**Evidence-based Practice Center Systematic Review Protocol**

**Project Title: Platelet-rich Plasma for Wound Care in the Medicare Population**

Initial Publication Date: March 4, 2020
Amendment Date: March 20, 2020
(Amendments Details-see Section VI)

## I. Background and Objectives for the Systematic Review

Chronic wounds are a common chronic medical condition with a high impact on the aging population, with chronic wounds or infections affecting nearly 15% of Medicare beneficiaries with a healthcare burden of $28 to $96 billion US dollars per year.[1] Conditions that are most commonly associated with wound formation include diabetes, pressure injuries, and venous or arterial diseases. Normal wound healing involves a complex process characterized by orderly and sequential events resulting in the restoration of tissue integrity and function.[2] The cascade of events starts from hemostasis, followed by inflammation, cell recruitment, migration, proliferation, tissue modeling and remodeling. Cytokines and growth factors play a key regulatory role.[3] Wound healing is further complicated by location, depth, size, and microbial contaminations. Aberrations of wound healing are associated with advanced age, certain medical comorbidities, and genetic predisposition. Chronic, non-healing wounds often necessitate costly long-term wound management and result in significant discomfort and frustration to patients.

Current treatment modalities focus on exposure of healthy, well-perfused tissue to promote epithelial cell migration, wound dressing to protect healing wounds from infection and promote the wound healing process, negative pressure wound therapy to optimize blood flow and apply pressure to promote wound closure, and hyperbaric oxygen.[4] New treatment modalities derived from the growing understanding of the activities of the many types of cytokines are aimed at optimizing the microenvironment with application of growth factors such as platelet-derived growth factor (PDGF), so that the healing process of chronic wound may be induced or accelerated.[5]

Autologous platelet-rich plasma (PRP) 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. PRP is thought to contain Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), Insulin Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor-β, and Hepatocyte Growth Factor (HGF), all of which been all shown to stimulate healing.[6] PRP has attracted significant interest because platelets possess various growth factors that are critical for tissue repair and regeneration, and they have antibacterial properties in traumatic injuries.[7, 8] Clinicians as well as patients face several key challenges and controversies with regard to the potential benefit of PRP for chronic wound care, including wide variety in dose and treatment duration and optimal preparation of PRP.

PRP preparations are being offered typically in a point-of-care setting, delivered as a preparation of aqueous suspension obtained by centrifugation of whole blood. PRP contains concentrated platelets, as few red blood cells as possible, and leukocytes at different levels for various indications. While there is no consensus, leukocyte-poor PRP are more commonly used for intra-articular application, leukocyte-rich PRP are more commonly used in soft tissue pathology such as tendinopathy and wound care for leukocyte's role in local cleaning and immune regulation of the wound healing process. [9, 10] Variability of PRP contents secondary to preparation technology and individual difference poses a challenge for research.[11]

Carriers are used for PRP delivery in wound care. Those include hydrogels, sponge-like dressings, powders/beads, nanoparticles and scaffolds. The carriers are necessary for increasing efficacy by promoting sustained delivery of various factors contained in PRP.[12] Different delivery systems were proposed for different settings. PRP gel combined with antibiotic-containing nanoparticles was proposed for optimal healing and infection.[13] Spongiform material consisting of chitosan and gelatin crosslinked with tannic acid was found to have good mechanical stability as well as antibacterial features. [14] Scaffolds containing chitosan only were also investigated with promising results.[15] Bioactive gelatin hydrogel granules combining PRP and basic FGF showed positive effects on angiogenesis on applied ischemic areas.[16]

In summary, this proposed systematic review will evaluate the overall effectiveness of treatment of diabetic foot ulcers, pressure ulcers, and venous ulcers with PRP, as well as the impact of PRP content, carriers, dosage, frequency and duration of application.

## II. The Key Questions (KQ)

**Comparative Effectiveness Questions:**

**KQ 1. What are the benefits and harms of treatment strategies including PRP alone with or without other wound care treatments compared to other wound care treatments in patients with diabetic, venous and pressure chronic wounds, for patient oriented outcomes such as at least the following:** completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements), time to complete wound closure, wound reoccurrence, risk of developing wound infection, amputation, hospitalization (frequency and duration), return to baseline activities and function, reduction of wound size, pain, opioid medication use, exudate and odor, quality of life and adverse effects.

**KQ 1.a. Describe the risk of bias in the studies examined by chronic wound type and study design.**

**KQ 1.b What are the differences in formulation techniques and components between these preparations? What are the differences in application techniques, frequency of application and "dosage" (amounts applied)?**

**KQ 1.c What are the study characteristics (such as those listed below) in each included investigation for each chronic wound type treated by PRP?**

a. Comparator (if standard care, describe in detail)

b. Study inclusion/exclusion criteria and patient characteristics of enrollees, including at least age, gender, and general health (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal), wound characteristics, and prior and concurrent wound treatments.

c. Wound characteristics of enrollees including at least wound type, wound size/depth/duration/severity, vascular status, infection status and whether there were inter- and intra-rater checks of wound measurements.

d. Basic study design and conduct information including at least method of patient enrollment, care setting, and use of run-in period

e. Definition of wound characteristics: definition of "failure to heal", and definition of a successfully healed wound (re-epithelialization)

f. Method of applying skin PRP including provider, frequency of application, definition of standard of care, and handling of infections

g. Measurement and assessment methods including method of assessment(s); frequency and time points for assessment(s) (including long term assessments for durability of heal); and blinding of assessors

**KQ 1.d Based on the included studies, what are the patient characteristics commonly considered for the initiation and continuation/discontinuation of PRP in patients with chronic wounds?**

**Contextual Questions:**

**KQ 2. What types of PRP preparations are currently being marketed in US medical practices (gel, liquid, etc.)?**

**Future Research Questions:**

**KQ 3. What PRP preparations are currently being investigated in ongoing trials?**

**KQ 4. What best practices in study design could be used to produce high quality evidence on PRP?**

**KQ 5. What are the evidence gaps found in this body of research?**

**Table 1. PICOTS**

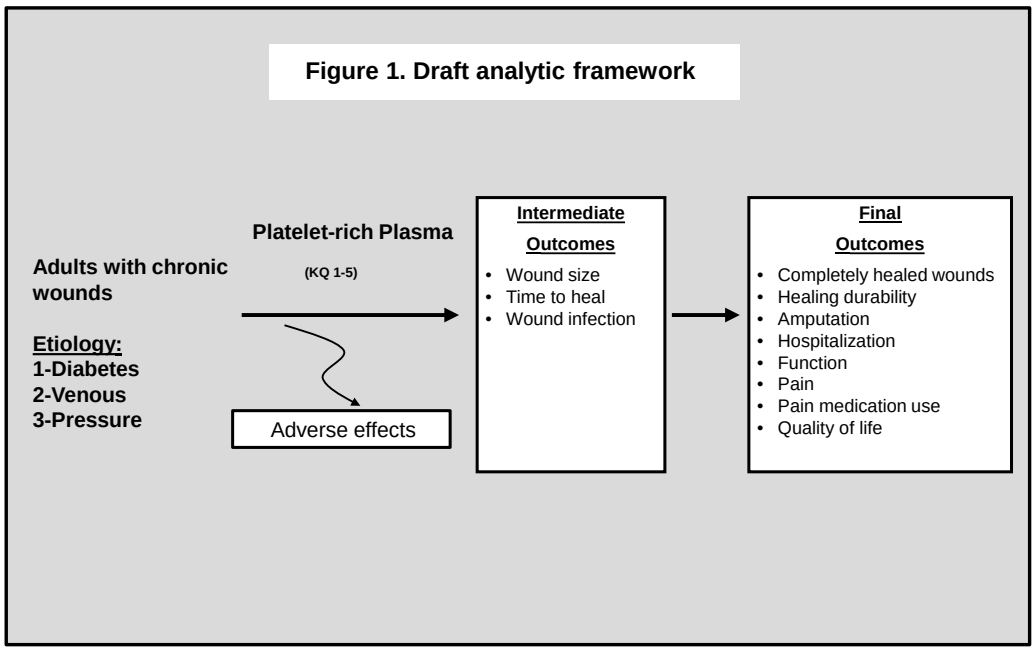
| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Populations | Adult patients (18 years and older) with<br>• Lower extremity diabetic wounds<br>• Lower extremity venous ulcers<br>• Pressure wounds in any location | • Animals<br>• Children (age < 18 years)<br>• Wounds of other etiologies<br>• Studies with mixed, non stratified diabetic wounds/venous ulcers/pressure wounds<br>• Traumatic wounds<br>• Peripheral arterial disease (PAD) related wounds in non diabetics (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).<br>• Wounds<4 weeks |
| Intervention | Any preparation of autologous platelet-rich plasma with or without other treatments | |
| Comparators | Any other wound care without PRP | None |

| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Outcomes | • Completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements versus failure to heal)<br>• Time to complete wound closure<br>• Healing durability (Time to wound reoccurrence)<br>• Wound infection (improvement of wound infection or reduced risk of developing wound infection)<br>• Amputation<br>• Hospitalization<br>• Return to baseline activities of daily living and function<br>• Wound size<br>• Pain<br>• Opioid medication use<br>• Quality of life<br>• Adverse effects | None |
| Timing | | None |
| Settings | Any | None |
| Study design | KQ 1<br>• Original data<br>• Any sample size<br>• RCTs<br>• Comparative observational studies<br>• Relevant systematic reviews, or meta-analyses (used for identifying additional studies) | *In vitro* studies, non-original data (e.g. narrative reviews, editorials, letters, or erratum), single-arm observational studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., non-longitudinal) studies, before-after studies that do not have a comparison group, survey |

| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Subgroup analysis | • Age<br>• Gender<br>• Settings<br>• Comorbidities (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal disease, liver disease)<br>• Wound characteristics (wound type, area, depth, volume, duration, severity, vascular status, infection status, and prior and concurrent wound treatments)<br>• Anatomical location (lower extremity diabetic wounds only)<br>• PRP formulation techniques<br>• PRP components<br>• PRP application techniques<br>• PRP frequency<br>• PRP "dosage" (amounts applied)<br>• PRP offloading procedures (e.g., total contact casting, removable CAM WalkerTM, irremovable offloading devices)<br>• Use of immunosuppressant medication<br>• Nutrition status<br>• Pain medication (opioids, others) | |
| Publications | Studies published in English only. | Foreign language studies |

Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial

## III. Analytic Framework




## IV. Methods

**Criteria for Inclusion/Exclusion of Studies in the Review:** We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

**Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions:** We plan to conduct a comprehensive database search, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search FDA, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, the International Working Group on the Diabetic Foot (IWGDF) website, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process

will be imported to a reference management system (EndNote® Version X9; Thomson Reuters, Philadelphia, PA).

Independent reviewers, working in pairs, will screen the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer will be retrieved for full-text screening. Independent reviewers, again working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus can't be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

**Data Abstraction and Data Management:** At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot-tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will review data extraction, and resolve conflicts. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

**Assessment of the Risk of Bias of Individual Studies:** We will evaluate the risk of bias of each included study using the Cochrane Collaboration's Risk of Bias 2 tool[17] for RCTs to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For comparative observational studies, we will use selected items from the Newcastle-Ottawa quality assessment scale.[18]Additional criteria will be adopted from other quality appraisal tools if deemed necessary.

**Data Synthesis -** We will qualitatively summarize key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQs.

We will determine whether meta-analysis is appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use the profile likelihood random effect method to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 3.[19, 20] In case that the profile likelihood method does not converge, we will use the DerSimonian-Laird random effect model with Hartung-Knapp-Sidik-Jonkman variance correction.[21] The fixed effect method based on the Mantel and Haenszel method will be adopted when the number of studies is 3 or less. We will evaluate heterogeneity between studies using $I^2$ indicator. To further explore heterogeneity, we plan to conduct subgroup analyses (details of the planned subgroup analyses are listed in Table 1). We will conduct sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests such as Egger linear regression test if the number of studies included in a direct comparison is large (n>=10).

**Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes:** We will grade the strength of the body of evidence (SOE) as per the EPC methods guide on assessing SOE.[22] We will grade SOE for most critical health outcomes, including completely closed/healed wounds, wound reoccurrence, amputation, hospitalization, pain, and quality of life. These outcomes are chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision making.

The SOE grading approach starts by a high SOE given to estimates derived from RCTs.[22] This grade may be lowered due to several methodological domains. The domains will be: 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; consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias. Observational studies will start with a low SOE which can be raised if the estimates of effect indicated a large effect, a dose-response gradient, or residual confounding in a direction that would strengthen the association.

We will assign SOE rating as high, moderate, low, or 'insufficient evidence to estimate an effect'. We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

**Assessing Applicability:** We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.[22] Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. We will focus on whether the populations, interventions, and comparisons in existing studies are representative of current practice. We will look for these characteristics, systematically abstract such factors and evaluate their impact on how applicable the evidence is to the question of interest. We will report any limitations in applicability of individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

## V. References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## VI. Summary of Protocol Amendments

| Date | Section | Original Protocol | Revised Protocol | Rationale |
|---|---|---|---|---|
| March 30, 2020 | Table 1: Population | Exclude: Studies with mixed, non | Exclude studies with mixed non stratified etiologies other than | Studies of patients who have more than one type of these |

| | | | | |
|---|---|---|---|---|
| | | stratified diabetic wounds/venous ulcers/pressure wounds | diabetic, venous or pressure wounds. | three etiologies may provide valuable information about these 3 types. |
| March 30, 2020 | Table 1: Intervention | None | Add autologous platelet lysate | Interventions using autologous platelet lysate may provide additional information of autologous platelet-rich plasma. |
| March 30, 2020 | IV. Methods | None | Qualitative synthesis and meta-analyses will be conducted separately by etiology (diabetic wounds, venous ulcers, pressure wounds, and mixed) and type of interventions (autologous platelet-rich plasma, and autologous platelet lysate), | Methods for analysis are changed due to the change of intervention and population. |

## VII. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

## IX. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

## X. Role of the Funder

This project was funded under Contract No. HHSA290201500013I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## XI. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).