmus Lundquist (Reapplix Inc.)	Introduction	Re. *In summary, this systematic review evaluates the overall effectiveness of treatment of lower extremity diabetic ulcers, lower extremity venous ulcers, and pressure ulcers with PRP, as well as the impact of PRP content, carriers, dosage, frequency and duration of application.* Comment: As outlined above, there are different PRP contents and constructs. As a result, we suggest including a statement on the risk of extrapolating clinical	This potential impact was addressed by subgroup analysis. The issue of applicability was addressed in the discussion.

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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 explicitly stated and logical Outcome measures are appropriate I cannot comment on statisitical methods	Thank you for the comments.
Peer reviewer #6	Methods	The inclusion and exclusion criteria are well justified and reasonable. The complete closure of a wound is endorsed by both CMS and FDA and is readily apparent to most observers; it is an excellent outcome measure. It is unfortunate that some of the other outcome measures haven't been adopted by the trialists in this field because the review suffers from and points out those gaps. In particular, hospitalization, quality of life and	Thank you for the comments. The need for standardized wound outcome measures is included in KQ#4.

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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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		It's an extraordinary review with a focus on excellent science of the highest evidentiary standards.	
Peer reviewer #10	Methods	P26 Briefly describe how the overall ROB is determined.	Revised in the methods section.
Public reviewer #3 - Jassy	Methods	Redacted	Commenter provided positive testimony about individual experience in contacting provider about successful treatment for personal medical problem
Public reviewer #4 - Rasmus Lundquist (Reapplix Inc.)	Methods	Re. *Assessment of the Risk of Bias of Individual Studies* Comment: In our view the use of the three categories (High, Moderate, Low) Risk of Bias 2 tool does not adequately separate the included studies in terms of study validity and quality. As an example, a major flaw in the Li 2015 study is the definition of healing: Complete healing (reduction rate of 100%) was defined as complete epithelial cover in the absence of discharge. Apart from that, in case the wounds were suitable for skin flap transplantation (if only granulation tissue	The Risk of Bias 2.0 tool by the Cochrane Collaboration was the latest version of the original Risk of Bias tool for randomized controlled trials. We follow the Cochrane's guidance to rate the overall risk of bias, which was added in this revision to clarify the approach. Wound closure and complete healing have both been defined as 'complete epithelialization' in studies that chose to adopt either of the terms. Wound healing has been used to describe the progress of wound that

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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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		To clarify that the 3C Patch does not add any components to PRP but provides structure we would suggest updating: Reapplix, Inc markets a patch product for delivery of PRP for treatment of chronic wounds: Reapplix 3C patch (Reapplix Inc/US; Southlake, TX) https://reapplix.com/about-3c-patch/. To: Reapplix, Inc markets a PRP gel with a 3-layered patch structure releasing cells to the wound bed for the treatment of chronic wounds: Reapplix 3C patch (Reapplix Inc/US; Southlake, TX) https://3cpatch.com.	those products in the context of FDA regulation
Peer reviewer #1	Results	The amount of detail in the results section was appropriate even though they were dependent on what each study reported. I do not know of any studies that were conducted during the time period that should have been included.	Thank you for the comments.
Peer reviewer #2	Results	Well done. As noted above would consider separating DFU studies based on flow	Thank you for the comments. We added the need to describe arterial flow status in KQ4 in the results.
Peer reviewer #3	Results	Sufficient amount of details of studies are clearly provided. Key messages are	Thank you for the comments.

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		explicit and applicable. No relevant studies were overlooked.	
Peer reviewer #4	Results	In general the amount of detail is acceptable. Are the characteristics of the studies clearly described? yes Are the key messages explicit and applicable? yes Are figures, tables and appendices adequate and descriptive? Yes Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? no	Thank you for the comments.
Peer reviewer #6	Results	The detail level is about right. The conclusions are supported by the results and can be understood from the key tables and figures. I know of no study that was missed.	Thank you for the comments.
Peer reviewer #7	Results	On page ES-3, line 20: no range of number of days or WMD shortened for wound healing was given, and possibly could have been reported as a "range" in Results section.	Added “range.”
Peer reviewer #7	Results	Page ES-3, line 50: Sixty percent of the pressure ulcers treated with saline are either less than stage 4, or more than stage 4. (same on page 16). Additional description in the Results section would be of value. Reader should not be required to look in Appendix D to understand that 60% were mostly stage 2 with some at stage 3.	We revised the sentence.

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Peer reviewer #8	Results	KQ1 is listed as "what are the patient characteristics . . ." - this is actually KQ1d, whereas KQ1 overall is about the efficacy of PRP (page 29, lines 20-25). Would clarify this in the way the headings are listed in the Results -Would recommend all or part of Appendix Figure P be included in the main document as it is a nice visual representation of the findings -For the PRP application in the venous ulcers - was this accompanied by compression similar to the non-PRP management?	Corrected. We prefer to put the forest plots in Appendix to reduce the length of the report.
Peer reviewer #8	Results	-A meta-analysis of the efficacy of PRP for all wound studies (diabetic foot ulcers, venous ulcers, pressure ulcers) was not performed. Was this due to severe bias? Would be worth discussing why and overall assessment was/could not be made.	It is clinically not relevant due to different mechanism
Peer reviewer #9	Results	The key messages are lucid and the figures, tables, and appendices adequate and descriptive. The authors do an excellent job of describing the characteristics of the studies and clearly represent their shortcomings (e.g.: offloading, PRP formulation techniques, concentration and volume, length of follow-up, and lack of stratification by comorbidities). Of particular note is the absence of a clear	Thank you for the comments.

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		standard of care against against which the efficacy experimental treatments might be measured. This review clarifies the ways in which standard of care varies from clinic to clinic and from patient to patient. I am not aware of new studies that should have been included but weren't.	
Peer reviewer #9	Results	One study of questionable value is: Karimi R, Afshar M, Salimian M, et al. The effect of platelet rich plasma dressing on healing diabetic foot ulcers. Nurs Midwifery Stud. 2016;5(3):e30314. The results of this study seem anomalous (diabetic foot ulcer surface area decreased approximately 12 cm after three weeks). Clearly, future research will be needed into the optimal formulation and application of PRP, the development of standardized treatment protocols (including optimal offloading techniques).	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 et al, 2016) and found no significant changes in the results.
Peer reviewer #10	Results	P30 An average wound size of 0.019 cm2 does not make sense clinically and is likely an error in the table because it does not fit the rest of the article (Milek 2017)	We doubled checked and found the number (0.019) was what the study (Milek, 2017) reported. As we also had some concerns about this study, we conducted

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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 et al, 2016) and found no significant changes in the results (Appendix Table O).
Peer reviewer #10	Results	P30 Provide the study reference number for the ones that have ROB in the indicated areas. Describe what is a high deviation. Game 2018 does not appear to have a high deviation from intended intervention	High risk of bias means a study suffers important risk of bias in the evaluated domain. 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

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			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 and one domain was rated as moderate risk.
Peer reviewer #10	Results	Appendix P101 How is the % Weight determined? Appendix P106 Ref 3 is to a supplement, when the full study was published in Lancet. No key message was applicable. PRP was given a moderate SOE for diabetic foot ulcers, but nothing could be learned on which patient would benefit from this treatment.	We used the DerSimonian-Laird random effect model with Hartung-Knapp-Sidik-Jonkman variance correction to pool the outcomes from the studies. The weight was the inverse variance of the outcome. % weight for a study was the weight from study divided by the total weight from all studies in the meta-analysis. We corrected the reference. The reviewer is correct in identifying that the literature is limited in terms of choosing patients who are

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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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		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 participants for analysis if they withdraw consent to data collection having had no trial procedures/intervention as long as this is pre-specified. This is still an ITT. As 256 patients were included we cannot think that this creates a moderate risk of bias. To put this in context the study by Karimi 2016 was also assessed as being at moderate risk of bias, yet this paper presented no ITT analysis, only a per protocol, there is some doubt as to whether there was true randomisation, and important baseline variables which could have influenced outcome such as arterial status and offloading are not described at all. The International working group of the Diabetic Foot (IWGDF) has published a 21 point checklist to aid assessment of studies related to the diabetic foot which	masked" and significantly 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, Figure 1). 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. For Karimi 2016, we rated "moderate risk" for randomization process, missing outcome data, and measurement of outcomes. The Cochrane Risk of Bias tool has addressed the issues listed in the comments (e.g. arterial disease) through evaluating different domains in the RCTs. For example, the baseline imbalance (for arterial disease) was

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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 used the Newcastle-Ottawa Scale. The confounder issues were evaluated as a part of “comparability between groups”. We added the citation for the IWGDF paper. For lower extremity diabetic ulcers, we included 14 RCTs and 1 observational study. For RCTs, the confounders are typically not an issue as the control and the intervention are theoretically balanced and have been evaluated using the Cochrane Collaboration Risk of Bias 2.0 tool. For the observational study, we already rated as high risk of bias. However, we agree that confounders can be an issue and discussed the heterogeneity as a limitation.

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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 evidence (SOE), we used five domains: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication

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			bias. Different studies contributed to two outcomes, the SOE ratings were different.
Peer reviewer #3	Discussion	The implications of the major findings are clearly stated, limitations adequately described, future research needs identified. This information helps facilitate translation into new research.	Thank you for the comments.
Peer reviewer #4	Discussion	Overall the implications and limitations of the studies are addressed. There are certain wound characteristics which can impact healing that are not discussed such as location of DFUs. It is known for example that forefoot ulcers are easier to heal than mid or hindfoot ulcers.I am not sure if this data can be teased out from the studies. Debridement and standards of care are not clearly defined in some of the studies .	Included studies unfortunately did not provide enough location information to analyze. We included this need in KQ#4. We agree that standard of care are not clearly defined in some of the studies. This is a limitation of this analysis that we have listed in the Limitations
Peer reviewer #4	Discussion	I did not see a future research section. I assume this is Key questions 4 and 5. We need more rigorously controlled studies where all patients are treated with strict standard of care which is explicitly stated. Durability of response is also important.	Future research needs are addressed in KQ 4 and 5. Wound recurrence was added to the future research section.
Peer reviewer #6	Discussion	The limitations are well-described and adequately addressed. The points about how to design better trials are accurate, but this research community has ignored	Thank you for the comments.

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		that same recommendation for quite a while, so unfortunately this may fall on deaf ears. Nevertheless it is adequately described and could translate into improved quality of research in this area.	
Peer reviewer #7	Discussion	Page ES-5, line 25: There is no difference in outcomes for harm, but no statistical power calculation was given for the ability to detect a difference in harm if there was a true difference. A statistical power calculation for harm as an outcome would be of value to readers.	Power calculation is typically used to guide trial development. It's rarely conducted in meta-analysis as it retrospectively collected existing data. However, we agree that power is an issue and added to the study limitations.
Peer reviewer #8	Discussion	Would add a comment to the discussion section about diabetic foot ulcers that studies assessing wound healing outcomes should be reporting wound characteristics with a standardized wound classification (e.g. SVS WIfI score, Wagner score, University of Texas, etc). Without standardized reporting, it is difficult to interpret efficacy results	This could be a point in best practice in future study design. We included this need in KQ#4.
Peer reviewer #9	Discussion	The implications of PRP for lower extremity diabetic ulcers is very clearly stated. There is a pressing need for more RCTs for venous and pressure ulcers. Further research into PRPs implications on pain and infection, in particular, are also needed.	Thank you for the comments.

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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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Hospitals of Derby and Burton NHS Foundation Trust)		statement is a UK study of infected ulcers; infection being one of the predictors of poor outcome. A better reference would be the national diabetic foot audit of England and Wales, a very large data set which includes data on site of ulcer, infection status, ischaemia, neuropathy as well as important diabetes related co-morbidities and is linked to routinely collected NHS outcome data.https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-footcare-audit/2014-2018.	
Public reviewer #4 - Rasmus Lundquist (Reapplix Inc.)	Discussion	Re. *Findings in Relation to What Is Known Lower Extremity Diabetic Ulcers* The International Working Group on the Diabetic Foot (IWGDF) produces international, multidisciplinary, evidence-based Guidance documents to inform health professionals all over the world on the prevention and management of diabetic foot disease. The IWGDF Guidance is written by clinicians, researchers and other experts-in-the-field from all over the world. https://iwgdfguidelines.org/ IWGDF published their 4-yearly recommendation document including single study assessments in 2019-2020:	We used the Cochrane Risk of Bias Tool for Randomized Trials 2.0 and the Newcastle-Ottawa Scale for observational studies, which are the most commonly used tools for appraising risk of bias. The summary of individual studies was listed in Appendix Table D. The IWGDF guidance on reporting standards has been added to KQ#4 in the report.

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		(https://iwgdfguidelines.org/guidelines/guidelines/)(https://iwgdfguidelines.org/wp-content/uploads/2020/03/Vas_et_al-2020-IWGDF-wound-healing-SR.pdf)(https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fdmrr.3284&file=dmrr3284-sup-0003-TablesS1.pdf) This should be commented, and We strongly recommend that the IWGDF guideline referenced be included in the final report.	
Public reviewer #4 - Rasmus Lundquist (Reapplix Inc.)	Discussion	We also encourage the authors to emphasize how the description of PRP preparation technologies are treated differently in these guidelines. The IWGDF guidelines include the following statement supporting the use of the 3C Patch: Consider the use of autologous combined leucocyte, platelet and fibrin as an adjunctive treatment, in addition to best standard of care, in non-infected diabetic foot ulcers that are difficult to heal. (GRADE strength of recommendation: weak; quality of evidence: moderate).	The objective of this systematic review is different from that of a guideline. In addition, the guideline recommendations may consider other factors besides the evidence on effectiveness in making their recommendation, such as values, preferences, resources, etc. We refrain from making recommendations and only summarize the evidence. Summary of clinical guidelines for different PRP preparation technologies is not pertinent to the objective of the study.

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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. Applicability Suggest adding the below wording or similar: The gels represent different subtypes ranging from some with lower platelet contents and added ascorbic acid (Driver 2006, Gude 2019) to one with high WBC levels and a 3-layered construct (Game 2018). Data size and quality (ROB) vary greatly within the category, which suggests that data on the individual technologies should be individually assessed.	This is already addressed in the “Applicability” section.
Public reviewer #4 - Rasmus Lundquist	Discussion	Re: KQ 1.b What are the differences in formulation techniques and components between these preparations? What are	The information is presented in Appendix H.

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(Reapplix Inc.)		the differences in application techniques, frequency of application and dosage (amounts applied)? Comment: As described elsewhere in these comments, the differences in formulation, techniques etc. should be described more specifically; The products used in the assessed trials included a diverse range of products from traditional PRPs made by centrifugation of anticoagulated blood followed by activation with extrinsic calcium and thrombin and gelling on the wound surface at application (Ahmed 2016, Li 2015, Saldalamachia 2004). A lower platelet level product including ascorbic acid were also gelled on the wound surface (Driver 2006 and Gude 2019) while another lower platelet level PRP were applied by impregnating gauze before application (Karimi 2016). One study used non-anticoagulated blood and a specialized device to form a patch, resulting in fibrin, high platelet and leukocyte levels being separated into three distinct layers. The patch was formed without addition of reagents and transferred to wound surface (Game 2018).	

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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 in such studies.	Thank you for the comment.

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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. "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 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, Figure 1). With these issues, we rated moderate

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		participants for analysis if they withdraw consent to data collection having had no trial procedures/intervention, as long as this is pre-specified. This is still an ITT. As 256 patients were included we cannot think that this creates a moderate risk of bias. To put this in context the study by Karimi 2016 was also assessed as being at moderate risk of bias overall (but low in this domain), yet this paper presented no ITT analysis, only a per protocol, there is some doubt as to whether there was true randomisation, and important baseline variables which could have influenced outcome such as arterial status and offloading are not described at all.	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. For Karimi 2016, we rated "moderate risk" for randomization process, missing outcome data, and measurement of outcomes.
Peer reviewer #1	Quality of the Report	Superior	Thank you for the comments.
Peer reviewer #2	Quality of the Report	Superior	Thank you for the comments.
Peer reviewer #3	Quality of the Report	Superior	Thank you for the comments.
Peer reviewer #4	Quality of the Report	Good	Thank you for the comments.
Peer reviewer #5 (Public reviewers)	Quality of the Report	Good	

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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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			follow a typical review article or text book format. Therefore, an abridged evidence summary is provided with “main points” section for individuals not interested in a lengthy message.