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Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

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Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses

as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Recombinant platelet-derived growth factor (i.e., becaplermin) **may be considered medically necessary** when used as an adjunct to standard wound management for the following indications (for further information on selection criteria, see Policy Guidelines next):

- Neuropathic diabetic ulcers extending into the subcutaneous tissue (when used according to the U.S. Food and Drug Administration labeled indication); and
- Pressure ulcers extending into the subcutaneous tissue.

Other applications of recombinant platelet-derived growth factor (i.e., becaplermin) **are considered experimental, investigational and/or unproven** including, but not limited to, ischemic ulcers, venous stasis ulcers, and ulcers not extending through the dermis into the subcutaneous tissue.

Use of platelet-rich plasma (i.e., autologous blood-derived preparations) **is considered experimental, investigational and/or unproven** for the treatment of acute or chronic wounds, including surgical wounds and nonhealing ulcers.

Policy Guidelines

Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet ALL of the following criteria:

1. Adequate tissue oxygenation, as measured by a transcutaneous partial pressure of oxygen of 30 mm Hg or greater on the foot dorsum or at the margin of the ulcer;
2. Full-thickness ulcer (i.e., stage III or IV), extending through dermis into subcutaneous tissues;
3. Participation in a wound management program, which includes sharp debridement, pressure relief (i.e., non-weight bearing), and infection control.

Appropriate candidates for becaplermin gel for the treatment of pressure ulcers should meet ALL of the following criteria:

1. Full-thickness ulcer (i.e., stage III or IV), extending through dermis into subcutaneous tissues;
2. Ulcer in an anatomic location that can be offloaded for the duration of treatment;
3. Albumin concentration >2.5 dL;
4. Total lymphocyte count >1000/µL;
5. Normal values of vitamins A and C.

Becaplermin promotes cellular proliferation and angiogenesis. The benefits and risks of this treatment should be carefully evaluated before prescribing in patients with known malignancy.

Becaplermin gel should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with becaplermin gel should be reassessed. (92)

Becaplermin is available in 2-, 7.5-, and 15-g tubes and is applied in a thin continuous layer, about 1/16 of an inch thick (i.e., 1.6 mm or the thickness of a dime). The amount of the gel used will depend on the size of the ulcer, measured in square centimeters. However, an average-sized ulcer, measuring 3 cm^2, treated for an average length of time of 85 days, will require a little more than one 15-g tube. If the ulcer is treated for the maximum length of time of 140 days, 1.75 of the 15-g tubes would be required.

Description

The use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), has been suggested as a treatment for wounds or other miscellaneous non-orthopedic conditions, including but not limited to, diabetic ulcers, pressure ulcers, venous stasis ulcers, and surgical and traumatic wounds.

Wound Healing Treatment

A variety of growth factors have been found to play a role in wound healing, including PDGF, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of PDGF, transforming growth factors (that function as a mitogen for fibroblasts, smooth muscle cells, and osteoblasts), and vascular endothelial growth factors. Recombinant PDGF has also been extensively investigated for clinical use in wound healing.

Autologous platelet concentrate suspended in plasma, also known as PRP, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets (releasing various growth factors) and results in the polymerization of fibrin from fibrinogen, creating a platelet gel. The platelet gel can then be applied to wounds or may be used as an adjunct to surgery to promote hemostasis and accelerate healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a transforming growth factor, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries.

Platelet-rich plasma is distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter International) and Hemaseel® (Haemacure Corp.) are examples of commercially available fibrin sealants. Autologous fibrin sealants can also be created from platelet-poor plasma. This policy does not address the use of fibrin sealants.

Wound Closure Outcomes

This policy addresses the use of recombinant PDGF products and PRP for non-orthopedic indications, which include a number of wound closure--related indications.

For this policy, the primary endpoints of interest for the study of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds (1):

- Incidence of complete wound closure;
- Time to complete wound closure (reflecting accelerated wound closure);
- Incidence of complete wound closure following surgical wound closure;
- Pain control.

Regulatory Status

Becaplermin

In 1997, becaplermin gel (Regranex®, Smith & Nephew), a recombinant PDGF product, was approved by the FDA for the following labeled indication:

"Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, Regranex Gel increases the complete healing of diabetic ulcers.

The efficacy of Regranex Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers…has not been evaluated...Regranex is not intended to be used in wounds that close by primary intention."

In 2008, the manufacturer added the following black box warning to the labeling for Regranex: “An increased rate of mortality secondary to malignancy was observed in patients treated with three or more tubes of Regranex Gel in a postmarketing retrospective cohort study. Regranex Gel should only be used when the benefits can be expected to outweigh the risks. Regranex Gel should be used with caution in patients with known malignancy.”

In 2018, the “Boxed Warning” and “Warnings and Precautions” were changed to remove “increased rate of cancer mortality” and “cancer mortality,” respectively.

Platelet-Rich Plasma

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research under the Code of Federal Regulation, Title 21, parts 1270 and 1271. Blood products such as PRP are included in these regulations.

Under these regulations, certain products including blood products such as PRP are exempt and therefore, do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP. (2)

Numerous PRP preparation systems have been cleared for marketing by the FDA through the 510(k) process. These devices are intended to concentrate patient plasma at the point of care during bone grafting procedures. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

Rationale

Currently, a large number of devices are available for the preparation of platelet rich plasma (PRP) or PRP gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is unknown whether platelet activation before an injection is necessary. (3-7)

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Recombinant Platelet-Derived Growth Factor for Diabetic Lower-Extremity Ulcers

Clinical Context and Therapy Purpose

The purpose of recombinant platelet-derived growth factor (PDGF) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with diabetic lower-extremity ulcers.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with diabetic lower-extremity ulcers.

Interventions

The therapy being considered is recombinant PDGF.

Comparators

Comparators of interest include standard wound care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity.

Follow-up at 20 weeks is of interest for recombinant PDGF to monitor relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A 2014 systematic review identified 6 RCTs (N=992 patients) that compared recombinant PDGFs with placebo or standard care. (8) There was a combined odds ratio of 1.53 (95% confidence interval [CI], 1.14 to 2.04; p=0.004) favoring recombinant PDGF for complete healing rate.

Sridharan et al. (2018) conducted a systematic review and meta-analysis of RCTs on topical growth factors compared with standard of care in patients with diabetic foot ulcers (DFUs). The primary outcome of concern was complete healing, and the second outcome of concern was the existence of adverse events. Rankogram was generated based on the surface under the cumulative ranking curve. In total, 26 studies with 2088 participants and 1018 adverse events

were included. The pooled odds ratio estimates for recombinant human epidermal growth factor (rhEGF), autologous -PRP, and recombinant human platelet-derived growth factor (rhPDGF) were 5.7 [95% CI, 3.34 to 10.37], 2.65 [95% CI, 1.65 to 4.54], and 1.97 [95% CI, 1.54 to 2.55] respectively. The surface under the cumulative ranking curve for rhEGF was 0.95; sensitivity analysis did not reveal significant changes from pooled estimates and rankogram. With regard to adverse events, no differences were observed for the overall risk of adverse events between the growth factors; however, the growth factors were observed to lower the risk of lower limb amputations compared to standard of care. The results lead the authors to conclude that rhEGF, rhPDGF, and autologous PRP significantly improved the healing rate when used as adjuvants to the standard of care. Compared to other growth factors, rhEGF performed better. The limitations of this study include the following: the strength of most of the outcomes assessed was low, and the findings may not be applicable for DFU with infection or osteomyelitis. (9)

Table 1. Systematic Reviews of Trials Assessing Recombinant Platelet-Derived Growth Factor for Diabetic Lower-Extremity Ulcers

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Sridharan et al. (2018) (9)	Dec 2016	RCTs	Patients with diabetic lower-extremity ulcers treated with platelet-derived growth factor	2088	RCTs	Pool analysis estimated rhEGF, PRP, rhPDGF

PRP: autologous platelet-rich plasma; RCT: Randomized Controlled Trial; rhEGF: recombinant epidermal growth factor; rhPDGF: recombinant human platelet-derived growth factor; N: number.

Retrospective Studies

A 2005 industry-sponsored study assessed the effectiveness of recombinant PDGF for diabetic neuropathic foot ulcers in actual clinical practice. (10) Among a cohort of 24,898 patients in wound care centers, those subjects whose wounds did not heal over an 8-week observation period were eligible for the study and were retrospectively assessed over 20 weeks or until they healed. Any subject with an open wound who was lost to follow-up was considered unhealed. Of the nearly 25,000 patients treated for foot ulcers, 2,394 (9.6%) received recombinant PDGF. A propensity score method with covariates to statistically model treatment selection was used to adjust for selection bias; results were stratified by 5 propensity score groups. Overall, the rate of healing was 26.5% in the control group and 33.5% in patients treated with recombinant PDGF. The relative risk (RR), controlling for the propensity to receive PDGF, was 1.32 (95% CI, 1.22 to 1.38) for healing and 0.65 (95% CI, 0.54 to 0.78) for amputation (6.4% in controls vs. 4.9% in the PDGF group). The analysis also indicated those who received PDGF were more likely to be younger, male, and have older wounds-factors not known to affect wound healing. These results support the clinical utility of recombinant PDGF for treatment of diabetic neuropathic foot ulcers in actual clinical practice.

Section Summary: Recombinant Platelet-Derived Growth Factor for Diabetic Lower-Extremity Ulcers

Published evidence includes an industry-sponsored study and 2 systematic reviews that showed an improvement in treatment over control for tested outcome measures.

Recombinant Platelet-Derived Growth Factor for Pressure Ulcers

Clinical Context and Therapy Purpose

The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with pressure ulcers.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with pressure ulcers.

Interventions

The therapy being considered is recombinant PDGF.

Comparators

Comparators of interest include standard wound care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for pressure ulcer symptoms would typically occur in the months after starting treatment.

Study Selection Criteria

Methodologically credible studies were selected using the principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Rees et al. (1999) conducted an RCT focusing on the use of becaplermin gel as a treatment for pressure ulcers. (11) Patient selection criteria included full-thickness ulcers and an anatomic location where pressure could be off-loaded during treatment. This latter patient selection criterion might have limited the number of patients with pressure ulcers who would have been considered candidates for becaplermin therapy. Patients were randomized to 1 of 4 parallel treatment groups and received either a placebo or 1 of 3 doses of becaplermin. All patients received a standardized program of good wound care. In the 2 groups of patients treated with

the once daily dosage (becaplermin 0.01% or 0.03%), the incidence of complete healing was significantly improved compared with the placebo group. There was no difference in outcome between the 0.01% and 0.03% groups, suggesting that there is no clinical benefit in increasing the potency above 0.01%. A third group received becaplermin 0.01% twice daily. That group did not report improved outcomes compared with placebo, a finding that is unexplained.

Section Summary: Recombinant Platelet-Derived Growth Factor for Pressure Ulcers
Published evidence includes a multicenter, double-blind RCT that showed an improvement in treatment over control for tested outcome measures.

Recombinant Platelet-Derived Growth Factor for Venous Stasis Leg Ulcers
Clinical Context and Therapy Purpose
The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with venous stasis leg ulcers.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with venous stasis leg ulcers.

Interventions
The therapy being considered is recombinant PDGF.

Comparators
Comparators of interest include standard wound care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for venous stasis leg ulcers symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Senet et al. (2011) in France, published a multicenter, double-blind RCT of becaplermin gel for venous leg ulcers. (12) There was no significant difference between the becaplermin (n=28) and control hydrogel (n=31) groups for any of the outcome measures, which included complete closure rates after 8 and 12 weeks, changed ulcer area, and changed ulcer-related pain and QOL.

Section Summary: Recombinant Platelet-Derived Growth Factor for Venous Stasis Leg Ulcers
Published evidence includes a multicenter, double-blind RCT that showed no difference between treatment and control for tested outcome measures.

Recombinant Platelet-Derived Growth Factor for Acute Surgical or Traumatic Wounds
Clinical Context and Therapy Purpose
The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with acute surgical or traumatic wounds.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with acute surgical or traumatic wounds.

Interventions
The therapy being considered is recombinant PDGFs.

Comparators
Comparators of interest include standard wound care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for acute surgical or traumatic wound symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. A 2005 prospective controlled trial alternately assigned 50 patients (fingertip wound area of ≥1.5 cm, with or without phalangeal exposure) to daily treatment with PDGF (n=25) or surgical reconstruction (n=25). (13) Statistical analysis showed that the baseline characteristics of the two groups were similar for patient age, wound area (2.2–2.4 cm), and distribution of fingertip injuries across the digits. Assessment by an independent physician showed that, compared with the surgical intervention, treatment with recombinant PDGF resulted in faster return to work (10 days vs. 38 days) and wound healing (25 days vs. 35 days), less functional impairment (10% vs. 22%), and less need for physical therapy (20% vs. 56%), respectively. Fingertips treated with PDGF were also reported to have satisfactory aesthetic results, while surgically treated fingertips were shorter and often unsightly. These results, if confirmed in additional RCTs, could lead to improvement in health outcomes for patients with fingertip injuries. However, this trial was limited by its small sample size, method of randomization, and potential for investigator bias (although examining physicians were blinded to treatment allocation, actual treatment might have been obvious).

Adverse Events

Growth factors cause cells to divide more rapidly. For this reason, the manufacturer of Regranex continued to monitor studies that started before its approval (in December 1997) for any evidence of adverse events, such as increased numbers of cancers. In a long-term safety study completed in 2001, more deaths from cancer occurred among patients who used Regranex than in those who did not. A subsequent study was performed using a health insurance database that covered the period from January 1998 through June 2003. This trial identified two groups of patients with similar diagnoses, drug use, and use of health services: one group used Regranex, and the other group did not. Results showed that there were more deaths from cancer among patients who were given 3 or more prescriptions for Regranex than deaths for those not treated with Regranex. No single type of cancer was identified; deaths from all types of cancer were observed. In 2008, the U.S. Food and Drug Administration (FDA) concluded that the increased risk of death from cancer in patients who used 3 or more tubes of Regranex was 5 times higher compared with those who did not use Regranex, prompting the manufacturer to add a black box warning to the labeling for Regranex. The risk of new cancers among Regranex users was not increased compared with nonusers, although the duration of follow-up of patients in this study was not long enough to detect new cancers.

Section Summary: Recombinant Platelet-Derived Growth Factor for Acute Surgical or Traumatic Wounds

Published evidence includes nonrandomized controlled trials reporting satisfactory aesthetic results. Larger RCTs are required to confirm and expound on these results.

Platelet-Rich Plasma for Chronic Wounds

Clinical Context and Therapy Purpose

The purpose of PRP is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with chronic wounds.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with chronic wounds.

Interventions
The therapy being considered is PRP.

Comparators
Comparators of interest include standard wound care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for chronic wound symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Diabetic Foot Ulcers
Systematic Reviews
A number of systematic reviews of the evidence on PRP have been published. (14-21) These reviews are heterogenous in whether they pooled data from studies reflecting a variety of wound types (14-16, 22, 23) or focused on specific wound types, primarily diabetic foot ulcers. (17-21) Results from the reviews that pooled data from a variety of wound types (14-16, 22, 23) are not discussed herein as their design precludes drawing conclusions about the applicability of the review findings to specific wound types. As the majority of the RCTs included in the systematic reviews were published post-2014, herein are summarized those systematic reviews that focused on specific wound types with search dates that extend to at least 2015. (19-21)

Four recent systematic reviews have evaluated studies of PRP for individuals with diabetic foot ulcers. (19-21, 24) Table 2 provides a crosswalk of the studies included in the systematic reviews.

Table 2. Comparison of Trials of Platelet-Rich Plasma in Individuals with Diabetic Foot Ulcers Included in Systematic Reviews

Primary Study (Year)	Li et al. 2019 (19)	Qu et al. 2020 (20)	Deng et al. 2023 (21)	Platini et al. 2024 (24)
Ahmed et al. (2017) (25)	X	X	X	X
Alamdari et al. (2021) (26)			X	X
Chen et al. (2008)[a] (27)	X			
Driver et al. (2006) (28)	X	X	X	
Elsaid et al. (2020) (29)		X	X	
Friese et al. (2007) (conference proceeding) (30)	X		X	
Game et al. (2018) (31)		X		
Gude et al. (2019) (32)		X		X
Goda et al. 2018 (33)				X
Habeeb et al. (2020) (34)			X	
Helmy et al. (2021) (35)			X	
Hossam et al. (2021) (36)			X	
Jeong et al. (2010) (37)			X	
Kakagia et al. (2007) (38)	X	X	X	
Karimi et al. 2016 (39)		X	X	
Li et al. (2012)[a] (40)			X	
Li et al. (2015) (41)	X	X	X	X
Liu et al. (2016)[a] (42)	X		X	
Liao et al. (2020) (43)			X	
Meamar et al. (2021) (44)			X	
Ma et al. (2014)[a] (45)	X			
Milek et al. (2017) (46)		X		
Qi et al. (2014)[a] (47)	X			
Rainys et al. (2019) (48)			X	X
Saad Setta et al. (2011) (49)	X	X	X	
Saldalamacchia et al. (2004) (50)	X	X	X	
Serra et al. (2013) (51)	X	X		X
Singh et al. (2018) (52)		X	X	
Steed et al. (1992) (53)			X	
Steed et al. (1996) (54)			X	
Tofigh et al. (2022) (55)			X	
Xie et al. (2020) (56)		X		X
Yang et al. (2017) (57)		X		
Zhang et al. (2016)[a] (58)	X			
Zhou et al. (2015)[a] (59)	X			
Zhu et al. (2012)[a] (60)	X			

[a] In Chinese

Tables 3 and 4 summarize the characteristics and results of the 4 systematic reviews that have evaluated studies of PRP for individuals with diabetic foot ulcers. (19-21, 24)

In their meta-analysis, Li et al. (2019) assessed the efficacy and safety of autologous platelet-rich gel for topical treatment of diabetic chronic cutaneous ulcers (19) Their analysis included 15 RCTs with 829 patients. Results indicated that autologous platelet-rich gel had a significant positive effect on healing rate, shorter healing time, and lower risk of infection than conventional treatment. Autologous platelet-rich gel also had a significantly lower incidence of infection when compared with conventional treatment (odds ratio [OR]=0.34; 95% CI: 0.15 to 0.77; p=.009). This meta-analysis was limited by a high or unclear risk of bias among the trials, which may indicate the trials were underpowered. Also, some studies had small sample sizes and limited outcome information. Further, 7 of the included trials are available only in the Chinese language. Finally, most of the trials were 8 to 12 weeks long and others only 2 to 5 weeks, making it difficult to analyze the relationship of time of observation to ulcer healing.

The Agency for Healthcare Research and Quality (AHRQ) (2020) published a Technology Assessment on Platelet-Rich Plasma for Wound Care in the Medicare Population. This Technology Assessment was requested by the Centers for Medicare & Medicaid Services to inform reconsideration of a National Coverage Decision on autologous blood-derived products for chronic non-healing wounds. (20) This Technology Assessment evaluates evidence in lower extremity diabetic ulcers, lower extremity venous ulcers and pressure ulcers. Separate meta-analyses were conducted for each wound type. Here the focus is on findings for lower extremity diabetic ulcers and those for the other populations are discussed below. Risk of bias of individual studies was assessed using the Cochrane Collaboration's Risk of Bias 2 tool and rated high in 8 RCTs (57.14%), moderate in 6 RCTs (42.86%) and high in the 1 observational study (100%). Strength of the body of evidence was rated based on the Evidence-based Practice Center methods guide. The findings of this Technology Assessment indicated that there is moderate-strength evidence that PRP modestly increases complete wound closure (see meta-analysis results in Table 4 below) and low-strength evidence that PRP may shorten time to wound closure (meta-analysis not feasible). However, due to risk of bias and severe imprecision, evidence is insufficient to draw conclusions about other important outcomes, including wound infection, amputation, pain reduction, and wound recurrence. Important limitations of the literature were described as "inadequate description of offloading and wound care procedures, wound characteristics, PRP formulation techniques, concentration and volume; inadequate length of follow-up, and lack of stratification by comorbidities and other patient characteristics, such as diabetes control, vascular perfusion, and under representation of older adults."

A meta-analysis by Deng et al. (2023) assessed 22 RCTs (N=1559) to determine the safety and efficacy of PRP to treat diabetic foot ulcers. (21) Results indicated PRP significantly increased the overall healing rate of diabetic foot ulcers compared with standard treatment (RR=1.42; 95% CI: 1.30 to 1.56; p<.001; I^2=55%). PRP increased the complete wound healing time of diabetic foot ulcers compared to conventional treatment (mean difference [MD]= -3.13; 95% CI:

-5.86 to -0.39; p<.001; I^2=97.5%) and resulted in a greater reduction in diabetic foot ulcer area (MD= 1.02; 95% CI: 0.51 to 1.53; p<.001; I^2=36%). The rate of amputation, reported by 3 trials, significantly reduced risk for the autologous PRP group (RR=0.35; 95% CI, 0.15 to 0.83; p<.001; I^2=0%). Four studies reported adverse events, and pooled analysis revealed a similar rate of events between the PRP and control groups (RR=0.96; 95% CI, 0.57 to 1.61; p>0.05; 35%). The authors reported no significant publication bias was detected by funnel plot analysis; however, a sensitivity analysis suggested that the pooled outcome assessment for time to wound healing may be affected by considerable inter-study variability. The low number of high-quality of studies available on PRP for diabetic foot ulcers and the low number of studies reporting some outcomes of interest were limitations of this meta-analysis.

Platini et al. (2024) conducted a systematic review and meta-analysis to assess the efficacy and safety of autologous platelet-rich plasma gel for managing diabetic foot ulcers in older adults (N=598) across 8 RCTs. (24) Compared with standard care, autologous PRP gel significantly improved wound healing rates (RR=1.32; 95% CI: 1.22 to 1.57; p<.0001; I^2=23%) and reduced the time to complete healing (MD=-16.97 days; 95% CI: -32.64 to -1.29; p<.0001; I^2=93%). PRP also shortened hospital stays (MD=-20.11 days; 95% CI: -38.02 to -2.20; p=.03) and decreased the amputation rate (RR=0.36; 95% CI: 0.16 to 0.84; p=.02; I^2=0%) when compared to conventional treatments. The authors also noted its infection prevention efficacy during early treatment was significant at one week (RR=0.56; 95% CI: 0.34 to 0.91; p=.02) and two weeks (p=.01), but when assessed from week 4 to 12, no significant differences were observed. No improvements in the reduction of wound surface area were noted in the included studies. Heterogeneity across outcomes varied but was particularly high in healing duration outcomes. Funnel plot analyses revealed minimal publication bias. Limitations included non-standardized dosages of PRP, high heterogeneity for some pooled estimates, and insufficient reporting of some clinical outcomes.

Table 3. Characteristics of Key Systematic Reviews with Meta-Analyses in Individuals with Diabetic Foot Ulcers

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Li et al. (2019) (19)	2004-2017	15	Patients with diabetic chronic cutaneous wounds/ ulcers that do not show signs of healing in 4 weeks	N=829 (14-117)	RCTs	NR
Qu et al. (2021) (20)	Inception-2020	14	Adults with lower extremity diabetic ulcers, lower extremity venous ulcers, or pressure ulcers in any location, or a mix of these 3 etiologies	N=1,096 (range NR)	RCTs	Median = 6 wk (range, none to 11 months)

Deng et al. (2023) (21)	Inception-2023	22	Adults with diabetic foot ulcers	N=1559	RCTs	NR
Platini et al. (2024) (24)	Inception-2024	8	Older adults with diabetic foot ulcers	N=598	RCTs	NR

NR: not reported; RCT: randomized controlled trial; wk: week(s); N: number.

Table 4. Results of Key Systematic Reviews with Meta-Analyses in Individuals with Diabetic Foot Ulcers

Study	Healing Rate	Healing Time	Complete Wound Healing	Risk of Infection	Wound Complications	Pain Reduction	Recurrence
Li et al. (2019) (19)							
RR	1.39						
MD		-9.18					
OR				0.34			
95% CI	1.29 to 1.50	-11.32 to -7.05		0.15 to 0.77			
P-value	<.001	<.001		0.009			
Qu et al. (2021) (20)							
RR			1.20	0.77			2.09
WMD						-1.10[a]	
95% CI			1.09 to 1.32	0.54 to 1.11		-1.81 to -0.39	0.31 to 13.93
P-value							
Deng et al. (2023) (21)							
RR	1.42				0.096		
MD		-3.13					
95% CI	1.30 to 1.56	-5.86 to -0.39			0.57 to 1.61		
P-value	<.001	<.001			0.203		
Platini et al. (2024) (24)							
RR	1.32	-16.97		0.56			
MD							
95% CI	1.22 to 1.57	-32.64 to -1.29		0.34 to 0.91			
P-value	<.0001	<.0001		0.02			

[a] Visual Analog Scale
CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio; WMD: weighted mean difference.

Randomized Controlled Trials
Key characteristics and results of several RCTs of diabetic foot ulcers published subsequent to the AHRQ review (2020) are summarized in Tables 5 and 6 below.

One RCT of PRP dressing with total-contact casting compared to standard saline dressing for diabetic foot ulcers (Gupta et al. [2021]) (62) did not find significant differences in rates of ulcer area reduction or absolute ulcer area reduction between groups over the 6-week study period. Another RCT of PRP versus standard wound care found accelerated rates of ulcer area reduction and decreased incidence of wound infections with PRP treatment; however, the difference in the percentage of healed surface between groups lost statistical significance at 6, 7, or 8 weeks of follow-up and it is unclear whether complete wound healing was achieved in either group. (36)

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Intervention	Control
Gupta et al. (2021) (62)	India	1	2016 to 2018	Individuals with diabetes mellitus with noninfected diabetic foot ulcers with total ulcer area of 20 cm^2 or less on the plantar surface	Autologous intralesional PRP therapy with total contact casting (n=30)	Saline dressing (n=30)
Hossam et al. (2022) (36)	Egypt	1	2018	Individuals with type 1 or 2 diabetes with non-ischemic revascularized chronic diabetic foot ulcers of more than 6 months duration with no clinical signs of	Autologous intralesional $CaCl_2$-activated PRP therapy (injection and/or gel) with saline gauze (n=40)	Standard wound care with moist dressing with or without collagenase ointment (n=40)

				infection, Wagner grade 1 or 2, and ASA physical status class 2		

ASA: American Society of Anesthesiologists; PRP: Platelet-rich plasma; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	Complete Healing	Percentage of Healed Surface Area[a]	Complete Healing Time	Pain	Quality of Life	Infection	Recurrence
Gupta et al. (2021) (62)	NR	6 weeks: 85.98% vs. 81.72%; p=NR	NR	NR	NR	NR	NR
Hossam et al. (2022) (36)	95% vs 77.8%[b]; p<.001	1 week: 23.1% vs. 0%; p=.002; 5 weeks: 89.2% vs. 60.1%; p<.001; 8 weeks: 96.7% vs. 95.5%; p=.529	NR	NR	NR	PRP: 4 (10%) Control: 18 (45%) with 4 resulting in amputation p<.001	NR

NR: not reported; PRP: Platelet-rich plasma; RCT: randomized controlled trial.

[a] Percentage of healed surface area in treatment vs. control groups.

[b] Proportion of patients with complete healing in treatment (n=38) vs. control groups (n=28) at 6 and 9 weeks, respectively.

Study relevance, design, and conduct limitations are summarized below in Tables 9 and 10.

Other Chronic Wound Types

The AHRQ (2020) Technology Assessment on Platelet-Rich Plasma for Wound Care in the Medicare Population described above also evaluated evidence on use of PRP in individuals with lower extremity venous ulcers and individuals with pressure ulcers. (20)

For individuals with lower extremity venous ulcers, the evidence included 8 RCTs and 3 observational studies (total N=615). The majority compared PRP to management without PRP. Risk of bias was described as moderate due to randomization and outcome measurement limitations. There were no significant differences between PRP versus management without

PRP in complete wound closure (RR=1.49; 95% CI: 0.72 to 3.06; 5 studies, N=250; I^2=29.4%), wound recurrence (RR=0.38; 95% CI: 0.09 to 1.57), wound infection (RR=0.79; 95% CI: 0.22 to 2.81), or quality of life as measured by the Chronic Lower Limb Venous Insufficiency Questionnaire (weighted mean difference [WMD]=10.99; 95% CI: -50.5 to 72.5). For the outcomes time to complete wound closure and pain, meta-analysis of 2 studies was not possible due to insufficient data and findings were mixed between studies on both outcomes. The strength of evidence was rated as 'insufficient' to draw conclusions on all outcomes. Oliveira et al. (2020) also conducted a meta-analysis of cost and effectiveness of studies of PRP for venous ulcers. (64) Based on fewer studies identified from searches only through July 2018, although their findings indicated greater reductions in wound area for PRP, findings were consistent with the ARHQ review in finding no significant difference in complete wound closure (RR=2.54; 95% CI, 0.42 to 15.30; 4 studies, N=156; I^2=69%).

For individuals with pressure ulcers, the AHRQ Technology Assessment (2020) (20) included 1 RCT and 1 comparative observational study (total N not reported). The comparator was serum physiological dressing in the RCT and saline dressing in the observational study. Risk of bias of the primary studies was described as moderate, due to limitations in the randomization process and outcome measurement, deviations from intended interventions, and selective outcome reporting. Although both studies found that PRP significantly reduced wound size (strength of evidence=insufficient), neither study evaluated other important outcomes, such as complete wound closure.

A meta-analysis by Fang et al. (2023) pooled data from 6 studies on patients treated for lower extremity venous ulcers with PRP. (65) A total of 294 patients were included, with 148 patients in the PRP group and 146 in the control group. PRP was found to have a greater reduction in elliptical area at the end of treatment compared to the control group (MD=-1.19; 95% CI, -1.8 to -.058; P=.0001) with a moderate quality of evidence. The healing rate also favored PRP over the control group (RR=5.73; 95% CI, 3.29 to 9.99; P<.00001) with a moderate quality to the evidence base. The authors suggest there may be publication bias in the calculation of these pooled estimates according to Egger's test.

Hu et al. (2024) conducted a systematic review and meta-analysis of 16 RCTs (N=699) to evaluate the efficacy and safety of PRP for venous ulcer treatment. (66) PRP demonstrated a significant improvement in complete ulcer healing (OR=5.06; 95% CI: 2.35 to 10.89; p<.01; I^2=58%) and a 47% greater reduction in ulcer size compared with standard therapy (MD=47%; 95% CI: 32% to 62%; p<.05; I^2=75%). PRP also significantly shortened healing time by an average of 3.25 months (MD=-3.25; 95% CI: -4.06 to -2.43; p<.05; I^2=49%). Recurrence rates were markedly reduced (OR=0.16; 95% CI: 0.05 to 0.50; I^2=18%), with no significant differences in infection (OR=0.89; 95% CI: 0.38 to 2.07; I^2=0%), VAS Pain scores (MD=1.19; 95% CI: -0.67 to 3.04; I^2=52%), or irritative dermatitis rates (OR=0.38; 95% CI: 0.08 to 1.90; I^2=0%). Funnel plot analysis and Egger’s test (p=.0079) suggested the potential for publication bias. Limitations included heterogeneity in PRP preparation, inconsistency in ulcer measurement methods, the potential for publication bias, moderate to high heterogeneity for some outcome estimates, and limited sample sizes.

Randomized Controlled Trials

Two RCTs of PRP for chronic wounds (Saha et al. [2020] and Shehab et al. [2023]) (67, 68) were identified as published subsequent to the AHRQ review (2020). (20) Key characteristics and results of selected RCTs are reported in Tables 7 and 8 below.

Saha et al.'s analyses included 91.5% (n=108) of randomized individuals. Participants were mostly males in their late 40s with trophic ulcer duration of 13.4 months. Reduction in ulcer surface area, the primary outcome, was significantly greater for the PRP group from the first week (38.96% vs 12.46%; p<.001) through the fifth (and last) week of follow-up (91.10% vs. 79.77%; p<.001). However, healing time and recurrence were not reported and there was no significant difference in complete healing rate.

Shehab et al. (2023) conducted an RCT of adjunct PRP in addition to compression therapy in individuals with post-phlebitic venous ulcers. (68) Forty patients were randomized 1:1 to either PRP and compression therapy or placebo. The median number of treatments was 6 (range 3 to 6). Both participants and outcome assessors were blinded to treatment allocation. The median ulcer surface area, the primary outcome, was significantly lower for the PRP group (4 cm^2 vs. 10 cm^2; p=.036) as well as the median volume of ulcers (1 cm^3 vs. 3 cm^3; p=.008). This translated to individuals in the PRP group experiencing a larger drop in ulcer area (74% vs 40%; p=.008) and volume (81% vs 48%; p=.013) compared to placebo. Differences in VAS pain scores were observed in favor of the PRP group at both the 3-month and 6-month follow-ups. Nine patients in the PRP group had complete wound healing, but the authors did not report the rate of complete healing in the control group, and healing time and recurrence were not reported.

Table 7. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Intervention	Control
Saha et al. (2020) (67)	Iran	1	2016 to 2018	Individuals with clinically diagnosed trophic ulcers due to leprosy	Autologous PRP therapy with total contact casting (n=59)	Only total contact casting (n=59)
Shehab et al. (2023) (68)	Egypt	1	2019 to 2020	Adults with chronic post-phlebitic lower limb venous ulcers	Autologous PRP therapy with compression therapy (n=20)	Placebo plus compression therapy (n=20)

PRP: platelet-rich plasma; RCT: randomized controlled trial; n: number.

Table 8. Summary of Key RCT Results

Study	Complete Healing	Healing Time	Pain	Quality of Life	Infection	Recurrence

Saha et al. (2020) (67)	22 (39.29%) vs. 11 (21.15%); p NR	NR	NR	NR	0 vs 0; p=.773	NR
Shehab et al. (2023) (68)	9 (45%) vs. NR	NR	BL: 6.5 vs 6.4; p=.43 3 mos: 1 vs 4.5; p<.0001 6 mos: 0.5 vs. 2.2; p<.001	NR	NR	NR

BL: baseline; Mos: months; NR: not reported; RCT: randomized controlled trial.

Tables 9 and 10 summarize the relevance and design and conduct limitations of selected RCTs.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Saha et al. (2020) (67)	4. Single site in Iran	4. Short duration of treatment; 8 weeks		1. Recurrence, quality of life not addressed 5. Clinical significance of difference in wound surface area not prespecified	1. 4 weeks follow-up post-treatment insufficient to assess long-term efficacy
Gupta et al. (2021) (62)	4. Single site in India	4. Short duration of treatment; 6 weeks	3. Total-contact casting not used in control group	1. Complete wound healing, recurrence, quality of life not addressed 5. Clinical significance of difference in wound surface area not prespecified	1. 6-week study period insufficient to assess long-term efficacy
Hossam et al. (2022) (36)	4. Single site in Egypt	1. Frequency and type of PRP treatment		1. Complete wound healing, recurrence,	1. 8-week study period insufficient to

		(injection and/or gel) not standardized 4. Short duration of treatment; 8 weeks		quality of life not addressed 5. Primary outcome differences and timepoints were not prespecified	assess long-term efficacy
Shehab et al. (2023) (68)	4. Single site in Egypt	1. Frequency and type of PRP treatment (injection and/or gel) not standardized 4. Short duration of treatment; 6 weeks	1. Placebo treatment not clearly defined	1. Recurrence, quality of life not addressed	

PRP: platelet-rich plasma.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Saha et al. (2020) (67)						
Gupta et al. (2021) (62)		1-3. Blinding not described			1. Power calculations not reported	3. Confidence intervals and/or p

						values not reported
Hossam et al. (2022) (36)		1-3. Blinding not described		1. High loss to follow-up or missing data; reasons for and extent of missingness unclear at all timepoints	1. Power calculations not reported	3. Confidence intervals not reported
Shehab et al. (2023) (68)					1. Power calculations not reported	4. Complete healing rate not reported for the control group

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Platelet-Rich Plasma for Chronic Wounds

The evidence for autologous PRP for a variety of chronic wounds includes systematic reviews, RCTs, which have been summarized in several systematic reviews, and nonrandomized trials. In meta-analyses of individuals with lower extremity diabetic ulcers, PRP demonstrated an improvement over the control groups in complete wound closure, recurrence rate, and healing time, but moderate to high risk of bias and imprecision preclude drawing conclusions on other important outcomes such as recurrence, infection, amputation, and quality of life. In individuals with venous ulcers, PRP did not demonstrate an improvement over the control groups in complete wound closure, recurrence, wound infection, or quality of life, although imprecision likely precluded identifying differences on these outcomes. In individuals with pressure ulcers,

although PRP reduced wound size, other important outcomes such as complete wound closure were not measured. Overall, the studies are small and of low quality, and the results should be interpreted with caution.

Platelet-Rich Plasma for Acute Surgical or Traumatic Wounds

Clinical Context and Therapy Purpose

The purpose of PRP is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with acute surgical or traumatic wounds.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with acute surgical or traumatic wounds.

Interventions

The therapy being considered is PRP.

Comparators

Comparators of interest include standard wound care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for acute surgical or traumatic wound symptoms would typically occur in the months after starting treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Surgical Wounds

Aortic Arch Repair

Zhou et al. (2015) reported on a double-blind RCT with 80 patients that assessed the effect of PRP on the amount of blood transfused in the perioperative period for elective ascending and transverse aortic arch repair. (69) An anesthesiologist prepared the PRP so that the surgeon was unaware of the treatment group. The volume of PRP transfused was 726 mL and led to a reduction in transfusion rates for red blood cells, frozen plasma, cryoprecipitate, and platelets

by 34% to 70% (p<0.02). Hospital length of stay was also reduced (9.4 days vs. 12.7 days). There was no difference in mortality between the 2 groups (one patient in each group) and no significant differences in postoperative complications or other outcome measures. Corroboration of the effect of PRP on perioperative blood transfusion is needed.

Sternotomy Wounds

Serraino et al. (2015) reported on a large series with historical controls that assessed the occurrence of deep sternal wound infections in patients who underwent cardiac surgery either with (2010 to 2012, 422 consecutive patients) or without (2007 to 2009, 671 consecutive patients) application of PRP. (70) The 2 groups were comparable at baseline. At the end of cardiac surgery, PRP gel was applied to the sternum before the closure of subcutaneous tissue. Rates of both deep and superficial wound infections were reduced in the patients treated with PRP (deep: 0.2% vs. 1.5%, superficial: 0.5% vs. 2.8%). Interpretation of these results is limited by likely differences in treatments over time. RCTs are needed to evaluate this potential use of PRP.

Zhu et al. (2023) published a meta-analysis of the effect of PRP on sternal wound healing. (71) Eleven studies with a total of 8961 cardiac surgery patients were included. Patients were either treated with PRP (n=3663) or control therapies (n=5298), with sample sizes ranging from 44 to 2000 participants. PRP was found to have a significantly lower rate of sternal wound infection (Odds ratio [OR], 0.11; 95% CI, 0.03 to 0.34; p<.001; I^2, 0%), deep sternal wound infection (OR, 0.29; 95% CI, 0.16 to 0.51; p<.001; I^2, 32%), and superficial sternal wound infection (OR, 0.20; 95% CI, 0.13 to 0.33; p<.001; I^2, 0%) compared to patients in the control cardiac surgery groups. All pooled estimates at no to low heterogeneity (0% to 32%). The poor quality of included studies, heterogeneous PRP preparations, and heterogeneous cardiac surgeries limit the interpretation of the results.

Otolaryngology

A 2008 double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children (age range, 4 to 15 years). (72) PRP was placed into the tonsil beds of half of the children, where it was directly visible. To compare pain symptoms and recovery, a daily diary was completed by the patient or a family member for 10 days after surgery. A FACES Pain Scale was used for children ages 4 to 7 years, while a numeric pain rating scale was used for children older than 7 years. Diaries from 83% of patients showed no differences in pain, medication doses, activity, and days eating solid foods between the 2 conditions.

El-Anwar et al. (2016) reported on an RCT that evaluated PRP in 44 children (age range, 12 to 23 months) undergoing repair of a complete cleft palate. (73) Speech and velopharyngeal valve movement on follow-up were evaluated by 3 judges who “usually assessed every patient blindly,” physical examination, video nasoendoscopy, and audio recording of audio perceptual assessment. At 6 months, PRP-treated patients had better nasality grade on audio perceptual assessment (p=0.024) and better velopharyngeal closure on endoscopy (p=0.016).

Dinaki et al. (2024) conducted an RCT evaluating submucosal PRP injection on wound healing after endoscopic sinus surgery in 30 patients with chronic rhinosinusitis. (74) Patients were randomized 1:1 to PRP (2.5 ml on each side) or control (no additional treatment with no placebo). PRP significantly reduced moderate crusting on endoscopy at 1 week (36.6% vs. 80%; p<.00001) through 12 weeks post-surgery (0% vs. 16.6%; p=.021). Bleeding was lower in the PRP group during the first 2 weeks (minimal bleeding: 33.3% vs. 66.6%; p=.004 at 1 week; 10% vs. 50%, p=.0003 at 2 weeks) but not significantly different between groups thereafter. Granulation tissue formation was reduced at 8 and 12 weeks in the PRP group (mild granulation: 30% vs. 60%; p=.021 at 8 weeks; 26.6% vs. 46.6%; p=.005 at 12 weeks). VAS scores improved significantly in the PRP group across all time points, with a median score of 0 (interquartile range [IQR]: 0 to 1) at 12 weeks compared to 2 (IQR: 1 to 2) in controls (p=.001). No significant differences were observed for adhesion or infection rates (p>.05). Limitations included the small sample size with an absence of power calculations, lack of double blinding, and absence of follow-up beyond 3 months.

Other Surgical Wounds

A 2011 Norwegian trial of PRP applied to saphenous vein harvest sites after wound closure found no differences in the incidence of wound infection or cosmetic result. (75)

Alamdari et al. (2018) published a clinical trial evaluating the efficacy of pleurodesis with a combination of PRP and fibrin glue compared with surgical intervention. The study population consisted of 52 esophageal cancer patients with postoperative chylothorax who did not respond to conservative management. Each member of the population was consecutively and randomly allocated to either a PRP fibrin glue pleurodesis arm or a surgical thoracic duct ligation arm. Twenty-six in each arm were treated with their respective interventions. The patients were distributed into the intervention arms in a way that made each group similar in terms of tumor size and patient demographics. This distribution procedure was not described. All patients (n=26) in the PRP treatment arm and 20 (76.9%) in the surgery arm were successfully treated (p=0.009). Seven patients (26.92%) of the PRP required a second application of the PRP fibrin glue after a week. The mean length of hospital stay was higher in the surgery group (53.50 ± 16.662 days) than the PRP group (36.04 ± 8.224 days; p < 0.001). The study was limited due to the fact the procedure for randomization was not described and, thus, its efficacy cannot be evaluated. (26)

Mohamadi et al. (2019) reported on an RCT of 110 participants in Tehran that evaluated the efficacy of PRP gel in wound healing time following pilonidal sinus surgery. (76) Each group included 55 participants. Follow-up duration was 9 weeks. In the treatment group, PRP was both injected into the wound weekly, as well as applied to the wound surface and covered with latex. In the control group, wound dressing was described as "classic", but no other details were provided. Little to no detail was provided about specific outcome assessment methods (i.e., "pain duration was inquired from participants"). All patients completed the study and were included in the outcome assessments. PRP significantly shortened mean healing time (4.8 vs. 8.7 weeks; p<.001), pain duration (1.3 vs. 3.4 weeks; p<.001), and antibiotic consumption duration (0.57 vs. 1.74 weeks; p<.001). This RCT also performed regression analyses to evaluate

the correlation between different factors in wound healing activity. Significant negative associations were found between healing time and wound volume and pain duration and angiogenesis. Notable limitations of this study included unclearly defined wound dressing in the comparator group, unblinded and poorly defined outcome assessment, short-term follow-up and lack of assessment of other important health outcomes.

Slaninka et al. (2020) published an RCT that evaluated PRP in 24 individuals in the Czech Republic who had undergone dermo-epidermal skin grafts taken from the thigh area. (77) Indications for skin grafts were primarily hard-to-heal lower leg wounds. PRP was applied to 1 thigh and covered with Vaseline-impregnated, open-weave gauze and gauze. The control was the other thigh, which was also covered with open-weave gauze and gauze, but without PRP. Of the 24 included individuals, 3 (12.5%) were excluded after developing infections. The infections were described as first occurring on the non-PRP wound and only subsequently occurring on the PRP wound after several days. PRP significantly shortened median healing time (14 days vs. 18 days; p=.026). No other outcomes were reported. Notable limitations of the RCT include its small sample size and that it did not address important health outcomes and harms.

Traumatic Wounds

Kazakos et al. (2009) reported on a prospective RCT that evaluated treatment of acute traumatic wounds (open fractures, closed fractures with skin necrosis, friction burns) with platelet gel in 59 consecutive patients (27 PRP, 32 controls). (78) Conventional treatment consisted of topical washing and cleaning of the wounds, removal of the necrotic tissue, and dressing in petroleum jelly gauze every 2 days. In all patients with open tibial fractures, an external fixation system was applied. PRP gel was applied to the wounds after surgical debridement and placement of the external fixation system. The time needed for preparation and application of the PRP gel was 52 minutes. After that, PRP gel was applied to the wounds once weekly in the outpatient clinic until there was adequate tissue regeneration (mean, 21 days) sufficient to undergo reconstructive plastic surgery. Control patients receiving conventional treatment required a mean of 41 days for adequate tissue regeneration. Pain scores were significantly lower in PRP-treated patients at 2 and 3 weeks (visual analog scale score, 58 PRP vs. 80 controls). Although these results are encouraging, additional study with a larger number of patients is needed.

Marck et al. (2016) reported on a randomized, double-blind, within-patient-controlled study in patients with deep dermal to full-thickness burns undergoing split-skin graft, comparing PRP with usual care. (79) The study randomized 52 patients, 50 of whom received the allocated PRP intervention. There were no significant differences in short-term (5 to 7 days) rates in graft take in the intervention and control areas on each patient. At 3, 6, and 12 months, there were no significant differences in skin appearance or epithelialization scores.

Yeung et al. (2018) performed a prospective RCT to test the efficacy of lyophilized platelet-rich plasma powder (LPRP) on the healing rate of wounds in patients with deep, second-degree burn injuries in comparison with a control group using a placebo. LPRP was dissolved in a solution and applied on deep second-degree burn wounds once per day for 4 consecutive days.

Twenty-seven patients with deep second-degree burns were recruited and then those that met eligibility criteria were randomized into 2 groups. The LRPR group received the intervention (n=15) and the control group received a placebo application (n=12). A concentration of 1.0 x 10^7 platelets/cm^2 (wound area) was sprayed on the wound evenly. Function was assessed by the percentage of wound closure and bacteria picking out rate at weeks 2 and 3. The mean burn area of control for the LPRP was 75.65 ± 50.72 cm^2 and 99.73 ± 70.17 cm^2 (p=0013), respectively. In the control group, the original wound area was 25.49 cm^2 at baseline, 23.79 cm^2 (6.67% healed) at week 2, and 4.34 cm^2 (86.40% healed) at week 3. In the LPRP group, the original wound area was 84.36 cm^2, followed by 23.96 cm^2 (71.59% healed) at week 2, and 0.63 cm^2 (99.24% healed) at week 3. The wound closure rate at week 2 in the LPRP group reached nearly 80% and was greater than 90% by week 3, showing a significant difference (p<0.05). Alternatively, in the control group, the wound closure rates were 60% and 80% in 2 and 3 weeks, respectively. The postoperative infection rate in the LPRP (26.67%) was lower than the control group (33.33%). Neither was significant, statistically. One limitation of this study is that the powder is made by an independent lab and dissolved in a specified amount of water. This provides an opportunity for accidental error-this may also be the case with some liquid PRP. (80)

Huang et al. (2021) published a meta-analysis of 8 RCTs representing 539 patients with burn wounds. (81) The healing rate of burn wounds was improved with PRP (OR, 4.43; 95% CI, 2.13 to 9.22), yielding a significantly shorter wound healing time (OR, -4.23; 95% CI, -5.48 to -2.98) compared to conventional dressings for both superficial and deep burn groups. Incidence of adverse events, pain scores, and scar scores was also all improved in the PRP treatment group. Interpretation of results is limited by risks of bias arising from lack of blinding, small study size, heterogenous PRP preparations, and short follow-up durations.

Imam et al. (2023) published a meta-analysis of 13 comparative studies, including 808 individuals with burn wounds who were treated with PRP (n=413) or standard wound therapy (n=395) with sample sizes ranging from 25 to 100 individuals. (82) PRP had a shorter healing time than compared to standard therapy (mean difference [MD], -5.80; 95% CI, -7.73 to -3.88; p<.001) as well as a higher healing rate (OR, 3.14; 95% CI, 2.05 to 4.8; p<.001) although these pooled estimates had substantial (I^2=93%) and moderate heterogeneity (I^2=42%), respectively. Individuals treated with PRP also had a higher percentage of graft take area (MD, 4.39; 95% CI, 1.51 to 7.26; p<.001) and higher percent of area healed (MD, 12.67; 95% CI, 9.79 to 15.55, p<.001) compared to standard therapy for burn wounds with a low level of heterogeneity. No differences were observed in the graft take ratio or infection rates which showed low heterogeneity across studies in the pooled estimates. Interpretation of results is limited by risks of bias arising from low overall study quality, small study sizes, heterogenous PRP preparations, limited number of studies included for some comparisons, and short follow-up durations.

Section Summary: Platelet-Rich Plasma for Acute Surgical or Traumatic Wounds

The evidence for autologous PRP for a variety of acute surgical or traumatic wounds includes systematic reviews and RCTs. For a variety of other conditions, studies have either not

demonstrated a benefit or have demonstrated small benefits in studies with methodologic limitations.

Summary of Evidence

Recombinant Platelet-Derived Growth Factors

For individuals who have diabetic lower-extremity ulcers who receive recombinant platelet-derived growth factors (PDGFs), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity. Results have shown improved rates of healing with use of recombinant PDGF for diabetic neuropathic ulcers and pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pressure ulcers who receive recombinant PDGF, the evidence includes single RCT. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Results have shown improved rates of healing with use of recombinant PDGF for pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have venous stasis leg ulcers or acute surgical or traumatic wounds who receive recombinant PDGF, the evidence includes small RCT's. Relevant outcomes are symptoms, change in disease status, morbid events, QOL and treatment-related morbidity. The level of evidence does not permit conclusions whether recombinant PDGF is effective in treating other wound types, including chronic venous ulcers or acute traumatic wounds. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Platelet-Rich Plasma

For individuals who have chronic wounds who receive platelet-rich plasma (PRP), the evidence includes meta-analyses of a number of small controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. In meta-analyses of individuals with lower extremity diabetic ulcers, PRP demonstrated an improvement over the control groups in complete wound closure and healing time, but moderate to high risk of bias and imprecision preclude drawing conclusions on other important outcomes such as recurrence, infection, amputation, and quality of life. In individuals with venous ulcers, PRP did not demonstrate an improvement over the control groups in complete wound closure, recurrence, wound infection, or quality of life, although imprecision likely precluded identifying differences on these outcomes. In individuals with pressure ulcers, although PRP reduced wound size, other important outcomes such as complete wound closure were not measured. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute surgical or traumatic wounds who receive PRP, the evidence includes a systematic review and a number of small, controlled trials. Relevant outcomes are

symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Current results of trials using PRP are mixed, and the studies are limited in both size and quality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Physicians

In 2015, the American College of Physicians (ACP) published guidelines on treatment of pressure ulcers. (83) The guidelines noted that "although low-quality evidence suggests that dressings containing PDGF [platelet-derived growth factors] promote healing, ACP supports the use of other dressings such as hydrocolloid and foam dressings, which are effective at promoting healing and cost less than PDGF dressings." A search of the ACP website on December 1, 2020, found that this 2015 guideline is now listed as inactive.

Association for the Advancement of Wound Care

The Association for the Advancement of Wound Care developed guideline recommendations for the management of pressure ulcers (2010) (84) and venous ulcers (2015) (85):

- Pressure ulcer: "Growth factors are not indicated for PU [pressure ulcers] at this time." (level C evidence – no randomized controlled trials (RCTs) available comparing growth factors with A-level dressings) (84)
- Venous ulcer: "Platelet derived growth factor has shown no significant effects on VU [venous ulcer healing or recurrence]." (level A evidence) (85)

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. (86) The guidance stated that neither autologous platelet-rich plasma gel nor platelet-derived growth factors should be offered in the treatment of diabetic foot ulcers.

Medicare National Coverage

In 2012, the Centers for Medicare & Medicaid Services (CMS) revised its national coverage decision on autologous blood-derived products for chronic non-healing wounds. (87, 88) This revision replaces prior noncoverage decisions. (89, 90)

The Centers for Medicare & Medicaid Services covers autologous PRP only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when all of the following conditions are met:

"The patient is enrolled in a clinical research study that addresses the following questions using validated and reliable methods of evaluation…

"The clinical research study must meet the requirements specified below to assess the effect of PRP for the treatment of chronic non-healing diabetic, venous and/or pressure wounds. The clinical study must address:

- "Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, venous and/or pressure wounds who receive well-defined optimal usual care, along with PRP

therapy, experience clinically significant health outcomes compared to patients who receive well-defined optimal usual care for chronic non-healing diabetic, venous and/or pressure wounds as indicated by addressing at least 1 of the following:

- Complete wound healing?
- Ability to return to previous function and resumption of normal activities?
- Reduction of wound size or healing trajectory which results in the patient's ability to return to previous function and resumption of normal activities?"

In response to a formal request from Nuo Therapeutics on May 9, 2019, CMS began a fourth reconsideration of its national coverage decision. (61) To inform this reconsideration, the Mayo Evidence-based Practice Center performed a technology assessment that was published by Qu et al (2020) and its results are described above in the Rationale section. (20) Following their review of this evidence, on December 21, 2020, CMS posted a Proposed Decision Memorandum that proposes to expand its 2012 Coverage with Evidence Development decision to cover any use of autologous PRP "...for the treatment of chronic non-healing diabetic wounds under section 1862(a)(1)(A) of the Social Security Act (the Act)." This decision is based on the evidence described above that is sufficient "...to demonstrate that patients with diabetic ulcers who are treated with autologous PRP have better outcomes (complete wound healing) when compared to patients who receive standard care." CMS additionally noted that a limitation of the evidence is that "None of these studies addressed whether or not PRP affected a patient's ability to return to previous function and resumption of normal activities, or resulted in reduction of wound size or healing trajectory as an intermediary towards a formal endpoint of a patient's ability to return to previous function and resumption of normal activities."

For other chronic non-healing wounds, "CMS proposes that coverage of autologous PRP for the treatment of all other chronic non-healing wounds will be determined by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act."

In April 2021, CMS published an updated decision memo following the fourth reconsideration of the national coverage analysis stating that CMS will "cover autologous platelet-rich plasma (PRP) for the treatment of chronic non-healing diabetic wounds under section 1862(a)(1)(A) of the Social Security Act (the Act) for a duration of 20 weeks, when prepared by devices whose FDA cleared indications include the management of exuding cutaneous wounds, such as diabetic ulcers. Coverage of autologous PRP for the treatment of chronic non-healing diabetic wounds beyond 20 weeks will be determined by local Medicare Administrative Contractors (MACs).

Coverage of autologous PRP for the treatment of all other chronic non-healing wounds will be determined by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act." (91)

Ongoing and Unpublished Clinical Trials

Some larger studies that might influence this policy are listed in Table 11.

Table 11. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05850611	The Effect of Combination Therapy of Oral Methylene Blue and Platelet-rich Plasma-fibrin Glue in Patients With Non-healing Diabetic Foot Ulcer: a Pilot Study	20	Sept 2024
NCT05996614	Evaluation of Platelet Rich Plasma in Skin Graft Take for Patients With Post Burn Raw Areas	40	Feb 2025
NCT06281483	Efficacy of Platelet-rich Plasma Versus Platelet-rich Fibrin Versus Conventional Treatment in Chronic Non-healing Skin Ulcers: A Comparative Study	36	Jan 2026
NCT06298110	The Effect of PRP on Wound Healing in High Risk Patients Undergoing Abdominal Hysterectomy	80	Sep 2024 (not yet recruiting)
NCT05979584	Platelet Rich Plasma VS Platelet Fibrin Plasma in Treatment of Diabetes Foot Ulcer: a Randomized Controlled Trial	56	Aug 2025
Unpublished			
NCT02071979[a]	Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS)	1500	Jan 2018 (terminated; updated 01/18)
NCT02312596[a]	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Non-Healing Diabetic Foot Ulcers	200	Dec 2021 (unknown)
NCT02312570[a]	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	200	Dec 2021 (unknown)
NCT02307448[a]	Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds	80	Dec 2022 (terminated)
NCT02402374[a]	Randomized, Placebo-controlled, Blind-assessor Study to Evaluate the Safety and Efficacy of Autologous Platelet Rich Plasma Gel Prepared With the RegenKit-BCT Plus Family of Kits for the Treatment of Diabetic Foot Ulcer	192	Dec 2020 (unknown)

NCT: national clinical trial; PRP: autologous platelet-rich plasma.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0232T, 0481T
HCPCS Codes	G0460, G0465, P9020, S0157, S9055

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

08/01/2025	Document updated with literature review. Coverage reorganized with movement of some criteria to Policy Guidelines; no change to policy intent. Added references 24, 33, 66, 74, 87 and 92.
09/15/2024	Document updated with literature review. Coverage unchanged. Added references 87-108.
06/15/2024	Document updated with literature review. Coverage unchanged. Added references 21, 23, 32-35, 38, 41-42, 46, 53, 63, 65, 68, 78, 83-86; others updated.
11/15/2023	Reviewed. No changes.
05/15/2022	Document updated with literature review. Coverage unchanged. References 21 to 51, 58, 59 and 63 added; others updated or deleted.
07/01/2021	Reviewed. No changes.
05/15/2020	Document updated with literature review. Coverage unchanged. References 12, 22, 23, 29 and 32 added.
04/15/2019	Reviewed. No changes.
11/01/2018	Document updated with literature review. Coverage modified to remove language specific to use of recombinant and autologous platelet-derived growth factors for orthopedic conditions; content moved to RX501.101. Document title changed from: Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and Other Miscellaneous Conditions. References 1-2, 16, 20, 23-25, 27-31 added.
07/15/2017	Reviewed. No changes.
06/01/2016	Document updated with literature review. 1) The following was added the experimental, investigational and/or unproven listing of indications for becaplermin: “ulcers not extending through the dermis into the subcutaneous tissue”. 2) The following was added to the experimental, investigational and/or unproven listing of autologous blood-derived preparations (i.e., platelet-rich plasma): surgical wounds. 3) The following orthopedic indications for primary use were added to the experimental, investigational and/or unproven listing: achilles tendinopathy, lateral epicondylitis, osteochondral lesions and osteoarthritis. 3) The following orthopedic indications for adjunctive use in the following surgical procedures were added to the experimental, investigational and/or unproven listing: ACL reconstruction, hip fracture, long-bone nonunion, patellar tendon repair, rotator cuff repair, spinal fusion and subacromial decompression surgery.
08/01/2015	Reviewed. No changes.
02/15/2014	Document updated with literature review. The following was added to the experimental, investigational and unproven coverage statement for autologous blood-derived preparations (i.e., platelet-rich plasma): “Experimental, investigational and unproven for all indications including but not limited to”. In addition, the following was also added to the listing of examples of experimental investigational and unproven indications for

	autologous blood-derived preparations (i.e., platelet-rich plasma): "adjunctive use in surgical procedures (e.g., orthopedic, reconstructive)".
07/15/2008	Revised/updated entire document; this policy is no longer scheduled for routine literature review and update.
11/15/2006	Revised/updated entire document
06/01/2001	Codes Revised/Added/Deleted
11/01/2000	Revised/updated entire document
04/01/1999	Revised/updated entire document
06/01/1998	Revised/updated entire document
07/01/1995	Revised/updated entire document
04/01/1993	Revised/updated entire document
01/01/1993	New medical document