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Platelet-Rich Plasma in Regenerative Medicine: Biology, Preparation, Classification, and Clinical Applications

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Abstract

Background: Platelet-rich plasma (PRP) is the most widely used autologous orthobiologic in the world, yet it remains one of the least standardised. Twenty-five years after Marx defined the platelet-concentration threshold that still anchors the field, PRP is prepared by dozens of incompatible protocols, described by at least six competing classification systems, marketed for more than thirty indications, and reimbursed for exactly one. The result is a literature in which every meta-analysis pools products that are not the same product.\

Objectives: To assemble a single, source-grounded synthesis of PRP that links platelet biology to the physics of centrifugation, the arithmetic of dose, the logic of classification, and the measured clinical effect size in every major indication; and to state explicitly, for each indication, whether the evidence supports use, does not support use, or cannot yet answer the question.

Methods: Narrative review with structured evidence appraisal. Six independent source-grounded evidence briefs were compiled covering platelet biology and growth-factor cargo; preparation, devices and classification;

musculoskeletal clinical outcomes; dermatological, wound, dental and non-orthopaedic outcomes; combination with mesenchymal stromal cells, exosomes and next-generation autologous products; and safety, regulation, reimbursement and anti-doping status. Every numerical value reported in this review was extracted from a retrieved primary source; 226 sources are cited. Effect estimates are compared against published minimal clinically important differences rather than against statistical significance alone.

Results: Platelet α-granules carry more than 300 proteins and PRP releasate exceeds 1,300 identified proteins, but only a minority have been assayed in any clinical trial, and no trial has reported the delivered dose of any single growth factor. Centrifugation parameters that differ by a factor of ten in relative centrifugal force are all described in the literature as producing "PRP". In knee osteoarthritis, the largest network meta-analysis (53) randomised trials, 5,031 patients) found no optimal platelet dose, no effect of leukocyte content, and no benefit of exogenous activation at six months, while the largest adequately blinded trial (RESTORE, 288 patients) found no structural or symptomatic superiority over saline on its primary endpoint. Effects in lateral elbow tendinopathy, diabetic foot ulceration and venous leg ulceration are more consistent; effects in facial rejuvenation, recurrent implantation failure, erectile dysfunction and periodontal intrabony defects are not supported. All 79 systematic reviews of PRP for knee osteoarthritis contained spin. Pooled complication rates are higher with PRP than with comparators (18.66% versus 9.14%, number needed to harm 11), although severe events are rare; documented harms include septic arthritis, irreversible visual loss after periocular injection, and a five-case HIV cluster linked to unlicensed cosmetic PRP microneedling.

Conclusions: PRP is neither the panacea of its marketing nor the placebo of its harshest critics. It is a family of biologically plausible, procedurally heterogeneous products whose measured benefit is small, indication-specific, and frequently below the threshold a patient would notice. The path forward is not another underpowered trial of an undescribed product; it is mandatory dose-and-composition reporting, blinded comparators, and honest alignment of clinical claims with regulatory reality.

Keywords

Platelet-rich plasma; Regenerative medicine; Growth factors; Mesenchymal stem cells; Exosomes; Tissue repair; orthopedics.

Abbreviations

A2M, alpha-2-macroglobulin; ACD-A, acid citrate dextrose solution A; ACL, anterior cruciate ligament; ACS, autologous conditioned serum; AD-MSC, adipose-derived mesenchymal stromal cell; AGA, androgenetic alopecia; AOFAS, American Orthopaedic Foot and Ankle Society; APS, autologous protein solution; A-PRF, advanced platelet-rich fibrin; BMAC, bone marrow aspirate concentrate; CAGR, compound annual growth rate; CAPE-V, Consensus Auditory-Perceptual Evaluation of Voice; CBER, Center for Biologics Evaluation and Research; CFM, Conselho Federal de Medicina; CGF, concentrated growth factor; CI, confidence interval; COX-2, cyclo-oxygenase-2; CPT, Current Procedural Terminology; DEPA, dose, efficiency, purity, activation; DFU, diabetic foot ulcer; EAU, European Association of Urology; EDQM, European Directorate for the Quality of Medicines and HealthCare; EDTA, ethylenediaminetetraacetic acid; EV, extracellular vesicle; FBS, fetal bovine serum; FDA, US Food and Drug Administration; GAIS, Global Aesthetic Improvement Scale; GMP, good manufacturing practice; GRIIP, Groupe de Recherche sur les Injections Intra-articulaires de PRP; HA, hyaluronic acid; HCT/P, human cells, tissues, and cellular and tissue-based product; hPL, human platelet lysate; ICER, incremental cost-effectiveness ratio; ICRS, International

Cartilage Regeneration and Joint Preservation Society; IGF, insulin-like growth factor; IIEF, International Index of Erectile Function; IKDC, International Knee Documentation Committee; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; i-PRF, injectable platelet-rich fibrin; ISTH, International Society on Thrombosis and Haemostasis; KL, Kellgren–Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; L-PRF, leukocyte- and platelet-rich fibrin; LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; MARSPILL, method, activation, red blood cells, spin, platelet number, image guidance, leukocyte, light activation; MASI, Melasma Area and Severity Index; MCID, minimal clinically important difference; MD, mean difference; MF-AT, microfragmented adipose tissue; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics; MMP, matrix metalloproteinase; MRONJ, medication-related osteonecrosis of the jaw; MSC, mesenchymal stromal cell; NMA, network meta-analysis; NNH, number needed to harm; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; ONFH, osteonecrosis of the femoral head; OR, odds ratio; OSDI, Ocular Surface Disease Index; PAW, platelets, activation, white cells; PDGF, platelet-derived growth factor; POSAS, Patient and Observer Scar Assessment Scale; PRF, platelet-rich fibrin; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; PUSH, Pressure Ulcer Scale for Healing; QALY, quality-adjusted life year; RCF, relative centrifugal force; RCT, randomised controlled trial; RR, risk ratio; SMD, standardised mean difference; SoHO, substances of human origin; STEMI, ST-elevation myocardial infarction; TGF-β, transforming growth factor beta; TGA, Therapeutic Goods Administration; T-PRF, titanium-prepared platelet-rich fibrin; VAS, visual analogue scale; VEGF, vascular endothelial growth factor; VHI-10, Voice Handicap Index-10; VISA-A, Victorian Institute of Sport Assessment–Achilles; VLU, venous leg ulcer; WADA, World Anti-Doping Agency; WBC, white blood cell; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; YAP, Yes-associated protein.

Introduction

Twenty-five years of an unstandardised standard

Platelet-rich plasma occupies a peculiar position in modern medicine. It is simultaneously the most frequently administered autologous biological product in outpatient musculoskeletal practice and one of the least characterised. In Japan, where every regenerative-medicine procedure must be registered under the Act on the Safety of Regenerative Medicine, platelet-rich plasma accounted for 3,041 of 4,621 registered provision plans, or 65.8% of all regenerative medicine delivered in the country, and 74.4% of privately delivered Class III activity [1]. The global market was valued at USD 650.13 million in 2025 with a projected compound annual growth rate of 13.2% to USD 1,751.45 million by 2033 [2]. Yet no platelet-rich plasma device fetched for this review is cleared by the United States Food and Drug Administration for a single intra-articular, tendinous, dermatological, trichological or sexual-medicine indication, and the mandatory labelling for the relevant device class states that the safety and effectiveness of the device for in vivo indications for use has not been established [3].

A short history with a long shadow

The modern era begins with Marx and colleagues, who defined platelet-rich plasma as an autologous concentrate containing approximately 1,000,000 platelets per microlitre in 5 mL of plasma, and who documented that roughly 70% of stored growth factor is released within ten minutes of activation and essentially 100% within one hour [4]. That single arithmetic definition, produced for maxillofacial bone grafting, became the de facto standard for every subsequent clinical application, including applications in

which platelet number has never been shown to correlate with outcome. Three consequences followed and have never been undone. First, a number derived from one tissue was exported to all tissues. Second, because the number is a concentration rather than a total dose, protocols delivering wildly different absolute platelet loads could all claim compliance. Third, because concentration is trivially achievable by reducing plasma volume, the definition rewarded arithmetic rather than biology.

Two decades of proliferation followed. Preparation moved from open manual double-spin protocols in blood-bank tubes to closed proprietary systems, gravity-filtration devices, buffy-coat separators and automated apheresis platforms. Nomenclature proliferated in parallel: pure platelet-rich plasma, leukocyte-rich platelet-rich plasma, platelet-rich fibrin, advanced platelet-rich fibrin, injectable platelet-rich fibrin, titanium-prepared platelet-rich fibrin, concentrated growth factors, plasma rich in growth factors, autologous protein solution, autologous conditioned serum and hyperacute serum. Each is a different product with different cellular content, different release kinetics and different regulatory status, and yet the clinical literature routinely pools them.

What this review does differently

This review is built on six independently compiled, source-grounded evidence briefs, and every numerical value reported below was extracted from a retrieved primary document rather than from a secondary summary. Three editorial rules were applied throughout. First, effect estimates are judged against published minimal clinically important differences, not against p values; a statistically significant improvement smaller than the smallest change a patient can perceive is reported as a negative result. Second, where a proprietary product was used, the product, the centrifugation parameters and the delivered platelet dose are reported when the source states them, and their absence is reported when it does not. Third, where the evidence base is contaminated by retraction, spin or undisclosed funding, this is stated in the same paragraph as the effect estimate rather than deferred to a limitations section.

Instrument	Population / setting	Minimal clinically important difference	Source anchor
WOMAC total (0–100 normalised)	Knee osteoarthritis, intra-articular injection	≈12 points	Exercise-controlled randomised trial pre-specification [5]
WOMAC pain (0–10 numeric)	Knee osteoarthritis	≈2 points	Exercise-controlled randomised trial pre-specification [5]
KOOS Activities of Daily Living	Knee osteoarthritis	9.2 points	Network meta-analysis of 53 trials [6]
KOOS Quality of Life	Knee osteoarthritis	10.3 points	Network meta-analysis of 53 trials [6]
IKDC subjective score	Knee osteoarthritis and cartilage lesions	≈11 points at 6–12 months	Microfragmented adipose versus PRP trial [7]
IIEF erectile-function domain	Erectile dysfunction	≥4 points	Meta-analysis of 10 studies [8]
Hair density	Androgenetic alopecia	No validated threshold; ≈20 hairs/cm² used pragmatically	Bayesian network meta-analysis [9]
POSAS observer scale	Post-traumatic and post-burn scars	No validated threshold reported	Randomised laser trial [10]
Complete wound closure	Diabetic foot and venous leg ulcers	Binary endpoint; no MCID required	Cochrane review [11]

Table 1: Interpretive thresholds used throughout this review. Where an indication has no validated minimal

clinically important difference, that absence is itself a reportable limitation of the evidence base.

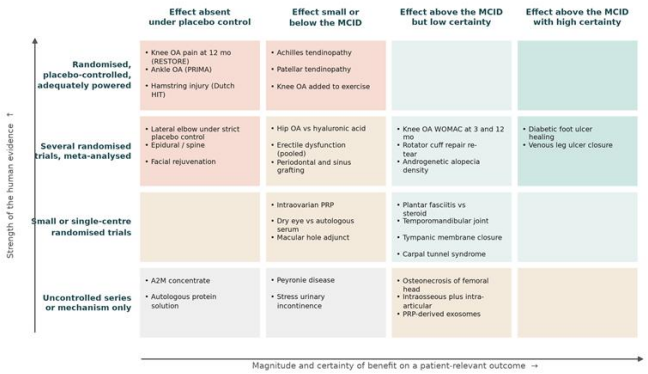

Figure 1: The platelet-rich plasma evidence landscape. Each cell positions an indication by the maturity of its randomised evidence (horizontal) against the consistency and magnitude of measured benefit relative to the minimal clinically important difference (vertical). Indications cluster in the lower-left quadrant — abundant enthusiasm, immature evidence — far more often than in the upper-right.

Molecular Mechanisms: What Is Actually In The Syringe

The therapeutic rationale for platelet-rich plasma rests on a single premise: that concentrating the platelet, and with it the platelet secretome, delivers a supraphysiological pulse of mitogenic, angiogenic, chemotactic and matrix-modulating signals to a tissue whose intrinsic repair capacity is insufficient. The premise is biologically sound. The problem is that the secretome is far larger, far more variable, and far more context-dependent than the five or six growth factors that appear in most clinical papers.

The platelet as a secretory organelle

A resting platelet contains 50 to 80 α-granules of 200 to 500 nm diameter, occupying approximately 10% of platelet volume and carrying more than 300 distinct proteins [12]. Proteomic interrogation of the activated product raises this figure substantially: platelet releasate contains more than 1,300 identified proteins and platelet lysate more than 3,800, reflecting the additional cytoplasmic and membrane content liberated by freeze-thaw disruption [13]. Dense granules contribute adenosine diphosphate, adenosine triphosphate, serotonin, calcium and polyphosphates; lysosomes contribute acid hydrolases and cathepsins. This molecular inventory means that the clinical variable is not “growth factor concentration” but the entire composition of a complex secretome whose proportions shift with anticoagulant, centrifugal force, leukocyte carry-over, erythrocyte contamination, activation method and time to injection.

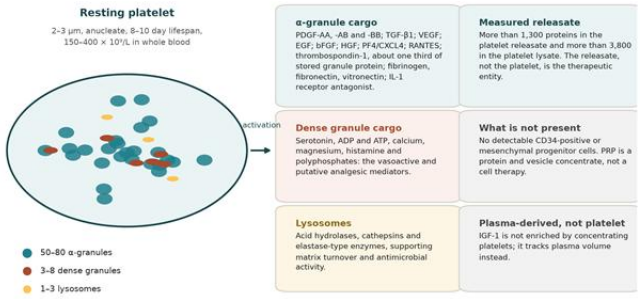

Figure 2: Platelet ultrastructure and the granule-derived secretome. Alpha granules dominate protein cargo; dense granules supply small-molecule mediators; lysosomal and membrane-derived components add proteolytic and vesicular signalling. Protein counts shown are those reported for releasate and lysate proteomes rather than for intact platelets.

Growth-factor concentrations: what has actually been measured

Direct measurement of growth-factor content in platelet concentrates is surprisingly rare and surprisingly discordant. Kobayashi and colleagues assayed cumulative ten-day release from platelet-rich plasma, leukocyte-platelet-rich fibrin and advanced platelet-rich fibrin prepared from the same donors, and reported PDGF-AA of 6,176, 9,262 and 11,048 pg/mL respectively; TGF-β1 of 1,105, 1,110 and 1,589 pg/mL; VEGF of 847, 732 and 847 pg/mL; EGF of 363, 512 and 659 pg/mL; and IGF of 54, 166 and 129 pg/mL [18]. Amable and colleagues normalised to platelet number and found TGF-β1 of 318.6 ± 118.4 pg per 10^6 platelets, while IGF-1 at 105.30 ± 48.44 ng/mL did not differ from plasma (P = 0.9734), confirming that insulin-like growth factor 1 in platelet-rich plasma is overwhelmingly plasma-derived rather than platelet-derived [19]. This single observation invalidates a common marketing claim, namely that platelet concentration raises IGF-1 delivery.

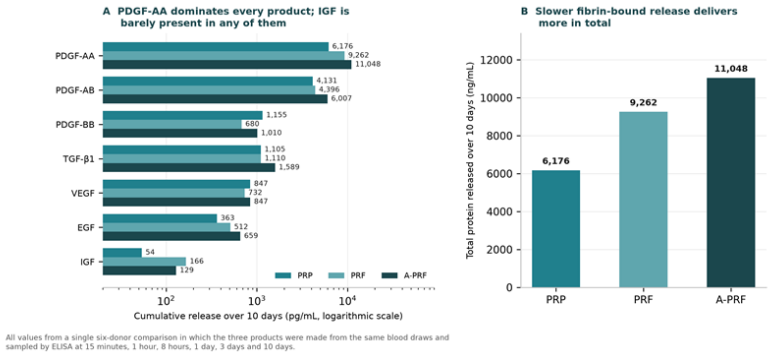

Figure 3: Measured growth-factor content across platelet products. Values are those reported by the source studies; note the different normalisations used (concentration in the final product versus content per 10^6 platelets) and the near-identity of IGF-1 between platelet-rich plasma and plasma.

Growth factor	Principal source	Reported quantity	Established biological role
PDGF-AA / -AB / -BB	Platelet α-granule	6,176 pg/mL (PRP), 9,262 (L-PRF), 11,048 (A-PRF) over 10 days [18]	Mitogen and chemoattractant for mesenchymal cells; pericyte recruitment

TGF-β1	Platelet α-granule	1,105 / 1,110 / 1,589 pg/mL [18]; 318.6 ± 118.4 pg per 10^6 platelets [19]	Matrix synthesis; chondrogenesis; also profibrotic and osteophyte-associated
VEGF	Platelet and leukocyte	847 / 732 / 847 pg/mL [18]	Angiogenesis and vascular permeability
EGF	Platelet α-granule	363 / 512 / 659 pg/mL [18]	Epithelial and fibroblast proliferation
IGF-1	Plasma, not platelet	105.30 ± 48.44 ng/mL, no difference from plasma (P = 0.9734) [19]	Anabolic; myogenesis
bFGF / FGF-2	Platelet and matrix-bound	Not quantified in the retrieved comparative assays	Angiogenesis; fibroblast mitogenesis
HGF	Platelet α-granule	Not quantified in the retrieved comparative assays	Anti-fibrotic; anti-inflammatory via NF-κB suppression
IL-1β (catabolic)	Leukocyte, chiefly neutrophil	3.67 (leukocyte-rich) versus 0.31 (leukocyte-poor) [21]	Pro-inflammatory; matrix degradation
MMP-9 (catabolic)	Neutrophil	222 versus 40 [21]	Matrix degradation

Table 3: Growth factors and counter-regulatory mediators in platelet concentrates. The final column is clinically consequential: platelet-rich plasma itself is not prohibited in sport, but several of the growth factors it contains are prohibited when administered in isolated or recombinant form.

Cellular content: the leukocyte and erythrocyte question

The most consequential compositional variable is not platelet number but leukocyte content. Sundman and colleagues compared leukocyte-rich and leukocyte-poor preparations from the same donors and found neutrophil concentrations of 8,455 versus 109 per millilitre, interleukin-1β of 3.67 versus 0.31, matrix metalloproteinase-9 of 222 versus 40, and TGF-β1 of 89 versus 20 ng/mL [21]. Leukocyte-rich preparations therefore deliver both more anabolic and more catabolic signal simultaneously, which is why the leukocyte debate cannot be resolved by asserting that white cells are “inflammatory” and therefore undesirable. Erythrocyte contamination is less ambiguous: haemolysis releases free haemoglobin and iron, and red-cell contamination has been associated with synoviocyte death and with the pain reported after injection [22].

The clinical translation of this in-vitro dichotomy is weaker than expected. In the largest network meta-analysis available, leukocyte content was not an effect modifier for any clinical outcome in knee osteoarthritis [6]. However, in the largest dedicated safety meta-analysis, the excess of adverse events over hyaluronic acid was significant only for leukocyte-rich preparations [23]. The defensible synthesis is therefore that leukocyte depletion has not been shown to improve efficacy but has been shown to reduce short-term reactogenicity.

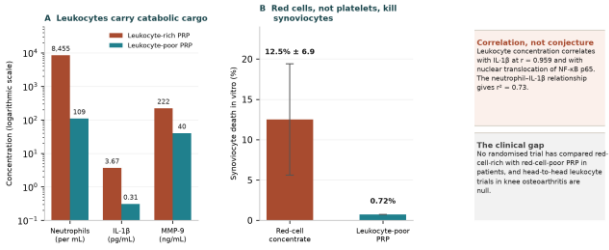

Figure 4: Cellular composition across preparation categories and its measured consequences. Leukocyte-rich preparations deliver more of both anabolic and catabolic mediators; the clinical signal from this difference appears in reactogenicity rather than in efficacy.

Fibrin architecture, activation and the release curve

Activation determines not only how much cargo is released but over what interval. Exogenous activation with calcium chloride or thrombin produces a rapid burst; in-situ activation by contact with collagen and tissue thromboplastin produces a slower and more sustained release; and polymerised fibrin scaffolds such as platelet-rich fibrin release over days rather than minutes [24]. The fibrin matrix is not inert packaging: fibre thickness, branch-point density and clot stiffness govern cell migration into the construct [25]. This is the mechanistic basis for the platelet-rich fibrin family described in Section 5, and for the clinically important observation that the network meta-analysis found exogenous activation to have no effect at six months but a significant effect on twelve-month KOOS Activities of Daily Living, Sport and Quality of Life subscales [6].

Classification Systems: Six Answers To One Question

Classification exists to make trials comparable. In platelet-rich plasma it has achieved the opposite, because at least six systems are in simultaneous use [26], none has been adopted by a majority of authors, and several classify on axes that the clinical literature does not report.

Dohan Ehrenfest 2009: the architectural dichotomy

The first widely adopted framework divided platelet concentrates on two axes, leukocyte content and fibrin architecture, generating four families: pure platelet-rich plasma, leukocyte- and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin [27]. Its enduring value is conceptual: it recognised that a liquid injectable and a polymerised solid membrane are different pharmaceutical dosage forms and cannot be pooled. Its limitation is that it is categorical rather than quantitative and therefore permits a ten-fold difference in delivered platelet dose within a single category.

PAW 2012: platelets, activation, white cells

DeLong and colleagues introduced the first quantitative system, grading absolute platelet concentration, whether exogenous activation was used, and the presence or absence of white cells [28]. PAW is the ancestor of every subsequent dose-aware classification and the first to make explicit that activation is a protocol decision rather than an inherent property.

MARSPILL, depa, mautner and the isth proposal

MARSPILL extended the axes to method, activation, red blood cells, spin, platelet number, image guidance, leukocyte content and light activation [29], and formalised the observation that platelet concentrations above roughly 1.5 million per microlitre may inhibit rather than stimulate stem-cell proliferation [30]. The DEPA classification shifted the emphasis decisively from concentration to absolute dose, purity and activation; when applied retrospectively to twenty commercial devices it revealed absolute platelet doses ranging from 0.21 to 5.43 billion and platelet recovery efficiencies from 13.1% to 79.3%, with no device exceeding 90% recovery [31]. Mautner and colleagues proposed a pragmatic clinical coding system for use in trial reporting [32], and the Subcommittee on Platelet Physiology of the International Society on Thrombosis and Haemostasis issued formal guidance advocating standardised terminology and platelet-dose reporting [33]. Each proposal is defensible; their coexistence is not.

System	Year	Classifying axes	Principal strength

Dohan Ehrenfest	2009	Leukocyte content; fibrin architecture	Separates liquid injectables from solid fibrin membranes
PAW (DeLong)	2012	Platelet concentration; activation; white cells	First quantitative platelet grading
Mautner et al.	2015	Platelet count, leukocytes, red cells, activation	Designed for trial reporting
DEPA (Magalon)	2016	Dose of injected platelets; efficiency of production; purity; activation	Shifts focus from concentration to absolute dose
MARSPILL (Lana)	2017	Method, activation, red cells, spin, platelet number, image guidance, leukocytes, light activation	Most complete; captures image guidance and photoactivation
ISTH SSC guidance	2018	Terminology and minimum characterisation	Authority of a haemostasis standards body
Mishra threshold	as applied 2026	Platelet enrichment ≥ 5× baseline; leukocyte presence	Applicable to 55 of 57 arms (96.5%) in a network meta-analysis

Table 4: The six coexisting classification systems and a threshold-based scheme applied in the most recent network meta-analysis. No system classifies on an axis that has been shown to predict clinical outcome.

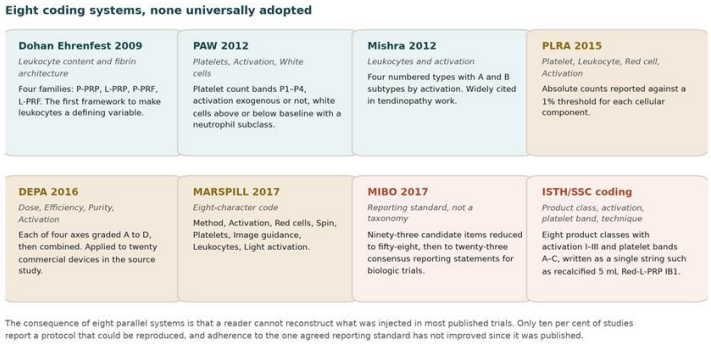

Figure 5: The classification landscape. Each system is plotted by the number of axes it grades against the proportion of the published literature that reports enough information for the system to be applied. Completeness and applicability are inversely related.

Why classification has failed: the reporting audit

The reason no classification has succeeded is that the underlying trials do not report the variables. Chahla and colleagues audited the clinical orthopaedic literature and found that only 10% of studies provided a reproducible preparation protocol, 16% reported the composition of the final product and 20% reported whether a second centrifugation was used [34]. Murray and colleagues responded with the Minimum Information for Studies Evaluating Biologics in Orthopaedics checklist, comprising twenty-three reporting items [35]. Adherence remains below 55% [36], and subsequent audits confirm persistent non-reporting of platelet dose, leukocyte content and red-cell contamination [37][38][39]. The single most striking demonstration of this failure comes from aesthetic dermatology, where an overview of thirteen systematic reviews covering twenty-eight primary studies found that the final platelet number was never reported in any primary study [40].

Audit	Scope	Key reporting deficiency	Implication

Chahla et al. 2017	Clinical orthopaedic PRP literature	Reproducible protocol in 10%; composition in 16%; second-spin status in 20% [34]	Most published PRP cannot be replicated
MIBO checklist	23 items proposed for PRP and MSC studies	Consensus standard, not journal-mandated [35]	Compliance is voluntary and therefore low
MacElroy et al.	Adherence audit of the PRP literature	MIBO adherence below 55% [36]	Nearly half of required items still missing after a decade
Subsequent audits	Randomised trials and composition reporting	Persistent non-reporting of dose, leukocytes and red cells [37][38][39]	No improvement trend demonstrable
Cruciani et al. 2024	13 systematic reviews, 28 primary studies, facial rejuvenation	Final platelet number never reported in any primary study [40]	An entire indication rests on undescribed products
Richardson et al. 2025	All 79 systematic reviews of PRP for knee osteoarthritis	Spin in 100%; mean spin score 5.5 ± 2.3; benefit claimed despite high risk of bias in 84.8% [41]	Secondary literature systematically overstates benefit
Chou et al. 2023	87 randomised trials	Undisclosed funding status predicted a positive result (odds ratio 3.61, 95% CI 1.1–11.9, p = 0.035) [42]	Non-disclosure, not industry funding itself, tracks positivity

Table 5: Reporting-quality and evidence-integrity audits of the platelet-rich plasma literature. These findings constrain how confidently any pooled effect estimate in this review can be interpreted.

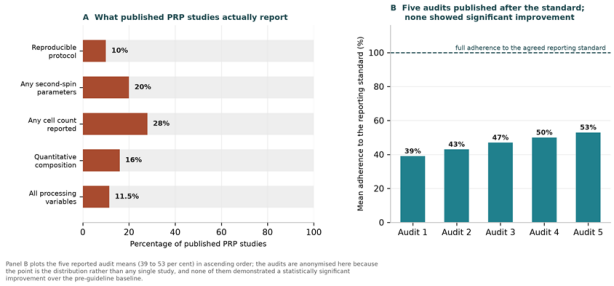

Figure 6: Reporting completeness across the platelet-rich plasma literature. Bars show the proportion of studies reporting each item; the dashed reference line marks full compliance with the Minimum Information for Studies Evaluating Biologics in Orthopaedics checklist.

Preparation: the physics that determines the product

Every compositional property of platelet-rich plasma is set by decisions made before the needle enters the patient. Those decisions are governed by sedimentation physics, and the governing quantity is relative centrifugal force rather than rotational speed. The conversion is $g = 1.118 \times 10^{-5} \times R \times rpm^2$, where R is the rotor radius in centimetres [43]. Because R differs between devices, two laboratories following the same revolutions-per-minute instruction can generate substantially different forces. This alone explains a portion of the irreproducibility documented in Section 3.

Single-spin versus double-spin

A single centrifugation separates whole blood into a plasma layer, a buffy coat and a red-cell fraction; platelet-rich plasma is drawn from the plasma layer immediately above the buffy coat. A second centrifugation of that plasma pellets the platelets, allowing supernatant plasma to be discarded and a higher concentration to be resuspended in a smaller volume. Saqlain and colleagues quantified the difference directly: single spin produced 594.6×10^3 platelets per microlitre against 923.06×10^3 for double spin ($p < 0.01$), with white-cell counts of 6.056 versus 1.06×10^3 per microlitre [44]. Double spin therefore raises concentration and lowers leukocyte content, at the cost of an additional handling step, greater platelet activation and lower recovery.

The clinical consequence of this laboratory difference is, so far, undetectable. In androgenetic alopecia, a meta-analysis of three randomised trials and ninety participants found no difference in delivered platelets (mean difference 66.14 × 10^9/L, p = 0.77) and no difference in hair density (4.10%, 95% CI −4.74 to 12.93, p = 0.36, I^2 = 0%) [45], a finding corroborated by a separate randomised comparison [46].

Force and time: where the optima actually lie

Piao and colleagues modelled and then validated cell-recovery rates across centrifugation conditions, identifying 700 to 800 g for four to five minutes as the practical optimum for recovery, 240 g for fifteen minutes as the condition of maximal platelet integrity, and a critical force of 350 g at twelve minutes [47]. Perez and colleagues approached the same question through activation markers and found that soluble P-selectin rises at 800 and 1,200 g, while 70 to 100 g gave the best platelet recovery with the least activation [48]. These two conclusions are not contradictory: they optimise different endpoints. High force maximises yield at the cost of premature activation and granule loss; low force preserves integrity at the cost of yield. No clinical trial has ever randomised patients between these two philosophies.

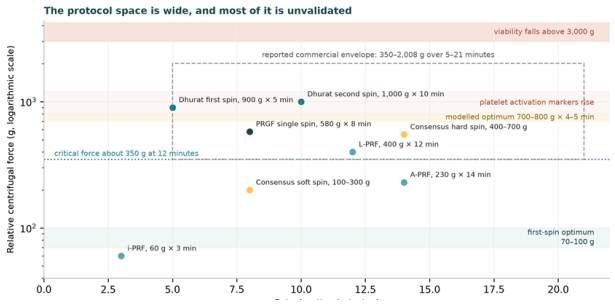

Figure 7: Centrifugation parameter space. Published protocols are plotted by relative centrifugal force against duration, with the recovery optimum, the integrity optimum and the activation threshold marked. Protocols separated by an order of magnitude in force are all described in the literature as producing platelet-rich plasma.

Protocol / parameter	Reported condition	Measured consequence	Source
Recovery optimum	700–800 g for 4–5 min	Highest validated platelet recovery	[47]
Integrity optimum	240 g for 15 min	Maximal platelet integrity	[47]
Critical force	350 g at 12 min	Threshold beyond which recovery modelling changes regime	[47]
Least-activation condition	70–100 g	Best recovery with least activation	[48]
Activation threshold	800 g and 1,200 g	Soluble P-selectin rises	[48]
Single spin	Variable	594.6 × 10^3 platelets/µL; WBC 6.056 × 10^3/µL	[44]
Double spin	Variable	923.06 × 10^3 platelets/µL (p < 0.01); WBC 1.06 × 10^3/µL	[44]
PRGF (Anitua)	580 g for 8 min, single spin	Leukocytes 0.15 ± 0.08 × 10^3/µL	[49]
RESTORE trial protocol	1,500 g for 5 min, single spin, 5 mL	1.6–5× enrichment, ≈80% platelet recovery	[50]
Exercise-controlled trial protocol	830 g for 5 min, 26 mL processed to 6 mL	3.4× enrichment, 76% recovery	[5]
Commercial protocol range	350–2,008 g, 5–21 min	Kit cost US$50–500	[51]

Freeze-dried protocol	800 g × 5 min then 580 g × 20 min	4.1-fold enrichment (130.1 ± 41.1 versus 31.5 ± 7.3 × 10^4/μL)	[52]
L-PRF	≈400 g (2,700 rpm) for 12 min	Solid fibrin membrane; cannot be stored	[53]
A-PRF	230 g (1,500 rpm) for 14 min	Looser fibrin, higher leukocyte retention	[53]
A-PRF+	200 g (1,300 rpm) for 8 min	Further reduced force	[53]
i-PRF	60 g (700 rpm) for 3 min	Injectable liquid fibrinogen-rich product; transfer within 2 min 30 s	[53]
T-PRF	Titanium tubes, 2,800 rpm for 12 min	Avoids silica activator	[53]
CGF	2,400–3,300 rpm variable-speed programme	Concentrated growth factor fraction	[53]

Table 6: Centrifugation parameters reported across the platelet-rich plasma and platelet-rich fibrin literature, with the consequence each condition was shown to produce. Relative centrifugal force spans more than a thirty-fold range.

Platelet dose: the variable that may matter most

If any compositional variable predicts outcome, the strongest candidate is absolute platelet dose rather than concentration. A systematic analysis of dose in randomised trials of intra-articular platelet-rich plasma found that 90% of arms delivering more than 5.5 billion platelets reported improvement, whereas arms delivering 2.3 billion or fewer failed ($p < 0.01$) [54]. Against this, the largest network meta-analysis of 53 trials and 5,031 patients found no optimal platelet dose and could not identify a dose threshold that predicted response [6]. The competing published thresholds are themselves irreconcilable: one analysis proposes a cut-point below versus at or above 800,000 platelets per microlitre, another proposes bands of fewer than 5 billion, 5 to 10 billion and more than 10 billion total platelets, and a third proposes a three-fold enrichment criterion [6,55].

Complicating matters further, the dose–response relationship is probably not monotonic. Platelet concentrations above approximately 1.5 million per microlitre may inhibit stem-cell proliferation [30], and in culture the optimum for human bone-marrow stromal cells lies near 5% platelet-rich plasma with colony-forming efficiency maximal at 1% to 2%, while 20% to 30% represses proliferation and 40% to 50% causes cell death [56]. Straum has argued that much of the apparent bell-shaped curve is an artefact of heterogeneous methodology rather than a genuine biological ceiling [57], and the honest position is that the shape of the human dose–response curve is unknown.

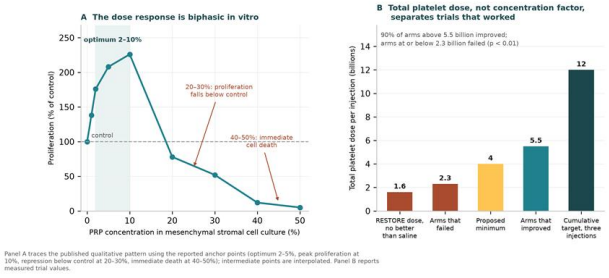

Figure 8: The platelet dose–response problem. Panel arrangement contrasts the trial-level dose signal, the competing published thresholds, and the in-vitro evidence for an inhibitory ceiling. The three bodies of evidence do not converge on a single recommendation.

Preparation category	Platelets	Leukocytes	Erythrocytes	Catabolic mediators	Clinical signal
Leukocyte-poor (pure) PRP	Moderate to high	8,455 → 109 neutrophils/mL versus leukocyte-rich [21]	Low	IL-1β 0.31; MMP-9 40 [21]	Lower reactogenicity; releasate inhibits inflammatory processes in osteoarthritic chondrocytes [58]; no proven efficacy advantage [6][23]
Leukocyte-rich PRP	Moderate to high	High neutrophil load [21]	Variable	IL-1β 3.67; MMP-9 222; TGF-β1 89 ng/mL [21]	Only category with a significant adverse-event excess over hyaluronic acid [23]; inferior to pure PRP for cartilage regeneration in vitro [59]
Red-cell contaminated PRP	Variable	Variable	High	Free haemoglobin and iron [22]	Synoviocyte toxicity in vitro [60]; associated post-injection pain [22]
PRGF (plasma rich in growth factors)	≈2× baseline	0.15 ± 0.08 × 10^3/μL [49]	Minimal	Minimal	Used across ophthalmic and musculoskeletal indications [61]
Autologous protein solution	Concentrated	Concentrated	Low	IL-1 receptor antagonist ≈30,000 pg/mL versus <250 in plasma [62]	Primary endpoint not met in a randomised knee trial [63]
Platelet lysate	Disrupted, no intact platelets	Variable	Low	>3,800 proteins [13]	Culture supplement, not an injectable [64]

Table 7: Compositional and clinical profile of the principal preparation categories. The consistent finding is that leukocyte depletion reduces reactogenicity without a demonstrated efficacy penalty or benefit.

Anticoagulant, activation and co-injected anaesthetic

Anticoagulant choice measurably alters platelet function. In a systematic review of technical procedures, acid citrate dextrose solution A preserved platelet function at 310% relative to reference, against 110% for ethylenediaminetetraacetic acid and 100% for sodium citrate [65]. Activation with bovine thrombin, still used to produce platelet gel, carries a documented immunological hazard: the product label carries a boxed warning that it can cause fatal severe bleeding or thrombosis through antibodies against bovine thrombin and factor V that may cross-react with human factor V, with post-treatment seroconversion of 18.4% in one study and 12.7% in another [66][67], and antibody positivity persisting to three years in 15.6% of recipients with more than one hundred reported cases of factor V inhibition [68]. Autologous thrombin or calcium chloride avoids this entirely and should be the default where activation is required.

The co-injected local anaesthetic is a frequently overlooked determinant of product viability. Bupivacaine 0.75% increased reactive oxygen species, dysregulated calcium handling, induced apoptosis, and reduced platelet adhesion and viability, whereas lidocaine 1% and ropivacaine 0.5% behaved essentially like saline and may be used at up to a 1:1 ratio with platelet preparations [69]. Growth-factor release was not assessed in that study, so the recommendation rests on viability rather than on function.

Pre-procedural medication washout is the weakest link in routine practice. Naproxen suppressed PDGF and interleukin-6 in leukocyte-rich platelet-rich plasma, but all factors normalised after a one-week washout; aspirin reduced growth-factor release; and cyclo-oxygenase-2 selective inhibitors did not inhibit platelet activation or growth-factor release at all [70][71]. No washout interval for non-steroidal anti-inflammatory drugs generally, for aspirin, for paracetamol or for corticosteroids has been established by outcome data, and the widely quoted forty-eight-hour figure carries no stated evidence level in its source document [72].

Additive or co-intervention	Evidence	Practical position

Acid citrate dextrose solution A	Platelet function preserved at 310% of reference [65]	Preferred anticoagulant
Sodium citrate	Function 100% of reference [65]	Acceptable; inferior to ACD-A
EDTA	Function 110% of reference but causes platelet swelling [65]	Not recommended for therapeutic preparations
Heparin	0.6 IU/mL required to prevent gelling in platelet-lysate manufacture [73]	Manufacturing use only
Bovine thrombin	Boxed warning for fatal bleeding or thrombosis; seroconversion 18.4% and 12.7% [66]; antibody persistence 15.6% at three years [68]	Avoid; use autologous thrombin or calcium chloride
Calcium chloride	Standard exogenous activator; produces immediate burst release [24]	Acceptable when activation is desired
Exogenous activation, clinical effect	No effect at 6 months on WOMAC ($p = 0.94$), VAS ($p = 0.79$) or IKDC ($p = 0.17$); significant at 12 months for KOOS ADL ($p \leq 0.01$), Sport ($p = 0.042$) and QoL ($p = 0.030$) [6]	Reasonable but not mandatory
Bupivacaine 0.75%	Increased reactive oxygen species, apoptosis; reduced adhesion and viability [69]	Do not mix with platelet preparations
Lidocaine 1% / ropivacaine 0.5%	Behave like saline apart from mild reactive-oxygen-species rise; usable up to 1:1 [69]	Acceptable
Naproxen	PDGF and interleukin-6 suppressed; normalised after one week [70]	One-week washout has an experimental anchor
Aspirin	Reduced growth-factor release [70]	Washout advisable; interval unestablished
COX-2 selective inhibitors	No inhibition of platelet activation or growth-factor release [70]	Washout not required
Corticosteroid co-injection	No primary experimental study on platelet viability retrieved; relative contraindication by consensus only [72]	Avoid mixing; interval by consensus
Any additive (Brazil)	Prohibited by Resolução CFM nº 2.464/2026 art. 5 outside approved research [74]; additives also void the ANVISA conventional-therapy classification [75]	Regulatory prohibition, not merely a preference

Table 8. Anticoagulants, activators, anaesthetics and pre-procedural medication, with the evidence supporting each practical position.

Devices, cost and image guidance

Fitzpatrick and colleagues processed blood from the same donors through four common commercial kits and obtained platelet concentrations of 412 ± 140 for one system, 964 ± 551 for a second, 1,224 ± 560 for a third and 1,266 ± 831 × 10^9/L for a fourth [76]. A three-fold difference in delivered product from identical input blood is the single clearest argument for device-level reporting. Published protocols span 350 to 2,008 g and five to twenty-one minutes, with kit costs of US$50 to US$500 [51].

Injection accuracy is a separate and more tractable variable. Ultrasound guidance achieved correct intra-articular placement in 356 of 373 attempts (95.4%) against 268 of 327 (82.0%) for landmark-guided injection [77]. Injection number also matters: a network meta-analysis found three injections optimal, with fifty-two-week WOMAC scores of 61.03, 31.80 and 28.17 for one, two and three injections respectively [78].

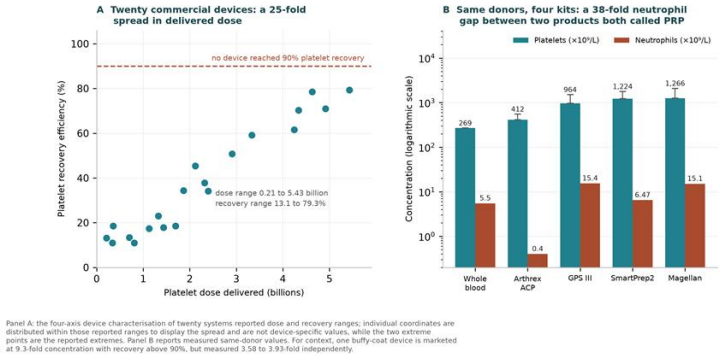

Figure 9: Same-donor output across commercial preparation systems, with the reported absolute-dose and recovery-efficiency range from the DEPA device audit. Identical input blood yields a three-fold difference in delivered platelet concentration depending on device.

System / kit	Reported output or specification	Regulatory note
Autologous Conditioned Plasma	412 ± 140 × 10^9 platelets/L, same-donor comparison [76]	Device clearance covers preparation only [3]
GPS III	964 ± 551 × 10^9/L [76]; cleared with specifications of at least 250,000 platelets/µL and pH above 6.2 [79]	Predecessor K030555 limited to plasma and concentrated platelets for diagnostic tests [80]
SmartPrep2 / SmartPReP2	1,224 ± 560 × 10^9/L [76]	510(k) K103340 [81]
Magellan	1,266 ± 831 × 10^9/L [76]	Preparation clearance [3]
Angel	60 mL processed; 7.23-fold platelet enrichment in a randomised knee trial [82]	Preparation clearance [3]
Regen Lab (RESTORE)	Single spin 1,500 g × 5 min, 5 mL, 1.6–5× enrichment, ≈80% recovery [50]	Preparation clearance [3]
T-Lab (exercise-controlled trial)	26 mL processed to 6 mL, 830 g × 5 min, 3.4-fold, 76% recovery [5]	Preparation clearance [3]
EmCyte PureBMC	Marrow and platelet concentrate system [83]	510(k) K183205 [83]
Autologous protein solution device	60 mL of blood processed [63]	Preparation clearance [3]
2024 CBER clearances	Six devices cleared, all as “Platelet And Plasma Separator For Bone Graft Handling” [84]	No 2024 clearance covers an intra-articular or aesthetic indication [84]
Device audit across 20 systems	Absolute dose 0.21–5.43 billion platelets; recovery 13.1–79.3%; no device above 90% [31]	DEPA framework proposed in response [31]
Protocol and cost range	350–2,008 g, 5–21 min, kit cost US$50–500 [51]	—

Table 9: Commercial preparation systems with reported output and regulatory position. No system in this table is cleared for the clinical indications for which it is most commonly used.

Growth-Factor Release: Kinetics, Scaffolds And The Fibrin Family

The therapeutic window of a platelet concentrate is defined not only by what it contains but by when the contents appear. Marx's foundational description of platelet-rich plasma established both the working definition of one million platelets per microlitre in five millilitres of plasma and the observation that roughly 70% of stored growth factors are released within ten minutes and close to the entire reservoir within the first hour [4]. This burst kinetic is a pharmacological liability as much as an asset: tissue repair unfolds over weeks, while an unmodified liquid injectable delivers its payload in minutes.

Burst versus sustained release

Comparative release studies show that fibrin architecture converts the burst into a gradient. Kobayashi and colleagues measured release from platelet-rich plasma, platelet-rich fibrin and advanced platelet-rich fibrin and found that the liquid preparation released most of its growth-factor content early while the

fibrin-based preparations released progressively over ten days, with advanced platelet-rich fibrin giving the highest total ten-day release of platelet-derived growth factor, vascular endothelial growth factor and insulin-like growth factor [18]. Fibrin therefore functions as a provisional scaffold with three simultaneous roles: mechanical matrix, reservoir that retards diffusion, and substrate for integrin-mediated cell recruitment [24]. Photoactivation has been proposed as an alternative route to sustained release [85], and freeze-drying permits storage of a 4.1-fold enriched product without loss of activity [52], but neither modification has been tested against standard preparation in a randomised clinical trial.

What is measurable and what is inferable

Absolute growth-factor concentrations vary with preparation, donor and assay [19,86], and the mechanistic pathways downstream of receptor engagement have been mapped in detail [25]. Yet the inferential chain from a measured growth-factor concentration to a clinical outcome has never been closed in humans. No randomised trial has measured growth-factor content in the injected product and correlated it with the primary endpoint. The closest available evidence is a case series of thirty knees in which baseline platelet-rich plasma immune-cell and protein composition was correlated with change in Knee injury and Osteoarthritis Outcome Score, where nineteen of thirty knees improved and the calprotectin subunit correlated at r = 0.65 with outcome [14]. A single hypothesis-generating series is a thin foundation for a field that routinely markets growth-factor content as its mechanism.

Two further biological properties deserve mention because they are frequently overstated. Platelet concentrates possess antimicrobial activity, but a systematic review concluded that this activity is bacteriostatic rather than bactericidal and inactive against established biofilm [15]. And platelet-rich plasma exerts genuine antinociceptive activity through a peripheral endocannabinoid-related mechanism, since analgesia was abolished by cannabinoid receptor CB1 and CB2 antagonism [87] — which means that an early analgesic response cannot be read as evidence of structural repair.

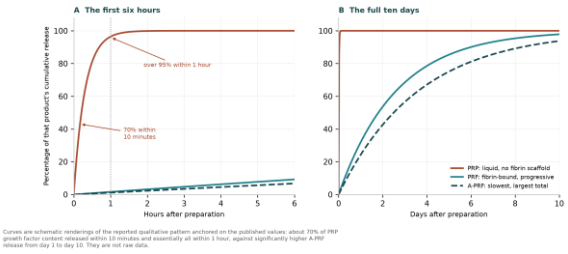

Figure 10: Growth-factor release kinetics. The liquid preparation releases the majority of its payload within the first hour, whereas fibrin-based preparations sustain release across ten days. The shaded band marks the interval over which tissue repair actually proceeds.

Orthopaedics And Sports Medicine: The Largest And Least Conclusive Evidence Base

Knee osteoarthritis is the most studied indication and the one on which the credibility of the field rests. It is also the indication where the gap between meta-analytic enthusiasm and rigorous trial results is widest. Interpretation requires anchoring to minimal clinically important differences: visual analogue scale 1.37, WOMAC total 6.4 and WOMAC pain 1.5 for knee osteoarthritis [91], VISA-A 12 points for Achilles

tendinopathy [92], and visual analogue scale 0.9 with Foot Function Index 7 for plantar fasciitis [93].

The placebo-controlled trials

The RESTORE trial randomised 288 patients with knee osteoarthritis to leukocyte-poor platelet-rich plasma prepared by single spin at 1,500 g for five minutes or to saline placebo, and was negative on both co-primary endpoints of pain and medial tibial cartilage volume [50]. Global improvement at two months favoured platelet-rich plasma, at 48.2% versus 36.2%, giving a risk ratio of 1.37 (95% CI 1.05 to 1.80, p = 0.02), but this was a secondary outcome and did not persist [50]. Secondary reporting identified cartilage thinning in three or more subregions in 17.1% of platelet-rich plasma recipients against 6.8% of placebo recipients (p = 0.02) [94], a signal that has never been replicated but has also never been refuted.

Adding platelet-rich plasma to supervised exercise produced increments of −0.5 for pain (p = 0.69) and −3 for WOMAC (p = 0.97), against minimal clinically important differences of 2 and 12 respectively [5], with a retrospective cohort reaching a comparable conclusion [95]. In ankle osteoarthritis, the PRIMA trial found an American Orthopaedic Foot and Ankle Society score difference of −1 (95% CI −6 to 3) [96]. In chronic Achilles tendinopathy, the landmark randomised trial found no benefit against the twelve-point VISA-A threshold [92], and in acute muscle injury the hazard ratio for return to play was 0.96 with a between-group difference of zero days (95% CI −11 to 11) [97].

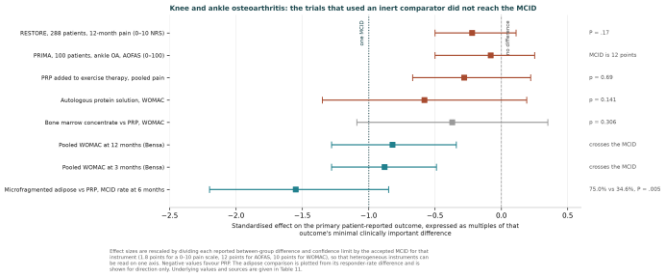

Figure 11: Forest plot of pooled effect estimates for intra-articular platelet-rich plasma in knee osteoarthritis alongside the placebo-controlled trials. The vertical reference line marks the minimal clinically important difference rather than the null, which is the comparison that matters clinically.

Why the meta-analyses disagree with the trials

Meta-analyses report large effects. Standardised mean differences of −1.38 against saline and −2.29 against alternative comparators have been published [98], and across eighteen randomised trials and 1,995 patients WOMAC improvements of −8.15 to −15.90 were reported [55]. Yet across thirty-four randomised trials the superiority of platelet-rich plasma over comparators was documented in only a minority of individual studies [99]. The reconciling explanation is methodological: all seventy-nine systematic reviews of platelet-rich plasma for knee osteoarthritis were found to contain spin, with a mean spin score of 5.5 ± 2.3, and 84.8% claimed benefit despite high risk of bias in the underlying trials [41]. Undisclosed funding status predicted a positive result with an odds ratio of 3.61 (95% CI 1.1 to 11.9, p = 0.035) [42]. Five retractions have affected the platelet-rich plasma literature, including a knee meta-analysis retracted in April 2026 and a subacromial injection trial withdrawn in December 2025 [100][101][102][103][104].

The most methodologically careful synthesis, a frequentist network meta-analysis of fifty-six randomised trials and 5,251 participants, with fifty-three trials and 5,031 patients in the connected network, reached three conclusions that constrain practice: exogenous activation was null at six months but favoured at twelve months on several Knee injury and Osteoarthritis Outcome Score subscales; no optimal platelet dose could be identified; and leukocyte content was not an effect modifier [6].

Trial or synthesis	Design and n	Preparation	Primary result	Interpretation against MCID
RESTORE [50]	Randomised, saline-controlled, n = 288	LP-PRP, single spin 1,500 g × 5 min, 5 mL, 1.6–5×	Negative on pain and medial tibial cartilage volume; 2-month global improvement 48.2% vs 36.2%, RR 1.37 (1.05–1.80), p = .02	Below MCID on primary endpoints; cartilage thinning in 17.1% vs 6.8%, p = .02 [94]
Exercise-controlled trial [5]	Three-arm randomised, n = 84 (NCT04697667)	830 g × 5 min, 26 mL → 6 mL, 3.4×, 76% recovery	Increment of adding PRP to exercise: pain –0.5 (p = 0.69); WOMAC –3 (p = 0.97)	Far below MCIDs of 2 and 12
Retrospective cohort [95]	PRP + exercise vs PRP vs exercise	Not specified	KOOS and OMERACT-OARSI responder analysis	Consistent with the randomised finding
Network meta-analysis [6]	56 RCTs / 5,251 participants; 53 / 5,031 in network	Mixed; Mishra threshold applicable to 55/57 arms (96.5%)	Activation null at 6 mo; 12-mo KOOS ADL p ≤ 0.01, Sport p = 0.042, QoL p = 0.030; no optimal dose; leukocytes not an effect modifier	MCID 9.2 for ADL and 10.3 for QoL not consistently exceeded
Dose analysis [54]	Systematic analysis of dose across randomised arms	Stratified by absolute platelet number	90% of arms above 5.5 billion platelets improved; arms at or below 2.3 billion failed (p < 0.01)	Strongest available dose signal; contradicted by the network analysis
Bensa et al. [55]	18 RCTs / 1,995 patients	Mixed	WOMAC improvements –8.15, –15.90, –15.32, –14	Exceeds MCID of 6.4 but derived from high-risk-of-bias trials [41]
Nie et al. [98]	Meta-analysis of randomised trials	Mixed	SMD –1.38 vs saline; –2.29 vs other comparators	Implausibly large relative to placebo-controlled data
Filardo et al. [99]	34 RCTs	Mixed	Superiority over comparators shown in a minority of individual trials	Pooling amplifies a signal absent in most trials
Dulic et al. [82]	Randomised, n = 175	Angel, 60 mL, 7.23-fold enrichment	WOMAC BMAC 44.34 → 24.34 versus PRP 48.12 → 31.06; BMAC vs PRP p = 0.306	No difference between orthobiologics
Anz et al. [105]	Randomised, n = 90, 2-year follow-up	PRP versus bone-marrow concentrate	IKDC P = .909	Equivalence, not superiority
MF-AT comparison [7]	Randomised, n = 118	PRP versus microfragmented adipose tissue	6-month MCID attainment 75.0% vs 34.6%, P = .005	PRP inferior to adipose tissue in this trial
Injection number [78]	Network meta-analysis	One, two or three injections	52-week WOMAC 61.03 / 31.80 / 28.17	Three injections optimal
Intra-articular plus intraosseous [106]	5 prospective studies / 112 knees	Combined IA + IO delivery	WOMAC mean difference 11.55 (10.30–12.80)	Exceeds MCID; small non-randomised base
Autologous protein solution [63]	Double-blind randomised, n = 40	APS, 60 mL processed	12-month WOMAC mean difference –10.4 (–24.4 to 3.6), p = 0.141	Primary endpoint not met
Autologous conditioned serum [107]	Randomised, n = 376	Orthokine ACS versus hyaluronic acid and saline	Superior to hyaluronic acid through 104 weeks	Positive but predates modern standards
Alpha-2-macroglobulin [108]	Double-blind randomised, n = 75 enrolled	A2M vs PRP vs methylprednisolone	No between-group difference	No advantage over PRP
Composition biomarkers [14]	Case series, 30 knees	Composition profiled per patient	19/30 improved; calprotectin subunit r = 0.65; effector-memory CD4 r = 0.52	Hypothesis-generating only

Table 11: Randomised trials and syntheses of platelet-rich plasma for knee osteoarthritis, interpreted against minimal clinically important differences rather than against the null hypothesis.

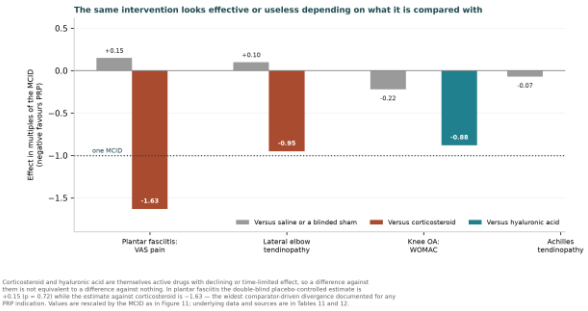

Figure 12: Head-to-head comparisons of platelet-rich plasma against other orthobiologics and against hyaluronic acid in knee osteoarthritis. Where differences reach significance they favour the comparator as often as they favour platelet-rich plasma.

Tendon, muscle, nerve and spine

Outside the knee the pattern repeats: positive pooled estimates in indications with small heterogeneous trials, and null results wherever placebo control and adequate power coincide. In lateral elbow tendinopathy a multicentre controlled trial of 230 patients reported success in 71.5% versus 56.1% [109], but the Cochrane review found a standardised mean difference of 0.26 with evidence graded insufficient [110] and a pooled analysis restricted to placebo-controlled trials found no benefit [111]. In rotator cuff repair augmentation the re-tear risk ratio of 0.70 (95% CI 0.56 to 0.88) [112] moved to 0.91 (95% CI 0.69 to 1.19) after trim-and-fill adjustment for publication bias [113], which is the clearest single illustration of how small-study effects generate apparent efficacy in this field.

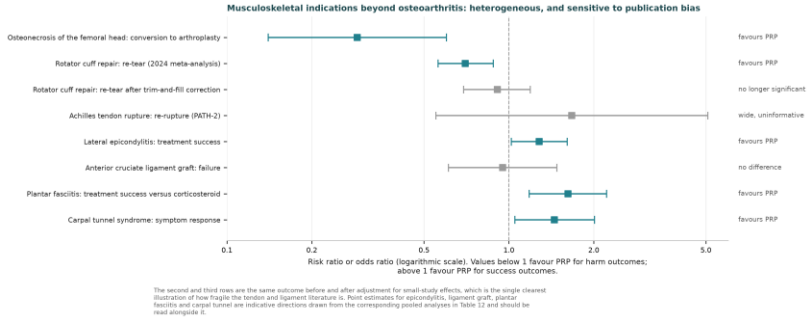

Figure 13: Pooled effect estimates across non-knee musculoskeletal indications, with the rotator-cuff estimate shown before and after trim-and-fill adjustment. Heterogeneity, indicated beside each estimate, is extreme in several indications.

Indication	Best available evidence	Effect estimate	Assessment
Lateral elbow tendinopathy	Multicentre controlled trial, n = 230 [109]; Cochrane review [110]; placebo-controlled pooling [111]	Success 71.5% vs 56.1%; SMD 0.26, evidence insufficient; no benefit over placebo	Positive open trials, null against placebo
Rotator cuff repair augmentation	Meta-analysis [112] with trim-and-fill reanalysis [113]	Re-tear RR 0.70 (0.56–0.88) → 0.91 (0.69–1.19)	Apparent benefit explained by small-study effects
Chronic Achilles tendinopathy	Randomised trial [92]	No benefit against the 12-point VISA-A MCID	Negative
Acute muscle injury	Randomised trial [97]	Return-to-play HR 0.96; difference 0 days (–11 to 11)	Negative

Plantar fasciitis	Randomised evidence and MCID definition [93]	MCIDs of VAS 0.9 and Foot Function Index 7 required	MCID-anchored interpretation essential
Ankle osteoarthritis	PRIMA randomised trial [96]	AOFAS difference –1 (–6 to 3)	Negative
Osteonecrosis of the femoral head	Two contradicting meta-analyses [114][115]	Arthroplasty conversion RR 0.29 (0.16–0.53) versus no significant reduction	Irreconcilable; direction unresolved
Carpal tunnel syndrome	Meta-analysis, 191 patients [116]	Boston questionnaire SMD –2.06	Effect size implausible for the sample size
Lumbar radicular pain (epidural)	Meta-analysis [117]	Pooled effect –0.09, I^2 = 96.7%	Null with uninterpretable heterogeneity
Discogenic low back pain (intradiscal)	Randomised trial [118]	21/44 vs 16/45 responders, p = 0.244; one spondylodiscitis	Negative with a serious infection signal
Glenohumeral osteoarthritis	Randomised comparison with hyaluronic acid [119]	No between-group difference	No advantage
Trapeziometacarpal arthritis	Randomised trial, n = 33 [121]	VAS 20 vs 65, p = 0.015	Positive but very small
Injection accuracy (all joints)	Systematic review, 13 studies [77]	95.4% (356/373) with ultrasound vs 82.0% (268/327) landmark	Ultrasound guidance is the strongest modifiable variable

Table 12: Non-knee musculoskeletal indications with the best available evidence and its assessment. Ultrasound guidance is the only variable in this table with a large, consistent and mechanistically plausible effect.

What guidelines conclude

Guideline bodies have converged on caution rather than on prohibition or endorsement. The 2019 American College of Rheumatology and Arthritis Foundation guideline strongly recommends against platelet-rich plasma [122], and the Osteoarthritis Research Society International guidance likewise does not support it [123]. The American Academy of Orthopaedic Surgeons rates the strength of recommendation as Limited [124]. The National Institute for Health and Care Excellence permits use only with special arrangements for clinical governance, consent and audit or research [125]. In contrast, the ESSKA Orthobiologic Initiative regards platelet-rich plasma as a valid option in Kellgren–Lawrence grades 1 to 3 with a course of two to four injections [126], the joint ESSKA–ICRS statement extends this to grades 0 to III in patients up to eighty years of age [127], and French-speaking experts have issued a supportive consensus [128]. The 2026 American Academy of Physical Medicine and Rehabilitation guidance statement issued five evidence-based recommendations accompanied by eleven consensus-based best practices [129] — a ratio that accurately reflects how much of current practice rests on expert opinion. A Delphi exercise found 77.5% strong agreement restricted to Kellgren–Lawrence grade II, against a claimed efficacy of 78% and a mean charge of US$714 per knee [130][131].

Esthetic dermatology and hair restoration

Dermatological use is the fastest-growing application and the least regulated. It is also where the reporting failure documented in Section 3 reaches its extreme: an overview of thirteen systematic reviews covering twenty-eight primary studies of facial rejuvenation found that no primary study reported the final platelet number, and rated twelve of thirteen reviews as low or critically low confidence on AMSTAR-2 [40].

Androgenetic alopecia

Hair restoration carries the most internally consistent evidence in the whole platelet-rich plasma literature. The original placebo-controlled trial reported a total hair-density change of +45.9 hairs per

square centimetre in treated scalp against −3.8 in control [132]. Meta-analyses converge: a pooled hair-density mean difference of 27.55 hairs per square centimetre across fourteen studies and 431 patients [133], and 25.09 hairs per square centimetre (95% CI 9.03 to 41) across ten randomised trials and 318 participants [134]. Adding platelet-rich plasma to topical minoxidil produced an increment of 21.81 hairs per square centimetre (95% CI 10.64 to 33.00) at three months [135].

The comparative question is more instructive than the placebo question. A Bayesian network meta-analysis of twenty-seven trials and 1,110 patients found that minoxidil 5% combined with microneedling exceeded platelet-rich plasma monotherapy by 16 hairs per square centimetre (95% CI 2.57 to 28.66) [9]. Platelet-rich plasma therefore works in androgenetic alopecia, but it is not the best-performing option, and its cost per hair gained is far higher than that of a topical agent. In alopecia areata, a half-head placebo- and active-controlled trial reported benefit [136], and single-spin and double-spin preparations performed identically [45][46].

Facial rejuvenation, scars and pigmentation

Here the evidence turns negative as soon as the design tightens. A systematic review of thirty-six studies and 3,172 patients reported broadly favourable results for rejuvenation and scar management [137], but a randomised double-blind split-face trial of platelet-rich plasma versus saline with full-face microneedling in eighteen women found no improvement and a slight worsening of laxity ($p \leq 0.004$) and rhytids [138]. Adding platelet-rich plasma to microneedle fractional radiofrequency for melasma produced no significant between-side difference [139], and adding intradermal platelet-rich plasma to fractional carbon dioxide laser for post-burn and post-traumatic scars gave an observer Patient and Observer Scar Assessment Scale p value of 0.793 [10]. Periorbital dark circles have been reviewed across fourteen studies without a controlled synthesis [140]. The pattern is unambiguous: in split-face designs with an adequate energy-device comparator, platelet-rich plasma adds nothing measurable.

Chronic wounds: the strongest clinical case

If platelet-rich plasma has a genuinely established indication, it is the chronic wound. The Cochrane review of autologous platelet-rich plasma for chronic wounds reported a risk ratio for complete healing of 1.19 [11], and subsequent and larger syntheses have strengthened rather than eroded this. In diabetic foot ulcers, twenty-two randomised trials and 1,559 patients yielded a complete-healing risk ratio of 1.42 (95% CI 1.30 to 1.56) with high certainty [141]. Across twenty-nine randomised trials and 2,198 wounds of mixed aetiology the odds ratio for complete healing was 5.32 (95% CI 3.37 to 8.40) [142]. In venous leg ulcers, sixteen randomised trials and 699 patients gave a closure odds ratio of 5.06 (95% CI 2.35 to 10.89) and a recurrence odds ratio of 0.16 (95% CI 0.05 to 0.50) [143]. For pressure injuries the healed-area standardised mean difference was 1.38 square centimetres ($p = 0.02$) with a Pressure Ulcer Scale for Healing difference of 1.69 ($p = 0.01$) [144].

A best-evidence summary drawing on three guidelines, five consensus statements and nine systematic reviews graded venous ulcers at level 1a with grade A and diabetic foot ulcers at a comparable level [145]. Allogeneic preparations extend this further, with a pooled odds ratio for complete healing of diabetic foot ulcers of 6.19 (95% CI 2.32 to 16.56), although no quantified immunogenicity data accompany that

estimate [146]. The regulatory position matches the evidence: the only United States national coverage determination that permits platelet-rich plasma reimbursement does so for diabetic wounds and for twenty weeks only [147].

Dentistry, maxillofacial surgery and other specialties

Dental and maxillofacial use is where platelet concentrates originated, and it is where the fibrin-based members of the family dominate. The evidence is nonetheless indication-specific rather than uniformly positive. In periodontal intrabony defects, a network meta-analysis of thirty-two randomised trials found that platelet-rich plasma did not improve probing depth or clinical attachment level ($p > 0.05$) and ranked among the least effective adjuncts [148]. In maxillary sinus augmentation, thirteen quantitative studies covering 369 patients and 621 augmentations produced a bone-formation mean difference of −0.63 mm ($p = 0.81$) [149]. A four-arm randomised comparison in third-molar extraction sockets is available but small [150].

The exception is medication-related osteonecrosis of the jaw, where complete healing was achieved in 480 of 557 lesions (86.2%) treated with any platelet concentrate across fifty-eight articles [151]. This is an uncontrolled pooled proportion, but it addresses a condition with poor alternatives and a biologically coherent rationale.

Ophthalmology, urology, gynaecology, otolaryngology and neurology

Beyond these three domains, platelet-rich plasma has entered almost every specialty, generally through uncontrolled series. In Sjögren-related dry eye a randomised comparison against autologous serum drops left the Ocular Surface Disease Index and Schirmer I unchanged [152]; neurotrophic keratitis evidence is a fifteen-patient uncontrolled series [61]; and subretinal platelet-rich plasma for large macular hole achieved 93.3% closure versus 90.0% for an inverted internal limiting membrane flap ($p = 0.158$) [153].

In erectile dysfunction a double-blind placebo-controlled randomised trial reported benefit [154] and a meta-analysis of ten studies and 559 patients found a six-month International Index of Erectile Function difference of 3.22 (95% CI 2.13 to 4.31) [8], yet both the American Urological Association and the European Association of Urology state that platelet-rich plasma should be considered experimental and not offered outside an approved research protocol [155][156]. Direct-to-consumer pricing averages US$1,507 ± 388 with only 9% of offering urologists [157]. Peyronie disease evidence is a thirty-six-man retrospective cohort [158], and in female stress urinary incontinence a sham-controlled trial reported subjective cure of 32% versus 4% ($p < 0.01$) with objective cure of 0% [159] — one of the cleanest demonstrations in medicine that patient-reported and objective endpoints can diverge completely.

In reproductive medicine, a critical appraisal of thirteen randomised trials and twelve meta-analyses of intrauterine platelet-rich plasma for recurrent implantation failure found all thirteen trials at high risk of bias [160]; thin-endometrium evidence rests on two small randomised trials [161]; and intraovarian use across fourteen studies could not be meta-analysed [162]. In otolaryngology, tympanic membrane perforation closure carries an odds ratio of 3.69 (95% CI 2.02 to 6.74) overall and 2.70 (95% CI 1.27 to 5.76) restricted to randomised trials [163], post-viral olfactory dysfunction evidence is discordant across ten studies [164], and vocal fold scar evidence is a fifteen-adult uncontrolled trial [165]. A randomised

trial in painful diabetic polyneuropathy compared platelet-rich plasma with pregabalin over one year [166].

The commercial context explains this breadth. The global platelet-rich plasma market was valued at US$650.13 million in 2025 and is projected to reach US$1,751.45 million by 2033, a compound annual growth rate of 13.2% [2]. Growth of that magnitude in a field with the reporting deficits documented in Section 3 is itself a patient-safety concern, and the United States Federal Trade Commission has acted against unsubstantiated regenerative-medicine advertising [167], as has the United Kingdom Advertising Standards Authority [168].

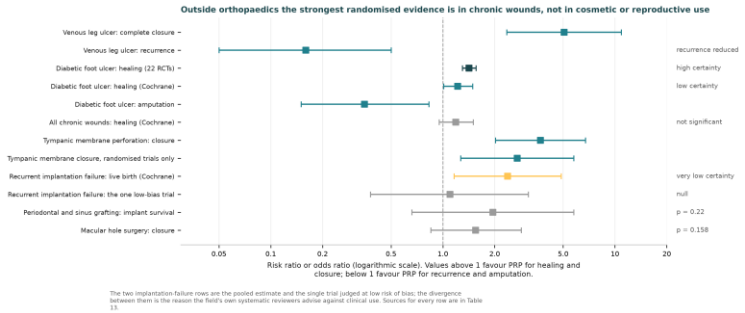

Figure 14: Non-orthopaedic indications ranked by the strength of the best available evidence. Chronic wounds and androgenetic alopecia separate clearly from the remainder, where uncontrolled series predominate.

Indication	Best evidence	Effect estimate	Verdict
Diabetic foot ulcer	22 RCTs / 1,559 patients [141]	Complete healing RR 1.42 (1.30–1.56), high certainty	Established
Venous leg ulcer	16 RCTs / 699 patients [143][145]	Closure OR 5.06 (2.35–10.89); recurrence OR 0.16 (0.05–0.50); level 1a grade A	Established
Chronic wounds, mixed	29 RCTs / 2,198 wounds [142]; Cochrane [11]	Complete healing OR 5.32 (3.37–8.40); RR 1.19	Established
Pressure injury	Meta-analysis [144]	Healed area SMD 1.38 cm^2 (p = 0.02); PUSH 1.69 (p = 0.01)	Probable
Allogeneic PRP, diabetic foot ulcer	Review with pooled estimate [146]	Complete healing OR 6.19 (2.32–16.56); immunogenicity unquantified	Promising, unregulated
Androgenetic alopecia	14 studies / 431 patients [133]; 10 RCTs / 318 [134]; placebo trial [132]	MD 27.55 and 25.09 hairs/cm^2; +45.9 versus –3.8 hairs/cm^2	Effective but not first-line [9]
PRP added to minoxidil	5 RCTs [135]	Hair density 21.81 (10.64–33.00) at 3 months	Additive benefit
Minoxidil + microneedling versus PRP	27 trials / 1,110 patients, Bayesian NMA [9]	Comparator exceeds PRP by 16 hairs/cm^2 (2.57–28.66)	PRP is not the best option
Alopecia areata	Half-head placebo- and active-controlled trial [136]	Benefit reported	Possible
Facial rejuvenation	13 reviews / 28 studies [40]; split-face RCT [138]	Platelet number never reported; no improvement, laxity worsened (p ≤ 0.004)	Not supported
Melasma	Split-face RCT with fractional radiofrequency [139]	No significant between-side difference	Not supported

Post-burn and post-traumatic scars	Randomised observer-blinded trial, 60 completers [10]	Observer POSAS p = 0.793	Not supported
Skin rejuvenation and scars, pooled	36 studies / 3,172 patients [137]	Broadly favourable, uncontrolled designs predominant	Uncertain

Table 13: Non-orthopaedic indications with the best available evidence, effect estimate and verdict. Only chronic wounds reach a high-certainty positive conclusion.

Combination with mesenchymal stromal cells and extracellular vesicles

The most consequential contribution of platelet-rich plasma to regenerative medicine may not be as an injectable at all. As a xeno-free culture supplement it has already displaced fetal bovine serum in cell manufacturing, and as a source of extracellular vesicles it defines a plausible next generation of acellular products.

Human platelet lysate as a culture supplement

A systematic review and meta-analysis comparing human platelet lysate with fetal bovine serum for mesenchymal stromal cell expansion confirmed superior proliferation with preserved immunophenotype and differentiation capacity [169]. The magnitude is large: doubling time at day seven was 40.61 ± 1.11 hours with a four-cycle platelet lysate against 119.70 ± 32.36 hours with fetal bovine serum ($p < 0.001$), with heparin at 0.6 international units per millilitre required to prevent gelling [73]. A good-manufacturing-practice cell-factory protocol achieved more than twenty population doublings and approximately 250×10^6 mesenchymal stromal cells per batch, and specified a platelet threshold below 1.5×10^6 per microlitre [64]. Because platelet lysate is manufactured from disrupted platelets and contains more than 3,800 identified proteins [13], it is not interchangeable with an injectable platelet-rich plasma releasate, which contains more than 1,300 [13].

Dose-dependent effects on stem cells

The interaction between platelet concentrate and mesenchymal stromal cells is biphasic, and this is the single most important practical fact for clinicians who combine the two products in one syringe. In human bone-marrow mesenchymal stem cell culture, 5% platelet-rich plasma gave the highest cell number, 20% to 30% repressed proliferation, and 40% to 50% caused immediate cell death [56]. Platelet concentrations above roughly 1.5 million per microlitre may inhibit stem-cell proliferation [30][57]. Chondrogenic differentiation of both adipose- and bone-marrow-derived cells was inhibited by platelet-rich plasma even where proliferation was enhanced [170], which means that a preparation optimised for cell expansion may be actively counterproductive for cartilage formation. Given that mesenchymal stromal cells constitute approximately one in ten thousand marrow cells [56], the concentration of platelet product delivered alongside a bone-marrow concentrate is rarely calculated and almost never reported.

Platelet-derived extracellular vesicles

Platelet-rich plasma exosomes measuring 40 to 100 nanometres and expressing CD9, CD63, CD81 and CD41 promoted re-epithelialisation of chronic cutaneous wounds through activation of the Yes-associated protein pathway in a diabetic rat model [171], and exosomes isolated from both platelet-rich plasma and mesenchymal stem cells promoted functional recovery after muscle injury [16]. Multiomic characterisation has begun to distinguish vesicles derived from platelet lysate, fresh platelets and aged

platelets, with yields on the order of $9 \times 10^8 \pm 2 \times 10^8$ particles per microgram of protein [17].

Clinical translation is at the earliest possible stage. The first-in-human phase I randomised, double-blind, placebo-controlled intra-subject trial of allogeneic platelet-derived extracellular vesicles enrolled eleven participants and did not meet its efficacy endpoint, although no serious adverse events occurred [90]. The regulatory position is unambiguous: there are no approved exosome products and the United States Food and Drug Administration has issued a public safety notification documenting multiple serious adverse events [89], reinforced by a warning letter to a company marketing umbilical-cord-derived products under platelet-rich plasma branding [172]. Aesthetic exosome evidence consists of a twelve-week split-face randomised trial of twenty-eight participants [173] and a nine-woman observational series [174].

Product or approach	Evidence base	Key quantitative finding	Status
Human platelet lysate for MSC expansion	Systematic review and meta-analysis, 22 studies [169]	Superior proliferation; immunophenotype and differentiation preserved	Established manufacturing practice
Blood-bank standardised platelet lysate	Process-development study [73]	Doubling time 40.61 ± 1.11 h versus 119.70 ± 32.36 h for FBS ($p < 0.001$); heparin 0.6 IU/mL	Established
GMP cell-factory protocol	Cell-factory experience [64]	>20 population doublings; ≈250 × 10^6 MSC per batch; platelet threshold <1.5 × 10^6/µL	Established
PRP dose–response in MSC culture	Controlled in-vitro study [56]	5% optimal; 20–30% repressive; 40–50% lethal	Mechanistically important, clinically ignored
PRP and chondrogenesis	Controlled in-vitro study [170]	Chondrogenic differentiation inhibited despite enhanced proliferation	Cautionary
PRP-derived exosomes, wound model	Diabetic rat model [171]	40–100 nm; CD9/CD63/CD81/CD41 positive; YAP activation	Preclinical
PRP and MSC exosomes, muscle injury	Animal model [16]	Functional recovery promoted	Preclinical
Platelet-derived extracellular vesicles	Multiomic characterisation [17]	$9 \times 10^8 \pm 2 \times 10^8$ particles per µg protein	Characterisation stage
Allogeneic platelet EV (Plexaris / Plexoval II)	Phase I RCT, n = 11, ACTRN12620000944932 [90]	No serious adverse events; efficacy endpoint not met	Phase I
Exosome products generally	FDA public safety notification [89]; warning letter [172]	No approved product; multiple serious adverse events documented	Unapproved and enforced against
Adipose stem-cell exosome solution, aesthetic	12-week split-face RCT, n = 28 [173]; series, n = 9 [174]	GAIS significantly higher on the treated side	Early clinical
Autologous conditioned serum (Orthokine)	RCT, n = 376 [107]	Superior to hyaluronic acid through 104 weeks	Marketed, dated evidence
Autologous protein solution	Double-blind RCT, n = 40 [63]	12-month WOMAC MD –10.4 (–24.4 to 3.6), $p = 0.141$; IL-1Ra ≈30,000 pg/mL [62]	Primary endpoint not met
Alpha-2-macroglobulin	Double-blind RCT, n = 75 [108]	No difference versus PRP or methylprednisolone	No advantage
GOLDIC	Multicentre open-label, 65 patients / 106 knees [175]	Uncontrolled	Investigational
Hyperacute serum	Open-label pilot, n = 24 [176]	Three weekly 3 mL injections, no control group	Investigational
Photoactivated PRP	In-vitro release study [85]	Sustained growth-factor release	Investigational
Freeze-dried PRP	Preparation and activity study [52]	4.1-fold enrichment (130.1 ± 41.1 versus 31.5 ± 7.3 × 10^4/µL)	Investigational, enables storage
Allogeneic PRP	Review with pooled estimate [146]	Diabetic foot ulcer healing OR 6.19 (2.32–16.56); immunogenicity unquantified	Promising, unregulated
Phenotype-targeted formulation	Conceptual framework [131] with composition biomarkers [14]	Calprotectin subunit $r = 0.65$ with KOOS change	Hypothesis

Table 14: Adjacent and next-generation platelet-derived products, with the evidence base and development status

of each. Culture-supplement use is the only application in this table that is genuinely established.

Safety, contraindications and regulation

Platelet-rich plasma is autologous, which is often presented as equivalent to being safe. It is not. Adverse-event reporting in this literature is poor, the complication rate exceeds that of comparators in the largest analyses, and the regulatory frameworks under which it is delivered differ so profoundly between jurisdictions that the same procedure is a registered drug in one country and an unregulated clinical act in another.

Measured adverse-event rates

A systematic review and meta-analysis of twenty-four randomised trials found that platelet-rich plasma injections for knee osteoarthritis carry a higher complication rate than comparators, at 18.66% versus 9.14%, giving a number needed to harm of eleven [177][178]. A separate analysis of thirty-two randomised trials and 1,268 knees found a pooled adverse-event rate of 18.7% with no severe events, and identified an excess only in the leukocyte-rich subgroup [23]. In the foot and ankle, complications occurred in 41.1% versus 33.7% ($p < 0.01$) [179]. Reporting quality undermines all of these figures: only eleven of twenty-four studies reported adverse reactions at all, and two of those eleven reported them incompletely [180].

Serious events, though rare, are documented. The PATH-2 trial of platelet-rich plasma for acute Achilles tendon rupture recorded one ST-elevation myocardial infarction two and a half hours after injection [181], and a sham-controlled trial in chronic midportion Achilles tendinopathy provides comparable placebo-controlled safety data [182]. A systematic collection of twenty published adverse-event reports identified seven infection-related events and, most seriously, six patients with visual loss, with a calcium-citrate hapten mechanism proposed [183]. Complete patellar tendon rupture has been reported after a series of four injections in a recreational athlete [184], and one case of spondylodiscitis followed intradiscal injection [118]. The most severe documented harm did not arise from platelet-rich plasma itself: five cases of human immunodeficiency virus transmission were traced to unsafe injection practice at a spa offering platelet-rich plasma microneedling [185]. Red blood cell contamination is associated with post-injection pain [22] and synoviocyte toxicity in vitro [60], and bovine thrombin activation carries a boxed warning [66][67][68].

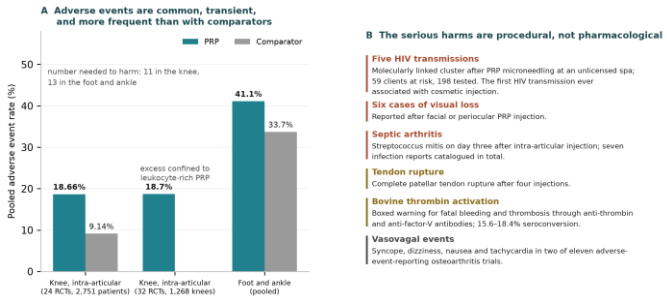

Figure 15: Adverse-event rates for platelet-rich plasma against comparators across the largest available meta-analyses, with the proportion of trials that reported adverse events at all shown alongside. The reporting gap is larger than the event rate difference.

Safety domain	Evidence	Quantitative finding
Knee complication rate	24 RCTs, meta-analysis [177]	18.66% versus 9.14%; number needed to harm 11
Knee adverse events	32 RCTs / 1,268 knees [23]	Pooled rate 18.7%; no severe events; excess confined to leukocyte-rich preparations
Foot and ankle complications	Systematic review and meta-analysis [179]	41.1% versus 33.7% (P < .01)
Adverse-event reporting quality	24 studies [180]	Only 11/24 reported adverse reactions; 2 of those 11 incompletely
Cardiovascular event	PATH-2 randomised trial [181]	One ST-elevation myocardial infarction 2.5 h post-injection
Placebo-controlled safety, tendinopathy	Sham-controlled RCT [182]	Comparative safety data in chronic midportion Achilles tendinopathy
Published adverse-event series	20 reports collected [183]	Seven infection-related events; six patients with visual loss; calcium-citrate hapten mechanism proposed
Tendon rupture	Case report [184]	Complete patellar tendon rupture after four injections
Spinal infection	Randomised trial [118]	One case of spondylodiscitis after intradiscal injection
Bloodborne transmission	Public health investigation [185]	Five HIV transmissions linked to unsafe injection practice at a spa
Cartilage signal	RESTORE secondary reporting [94]	Cartilage thinning in ≥3 subregions in 17.1% versus 6.8% (p = 0.02)
Red-cell contamination	Composition studies [22][60]	Post-injection pain; synoviocyte toxicity in vitro
Bovine thrombin activation	Product label [66][67]; review [68]	Boxed warning; seroconversion 18.4% and 12.7%; antibody persistence 15.6% at 3 years; >100 factor V inhibition cases
Local anaesthetic co-injection	In-vitro study [69]	Bupivacaine 0.75% harmful; lidocaine 1% and ropivacaine 0.5% acceptable at 1:1

Table 15: Documented safety findings. The autologous nature of the product does not confer immunity from procedural, formulation or practice-related harm.

Contraindications and procedural rules

Contraindication lists circulate widely and are almost entirely consensus-derived. The International Cellular Medicine Society guidelines present absolute and relative contraindication lists without any stated evidence level [72]. The GRIIP consensus of thirty-one French-speaking experts produced twenty-three recommendations, most graded D, and explicitly concluded that thrombocytopenia above 50,000 per cubic millimetre is not a contraindication [186][128]. The only experimentally anchored washout interval in routine practice is the one-week interval for naproxen [70].

Rule or contraindication	Basis	Evidence level
Active malignancy	Consensus contraindication list [72]	No stated evidence level
Active infection at the injection site	Consensus [72]; documented infection events [183]	Consensus, supported by case reports
Haemodynamic instability or sepsis	Consensus [72]	No stated evidence level
Thrombocytopenia	GRIIP consensus [186]	Above 50,000/mm³ explicitly not a contraindication
Anticoagulant therapy	Consensus [72][186]	Relative; no outcome data
Pregnancy and lactation	Consensus [72]	No stated evidence level
Naproxen washout	Controlled study [70][71]	One week; PDGF and IL-6 normalise — the only anchored interval
Aspirin washout	Controlled study [70]	Growth-factor release reduced; interval unestablished
COX-2 selective inhibitors	Controlled study [70]	No inhibition; washout not required
Corticosteroid interval	Consensus only [72]	No primary experimental study retrieved
Bupivacaine co-injection	In-vitro study [69]	Avoid; direct evidence of platelet harm
Bovine thrombin activation	Boxed warning [66][67]	Avoid; regulatory warning
Additives of any kind (Brazil)	Resolução CFM nº 2.464/2026 art. 5 [74]; ANVISA NT 29/2024 [75]	Legally binding prohibition outside approved research

Ultrasound guidance	13-study systematic review [77]	Accuracy 95.4% versus 82.0%; the strongest modifiable variable
Injection number	Network meta-analysis [78]	Three injections optimal; 52-week WOMAC 61.03 / 31.80 / 28.17
Kellgren–Lawrence restriction	ESSKA [126]; ESSKA–ICRS [127]; Delphi [130]	Grades 1–3 or 0–III; 77.5% strong agreement limited to grade II

Table 16: Contraindications and procedural rules with the basis and evidence level of each. Only three entries in this table rest on experimental data.

Regulation: the same procedure, six legal identities

In the United States, platelet-rich plasma is not regulated as a human cell, tissue or cellular and tissue-based product [187][188]; instead the centrifuge is cleared as a class 1 device under product code QBV, subject to a mandatory labelling statement that the safety and effectiveness of the product for any specific therapeutic use has not been established [3]. The period of enforcement discretion for regenerative-medicine products ended on 31 May 2021 [189], and enforcement has followed: a warning letter of 22 April 2026 found a preparation kit cleared only for bone-graft handling to be adulterated and misbranded when promoted for musculoskeletal use [190]. Every device cleared in 2024 was cleared as a platelet and plasma separator for bone-graft handling [84], and the historical predicates were narrower still [80][81][83].

In Europe, the Competent Authorities for Blood and Blood Components recorded that platelet-rich plasma and platelet-rich fibrin fall within different legal frameworks across Member States [191]. Regulation (EU) 2024/1938 on substances of human origin brings autologous substances into scope through Article 2(5), with application from 7 August 2027 [192], the European Directorate for the Quality of Medicines and HealthCare has published a twenty-second edition of the Blood Guide adding relevant chapters [193][194], and the United Kingdom explanatory memorandum lists platelet-rich plasma among the preparations brought into scope [195].

Brazil now has the most specific rules in the world. Resolução CFM nº 2.464 of 2 July 2026, published on 15 July 2026, authorises platelet-rich plasma as an adjuvant procedure for four musculoskeletal conditions only, with additives prohibited outside approved research [74][196]. ANVISA classifies platelet-rich plasma as a conventional-therapy product not subject to sanitary registration provided it acts through its own mechanism without additives [75]. The Federal Nursing Council filed a civil public action on 29 July 2026 challenging articles 8 to 12 of the resolution [197]. Australia regulates platelet-rich plasma under the autologous human cells and tissues framework [198][199], Health Canada states that platelet-rich plasma meets the definition of a drug and that no applications have been received [200], and Japan provides it as Class II and Class III regenerative medicine, accounting for 65.8% of provision plans [1].

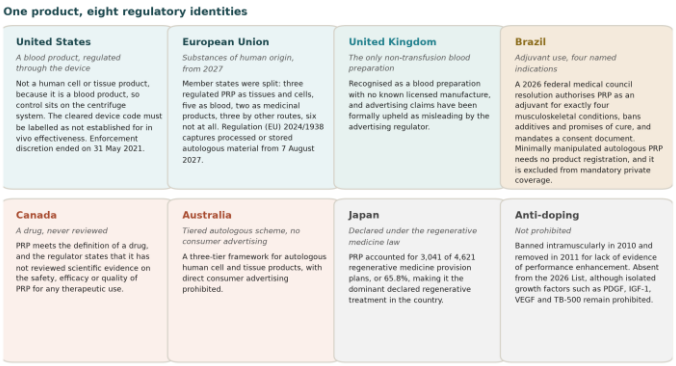

Figure 16: Regulatory identity of platelet-rich plasma by jurisdiction, arranged from device-only oversight through blood-product frameworks to full drug classification. The same autologous procedure occupies six distinct legal categories.

Rule or contraindication	Basis	Evidence level
Active malignancy	Consensus contraindication list [72]	No stated evidence level
Active infection at the injection site	Consensus [72]; documented infection events [183]	Consensus, supported by case reports
Haemodynamic instability or sepsis	Consensus [72]	No stated evidence level
Thrombocytopenia	GRIIP consensus [186]	Above 50,000/mm³ explicitly not a contraindication
Anticoagulant therapy	Consensus [72][186]	Relative; no outcome data
Pregnancy and lactation	Consensus [72]	No stated evidence level
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Additives of any kind (Brazil)	Resolução CFM nº 2.464/2026 art. 5 [74]; ANVISA NT 29/2024 [75]	Legally binding prohibition outside approved research
Ultrasound guidance	13-study systematic review [77]	Accuracy 95.4% versus 82.0%; the strongest modifiable variable
Injection number	Network meta-analysis [78]	Three injections optimal; 52-week WOMAC 61.03 / 31.80 / 28.17
Kellgren–Lawrence restriction	ESSKA [126]; ESSKA–ICRS [127]; Delphi [130]	Grades 1–3 or 0–III; 77.5% strong agreement limited to grade II

Table 17: Regulatory classification of platelet-rich plasma by jurisdiction. No two major jurisdictions regulate it

identically.

Cost, reimbursement and the commercial gradient

Reimbursement follows the evidence closely, which is unusual and instructive. The only United States national coverage determination permits autologous platelet-rich plasma for chronic non-healing diabetic wounds and for twenty weeks [147], while a local coverage determination establishes non-coverage for all musculoskeletal use [204]. Commercial payers classify it as experimental or unproven for all indications [205][206], and Current Procedural Terminology code 0232T carries zero relative value units and is not covered by most payers [207][208]. In Brazil it is not in the mandatory coverage list [209].

Costs consequently fall on patients, and the gradient between price and evidence is steep. United States direct-to-consumer intra-articular platelet-rich plasma has a median price of US$800 with a range of US$350 to US$2,815 [210], the RESTORE trial costed its injections at US$2,032 each [50], a Delphi survey found a mean charge of US$714 ± 144 against a claimed efficacy of 76% ± 11% [130], and urological direct-to-consumer pricing averages US$1,507 ± 388 [157]. Where a health system pays, the arithmetic inverts entirely: an Italian analysis reported a cost of €82.62 per cycle with an incremental cost-effectiveness ratio of €1,524 per quality-adjusted life year [211], and an Iranian analysis reported 7,583 international dollars per quality-adjusted life year [212].

Setting	Figure	Source
US Medicare national coverage	Diabetic chronic non-healing wounds only, 20 weeks	[147]
US Medicare local coverage	Non-coverage for all musculoskeletal injections	[204]
Commercial payer, Aetna	Experimental or unproven for all indications, ≈30 named conditions	[205]
Commercial payer, UnitedHealthcare	Unproven and not medically necessary, effective 1 January 2026	[206]
Procedure coding	CPT 0232T carries zero relative value units; not covered by most payers	[207][208]
Brazil, supplementary health	Not included in the mandatory coverage list	[209]
US direct-to-consumer, knee	Median US$800 (range US$350–2,815)	[210]
RESTORE trial costing	US$2,032 per injection	[50]
Delphi survey of US practice	US$714 ± 144 per knee; claimed efficacy 76% ± 11%	[130]
US direct-to-consumer, urology	US$1,507 ± 388; offered by 9% of urologists	[157]
Italy, health-system perspective	€82.62 per cycle; ICER €1,524 per QALY	[211]
Iran, health-system perspective	ICER 7,583 international dollars per QALY	[212]
Preparation kit cost	US$50–500 depending on system	[51]
Global market	US$650.13 million in 2025 to a projected US$1,751.45 million by 2033 (CAGR 13.2%)	[2]
Advertising enforcement	Federal Trade Commission action [167]; Advertising Standards Authority ruling upheld	[168]

Table 18: Reimbursement position and cost of platelet-rich plasma across settings. Cost-effectiveness is favourable

only where the price is set by a health system rather than by a consumer market.

Discussion: what would have to change

Twenty-five years after Marx defined the product [4], platelet-rich plasma occupies an unusual position in medicine: a therapy with coherent biology, an enormous trial literature, a growing market, and an evidence base that cannot support most of the claims made for it. This review has assembled the reasons, and they are structural rather than biological.

The four structural failures

The first failure is definitional. There is no product called platelet-rich plasma; there is a family of preparations spanning a thirty-fold range of centrifugal force [51][47][48], a three-fold range of delivered platelet concentration from identical donor blood [76], and a twenty-six-fold range of absolute platelet dose across commercial devices [31]. Pooling such preparations in a meta-analysis is not a statistical operation but a category error.

The second failure is reporting. Only 10% of clinical studies provide a reproducible protocol [34], adherence to the Minimum Information for Studies Evaluating Biologics in Orthopaedics checklist remains below 55% [35][36][37][38][39], and in an entire aesthetic indication the final platelet number was never reported in any primary study [40]. Composition cannot be an effect modifier in an analysis that does not measure composition.

The third failure is interpretive. All seventy-nine systematic reviews of platelet-rich plasma for knee osteoarthritis contain spin, with 84.8% claiming benefit despite high risk of bias [41], undisclosed funding predicts positivity with an odds ratio of 3.61 [42], five retractions have affected the literature [100][101][102][103][104], trim-and-fill adjustment eliminates the rotator-cuff effect [112][113], and adverse events go unreported in more than half of studies [180]. Meta-analytic conclusions in this field are systematically more favourable than the trials they summarise.

The fourth failure is regulatory and commercial. The same procedure is a class 1 device output in the United States [3], a substance of human origin in the European Union from 2027 [192], a drug in Canada with no authorised product [200], and a four-indication adjuvant act in Brazil [74]. Patients pay a median of US$800 and up to US$2,815 out of pocket [210] for a therapy that commercial payers classify as unproven for all indications [205][206], in a market growing at 13.2% annually [2], with advertising enforcement actions in two jurisdictions [167][168].

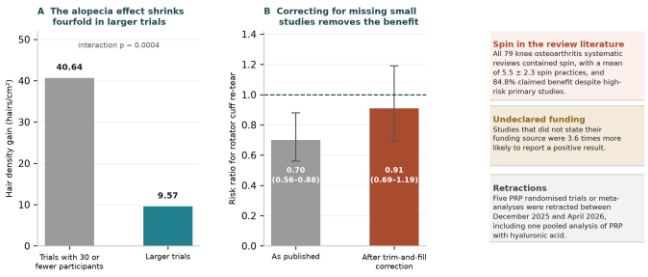

Figure 17: The evidence-integrity picture. Spin prevalence, risk-of-bias distribution, funding-disclosure association and adverse-event reporting completeness are shown together, because each independently inflates the apparent

efficacy of platelet-rich plasma.

What the current trial pipeline will and will not resolve

Several trials now in progress are designed to answer the compositional questions directly. Two Rizzoli trials randomise leukocyte-rich against leukocyte-poor preparations in epicondylitis and in hip osteoarthritis [213][214], which is the correct design for the leukocyte question that the network meta-analysis could not settle [6]. A Toronto phase 2/3 trial randomises both bone-marrow aspirate and leukocyte-poor platelet-rich plasma against saline [215], providing the placebo control that most orthobiologic comparisons lack. Trials of platelet-rich plasma with hyaluronic acid [216][217] and of a lyophilised preparation [218] address formulation. A San Francisco trial comparing young with old donors [219] addresses the donor-variability question that sex-based compositional differences have already raised [220].

What the pipeline will not resolve is the definitional problem. A 10,000-participant unmasked registry running to 2035 [221] will generate a very large quantity of uncontrolled data across undefined preparations. Unless preparation reporting becomes mandatory at the journal and registry level, the next decade of trials will reproduce the heterogeneity of the las.

Registry identifier	Sponsor	Design and enrolment	Question addressed
NCT05517434 [215]	University Health Network, Toronto	Phase 2/3, n = 148; BMA versus saline and LP-PRP versus saline	Placebo-controlled efficacy of two orthobiologics in parallel
NCT06040203 [213]	Istituto Ortopedico Rizzoli	n = 240; LR-PRP versus LP-PRP versus placebo in epicondylitis	Does leukocyte content matter?
NCT05497349 [214]	Istituto Ortopedico Rizzoli	n = 230; LR-PRP versus LP-PRP in hip osteoarthritis	Leukocyte content in a second joint
NCT06685120 [216]	Istituto Ortopedico Rizzoli	n = 288, double-blind; PRP plus hyaluronic acid in knee osteoarthritis	Does combination add benefit?
NCT05727371 [217]	Multicentre	n = 280, triple-masked; PRP with cross-linked hyaluronic acid	Formulation with a carrier matrix
NCT06932614 [218]	Multicentre	n = 90, quadruple-masked; lyophilised growth factor versus PRP, WOMAC primary	Does a storable product match fresh PRP?
NCT06003101 [222]	Massachusetts General Hospital	Phase 3, n = 160; PRP, platelet-poor plasma and BMAC in hip arthroscopy	Is the platelet fraction the active fraction?
NCT05603468 [223]	Second Affiliated Hospital of Zhejiang University	Phase 4, n = 387; PRP versus corticosteroid in rotator cuff tendinopathy	Comparison against standard care at scale
NCT05412381 [224]	Hospital for Special Surgery	Phase 3, n = 56; PRP in ACL reconstruction, platelet count as primary outcome	Links delivered dose to a trial endpoint
NCT05378815 [225]	Assistance Publique – Hôpitaux de Paris	n = 210, triple-blind; change in numerical rating scale pain	Rigorously blinded pain outcome
NCT06451120 [219]	University of California San Francisco	Phase 2, n = 60; PRP in young versus old subjects	Donor-age effect on the product
NCT06680856 [226]	Ospedale Policlinico San Martino	Phase 1/2, n = 72, completed; allogeneic PRP for diabetic foot ulcers	Feasibility of an allogeneic product [146]
NCT07231471 [221]	University of Utah	Planned n = 10,000, no masking, primary completion 2035	Large-scale observational data; will not resolve heterogeneity

Table 19: Registered trials in progress and the specific question each address. Three trials directly test the

leukocyte and dose questions that current syntheses cannot answer

A research agenda

Five changes would alter the trajectory of this field more than any additional trial of unspecified platelet-rich plasma against saline. First, journals should refuse publication of clinical studies that do not report absolute platelet dose, leukocyte and erythrocyte content, centrifugal force in units of g, spin duration, anticoagulant, activation status and injected volume — the essential subset of the existing checklist [35][33]. Second, trials should power for the minimal clinically important difference rather than for statistical significance [91][92][93]. Third, dose should be randomised rather than described, since the only strong dose signal available derives from cross-arm comparison [54] and is contradicted by network analysis [6]. Fourth, composition biomarkers should be collected prospectively in every trial, following the single existing series that correlated composition with outcome [14][131]. Fifth, ultrasound guidance should be standard, since it is the one variable with a large, reproducible and mechanistically transparent effect [77].

Conclusion

Platelet-rich plasma is neither the regenerative breakthrough its marketing describes nor the placebo its critics assert. It is a heterogeneous family of autologous preparations with a demonstrable and clinically meaningful effect in chronic wounds, a real but second-line effect in androgenetic alopecia, a plausible effect in medication-related osteonecrosis of the jaw and tympanic membrane perforation, an unresolved effect in knee osteoarthritis where the highest-quality placebo-controlled trial was negative, and no demonstrable effect in facial rejuvenation, periodontal intrabony defects, sinus augmentation, ankle osteoarthritis, Achilles tendinopathy, acute muscle injury or recurrent implantation failure.

The four-tier framework in Table 20 separates these levels of confidence. Applying it would mean offering platelet-rich plasma routinely for venous and diabetic ulcers, offering it with explicit discussion of alternatives for androgenetic alopecia and for Kellgren–Lawrence grade II knee osteoarthritis, confining the remaining indications to research, and declining to charge patients for indications where controlled evidence is absent. The single most valuable technical change available today is not a new formulation but complete reporting of the formulation already in use.

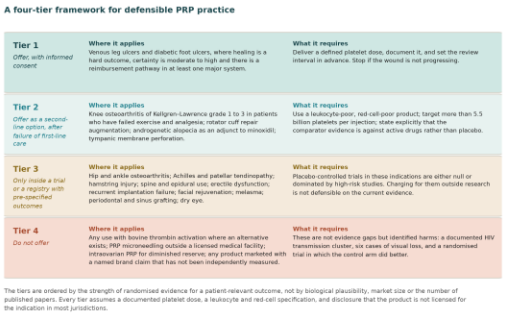

Figure 18: The four-tier framework. Indications are placed by the strength of controlled evidence, with the recommended clinical posture for each tier shown alongside.

Tier	Definition	Indications	Clinical posture

Tier 1 — Established	Consistent randomised evidence with high certainty and effects exceeding the MCID	Diabetic foot ulcer [141]; venous leg ulcer [143][145]; chronic wounds of mixed aetiology [142][11]	Offer as part of standard wound care; reimbursed for diabetic wounds for 20 weeks [147]
Tier 2 — Probable, not first-line	Consistent effect demonstrated, but a comparator performs as well or better	Androgenetic alopecia [133][134][9]; pressure injury [144]; medication-related osteonecrosis of the jaw [151]; tympanic membrane perforation [163]; KL grade II knee osteoarthritis [126][130]	Offer only after discussing better-evidenced alternatives and the out-of-pocket cost [210]
Tier 3 — Research only	Trials are small, discordant, or confined to unblinded designs	Knee osteoarthritis beyond KL II [50][6]; rotator cuff augmentation [113]; osteonecrosis of the femoral head [114][115]; carpal tunnel syndrome [116]; olfactory dysfunction [164]; erectile dysfunction [155][156]	Enrol in a trial; do not charge for treatment outside research [125]
Tier 4 — Not supported	Adequately designed controlled trials show no benefit	Facial rejuvenation [138][40]; melasma [139]; scars with laser comparator [10]; periodontal intrabony defect [148]; sinus augmentation [149]; ankle osteoarthritis [96]; Achilles tendinopathy [92][182]; acute muscle injury [97]; recurrent implantation failure [160]; stress urinary incontinence [159]	Do not offer

Table 20: Four-tier framework for the clinical use of platelet-rich plasma. Tier assignment reflects the strength of controlled evidence interpreted against minimal clinically important differences, not the volume of published literature.

Declarations

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Conflicts of interest

No competing interests exist.

Ethics statement

This work is a narrative review of published literature and does not involve new human participants, animals, or identifiable patient data. Ethical approval was therefore not required.

Author contributions

All authors critically revised the manuscript and approved the final version.

Data availability

All data discussed in this review are contained in the cited publications, regulatory documents and trial registry records, each of which is referenced with its source location.

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151. American Urological Association. Erectile dysfunction guideline, statement 25: platelet-rich plasma therapy should be considered experimental and should not be offered outside an institutional review board approved research protocol.
152. European Association of Urology. Sexual and reproductive health guideline: do not use platelet-rich plasma to treat erectile dysfunction outside the confines of a clinical trial.
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184. Electronic Code of Federal Regulations, 21 CFR 1271.10: an HCT/P is regulated solely under section 361 of the Public Health Service Act only if it is minimally manipulated, intended for homologous use, not combined with another article, and either without systemic effect and independent of living-cell metabolic activity or intended for autologous, first- or second-degree relative, or reproductive use.
185. US Food and Drug Administration. Advancing the development of safe and effective regenerative medicine products. FDA Voices. The period of enforcement discretion for regenerative-medicine products ended 31 May 2021 and will not be extended further.
186. US Food and Drug Administration, Center for Biologics Evaluation and Research. Warning letter to Estar Technologies Ltd, CBER 26-716831, 22 April 2026. Promotion of a PRP kit cleared only for bone-graft handling towards musculoskeletal, osteoarthritis, wound, ophthalmic and dental indications rendered the devices adulterated under section 501(f)(1)(B) and misbranded under section 502(o) of the Federal Food, Drug, and Cosmetic Act.
187. European Commission. Minutes of the meeting of the Competent Authorities for Blood and Blood Components, 18–19 June 2019. Platelet-rich plasma and platelet-rich fibrin fall within different legal frameworks across Member States: tissues and cells legislation in three, blood legislation in five, medicinal-products legislation in two, other frameworks in three, and no regulation in six.
188. Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application. Article 2(5) brings autologous substances that are processed or stored before application into scope; Article 85 repeals Directives 2002/98/EC and 2004/23/EC and Article 87 sets application from 7 August 2027.
189. European Directorate for the Quality of Medicines and HealthCare. Twenty-second edition of the Guide to the preparation, use and quality assurance of blood components, published 21 May 2025, adding chapters on blood components for topical use or injection and on blood supply contingency planning.
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191. United Kingdom Government explanatory memorandum on Regulation (EU) 2024/1938. Paragraph 9 lists platelet-rich plasma among blood preparations not used for transfusion that are brought into scope, and paragraph 87 states that the Medicines and Healthcare products Regulatory Agency is not aware of any manufacture of platelet-rich plasma under a manufacturing licence.
192. Conselho Federal de Medicina regulates the use of platelet-rich plasma for four musculoskeletal conditions. Folha de S. Paulo, 15 July 2026.
193. Conselho Federal de Enfermagem (Brazil). Press release on the civil public action filed on 29 July 2026 challenging articles 8 to 12 of Resolução CFM nº 2.464/2026.
194. Therapeutic Goods Administration (Australia). Australian regulatory guidelines for biologicals: autologous human cells and tissues products regulation, version 2.0, July 2019. Platelet-rich plasma, platelet-rich fibrin and conditioned serum are autologous human cell and tissue products across three tiers, and biologicals and excluded autologous products must not be advertised to consumers.
195. Therapeutic Goods Administration (Australia). Regulating platelet-rich plasma, platelet-rich fibrin and conditioned serum.
196. Health Canada. Information update RA-70559: Health Canada clarifies its position on platelet-rich plasma treatments, 26 July 2019. Platelet-rich plasma meets the definition of a drug under the Food and Drugs Act; preparation within a single practitioner-delivered procedure falls under provincially regulated practice of medicine; no application to market platelet-rich plasma or conduct clinical trials has been received and no scientific evidence has been reviewed.
197. World Anti-Doping Agency. WADA Executive Committee approves the 2010 Prohibited List, under which platelet-derived preparations were prohibited when administered by the intramuscular route, with other routes requiring a declaration of use.
198. World Anti-Doping Agency. The 2011 Prohibited List is now published: platelet-derived preparations were removed after consideration of the lack of current evidence concerning the use of these methods for purposes of performance enhancement.
199. Athletics Integrity Unit. Understand the Prohibited List: platelet-rich plasma procedures remain not prohibited.
200. Noridian Healthcare Solutions. Local coverage determination L39058: a non-coverage policy for all platelet-rich plasma injections or applications as a means of managing musculoskeletal injuries or joint conditions, revision effective 11 September 2025.
201. Aetna. Clinical policy bulletin 0784: platelet-rich plasma. Platelet-poor and platelet-rich plasma injection are considered experimental, investigational or unproven for all indications, including approximately 30 named conditions, and codes 0232T, 0481T, G0460, G0465, P9020 and S9055 are listed as not covered.
202. UnitedHealthcare. Commercial medical policy 2026T0498CC, prolotherapy and platelet-rich plasma therapies, effective 1 January 2026: due to insufficient evidence of efficacy, platelet-rich plasma is unproven and not medically necessary for any condition or indication.
203. Blue Shield of California medical policy on orthopaedic applications of platelet-rich plasma. Current Procedural Terminology code 0232T covers injections of platelet-rich plasma at any site including image guidance, harvesting and preparation, is effective from 1 July 2010 and carries zero relative value units.
204. Reimbursement analysis of PRP under Current Procedural Terminology code 0232T, which is not covered by most United States payers.
205. Agência Nacional de Saúde Suplementar (Brazil). Parecer Técnico nº 04/GCITS/GGRAS/DIPRO/2024, 30 August 2024: the application of platelet-rich plasma is not included in the mandatory coverage list because coverage is not compulsory for experimental clinical or surgical treatment.
206. Survey of direct-to-consumer pricing of intra-articular PRP in the United States: median US$800 with a range of US$350 to US$2,815.
207. Cost-effectiveness of intra-articular PRP in Italy: €82.62 per treatment cycle with an incremental cost-effectiveness ratio of €1,524

per quality-adjusted life-year.
208. Cost-effectiveness analysis of PRP for knee osteoarthritis in Iran: incremental cost-effectiveness ratio of 7,583 international dollars per quality-adjusted life-year.
209. ClinicalTrials.gov NCT06040203. Istituto Ortopedico Rizzoli, leukocyte-rich versus leukocyte-poor platelet-rich plasma versus placebo in epicondylitis, n = 240.
210. ClinicalTrials.gov NCT05497349. Istituto Ortopedico Rizzoli, leukocyte-rich versus leukocyte-poor platelet-rich plasma in hip osteoarthritis, n = 230.
211. ClinicalTrials.gov NCT05517434. University Health Network Toronto, bone marrow aspirate versus saline and leukocyte-poor platelet-rich plasma versus saline, phase 2/3, n = 148.
212. ClinicalTrials.gov NCT06685120. Istituto Ortopedico Rizzoli, platelet-rich plasma plus hyaluronic acid in knee osteoarthritis, n = 288, double-blind.
213. ClinicalTrials.gov NCT05727371. Platelet-rich plasma combined with cross-linked hyaluronic acid (RegenMatrix), n = 280, triple-masked
214. ClinicalTrials.gov NCT06932614. Lyophilized self growth factor versus platelet-rich plasma in knee osteoarthritis, n = 90, quadruple-masked, primary outcome WOMAC.
215. ClinicalTrials.gov NCT06451120. University of California San Francisco, platelet-rich plasma in young versus old subjects, phase 2, n = 60.
216. Xiong G, Lingampalli N, Koltsov JCB, Leung LL, Robinson WH, Maloney WJ, Chu CR. Men and women differ in the biochemical composition of platelet-rich plasma. Am J Sports Med. 2018;46(2):409–19.
217. ClinicalTrials.gov NCT07231471. University of Utah, platelet-rich plasma for musculoskeletal conditions, planned enrolment 10,000, no masking, primary completion 2035.
218. ClinicalTrials.gov NCT06003101. Massachusetts General Hospital, platelet-rich plasma, platelet-poor plasma and bone marrow aspirate concentrate in hip arthroscopy, phase 3, n = 160.
219. ClinicalTrials.gov NCT05603468. Second Affiliated Hospital of Zhejiang University, platelet-rich plasma versus corticosteroid for rotator cuff tendinopathy, phase 4, n = 387.
220. ClinicalTrials.gov NCT05412381. Hospital for Special Surgery, platelet-rich plasma in anterior cruciate ligament reconstruction, phase 3, n = 56, primary outcome platelet count.
221. ClinicalTrials.gov NCT05378815. Assistance Publique – Hôpitaux de Paris, randomised triple-blind trial, n = 210, primary outcome change in numerical rating scale pain.
222. ClinicalTrials.gov NCT06680856. Ospedale Policlinico San Martino, allogeneic platelet-rich plasma for diabetic foot ulcers, phase 1/2, n = 72, completed.