Journal of Orthopaedics Study and Sports Medicine

Genesis-JOSSM-4(1)-38
Volume 4 | Issue 1 | 2026
Open Access
ISSN: 3139-5635

Bone Marrow Aspiration in Regenerative Medicine: Biology, Preparation, Classification, and Clinical Applications a Comprehensive Evidence-Graded Review of 236 Primary Sources Spanning Marrow Cell Biology, Harvest Anatomy, Concentration Physics, Dose-Response, Orthopaedic and Non-Orthopaedic Outcomes, Safety, Regulation and Reimbursement

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Citation: Kume MH, Furlan B, Boacentura CG, Probst MA, Peracchi E, et al. Bone Marrow Aspiration in Regenerative Medicine: Biology, Preparation, Classification, and Clinical Applications A Comprehensive Evidence-Graded Review of 236 Primary Sources Spanning Marrow Cell Biology, Harvest Anatomy, Concentration Physics, Dose–Response, Orthopaedic and Non-Orthopaedic Outcomes, Safety, Regulation and Reimbursement. J Orthop Study Sports Med. 4(1):1-45.

Received: August 17, 2026 | **Published:** October 02, 2026

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Abstract

Background: Bone marrow aspiration is the oldest and most anatomically demanding of the autologous orthobiologic procedures, and the only one whose product is routinely described in public and in print as a stem cell treatment. Neither description survives contact with the measured composition of the fluid. A clinically typical aspirate contains one colony-forming fibroblastic progenitor per approximately thirty thousand nucleated cells, and the best measured effect of point-of-care concentration is a roughly five-fold enrichment of that rare population. Between the biology and the marketing lies a literature in which the single most decisive processing variable, relative centrifugal force, was reported in none of forty-six studies audited.

Objectives: To assemble a single source-grounded synthesis that connects marrow cell biology to the anatomy and physics of harvest, the arithmetic of concentration and dose, the competing classification systems, and the measured clinical effect size in every indication for which controlled data exist; and to state 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 marrow cell biology and the stem cell nomenclature problem; harvest anatomy, needle mechanics and reporting standards; concentration devices, classification systems and dose–response; musculoskeletal clinical outcomes against published minimal clinically important differences; non-orthopaedic and systemic administration; and safety, regulation, reimbursement, anti-doping status and the methodological quality of the literature. Every numerical value reported here was extracted from a retrieved primary source; 236 sources are cited. Effect estimates are compared against published minimal clinically important differences rather than against statistical significance alone.

Results: Marrow aspirate is a haematopoietic fluid diluted by peripheral blood in proportion to the volume drawn from each needle position; progenitor density falls steeply beyond the first one to two millilitres per placement, and the connective tissue progenitor prevalence declines with donor age from roughly one in ten thousand nucleated cells in adolescence toward one in two hundred thousand in the eighth decade. Point-of-care concentration delivers a median five-fold progenitor enrichment; it concentrates the anti-inflammatory interleukin-1 receptor antagonist 22.8-fold relative to platelet-rich plasma while leaving platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor beta 1 and bone morphogenetic protein 2 statistically indistinguishable. Five separate dose thresholds have been published in five different units, and none has been validated prospectively. In knee osteoarthritis, marrow concentrate is statistically superior to hyaluronic acid at six and twelve months yet the point estimates lie below the minimal clinically important difference; the only adequately powered four-arm head-to-head trial identified no orthobiologic superior to corticosteroid or to any other orthobiologic; and a trial using a contralateral saline control within the same patient found no between-knee difference. Outside the musculoskeletal system the pattern is sharper still: a benefit for amputation in critical limb ischaemia across all randomised trials collapses to the null when analysis is restricted to placebo-controlled trials, and adequately powered trials in myocardial infarction, advanced heart failure, multiple sclerosis and perianal fistula were neutral. Harvest is very safe; the injection is a different question and carries the same complication rate as its comparators. Two published market sizings of the same procedure differ by a factor of 13.9, every major United States payer reviewed designates the procedure investigational, and 67.9% of the systematic reviews of the field are rated critically low on AMSTAR-2 while 75.0% contain spin in the abstract.

Conclusions: The defensible uses of bone marrow aspiration today are those in which the marrow serves as an osteogenic graft adjunct to a mechanically stabilised construct, and core decompression of early-stage femoral head osteonecrosis. Intra-articular and augmentation uses are reasonable inside a registry or a trial and should be presented to patients as such. Intradiscal, intraosseous, systemic and stem cell branded uses are research activities, and in several jurisdictions, including Brazil, the addition of marrow concentrate to platelet-rich plasma outside approved research is expressly prohibited. The single reform with the largest expected effect on the credibility of this field costs nothing: report relative centrifugal force and spin duration instead of revolutions per minute, report the harvest and processing variables that the Minimum Information for Studies Evaluating Biologics in Orthopaedics checklist already specifies, and stop calling the product a stem cell therapy.

Keywords

Bone marrow aspirate; Bone marrow aspirate concentrate; Mesenchymal stromal cells; Connective tissue progenitors; Colony-forming unit-fibroblast; Orthobiologics; Knee osteoarthritis; Osteonecrosis; Relative centrifugal force; Regulatory science.

AAOS, [illegible] verse event; AMSTAR-2, A MeaSurement Tool to Assess systematic Reviews version 2; ANVISA, Agência Nacional de Vigilância Sanitária; ATMP, advanced therapy medicinal product; AUC, area under the curve; b-FGF, basic fibroblast growth factor; BMA, bone marrow aspirate; BMAC, bone marrow aspirate concentrate; BMP-2, bone morphogenetic protein 2; CBMA, concentrated bone marrow aspirate; CD, cluster of differentiation; CFM, Conselho Federal de Medicina; CFR, Code of Federal Regulations; CFU-F, colony-forming unit-fibroblast; CI, confidence interval; CLI, critical limb ischaemia; CPT, Current Procedural Terminology; CQA, critical quality attribute; CT, computed tomography; CTP, connective tissue progenitor; DFU, diabetic foot ulcer; DOSES, donor, origin tissue, separation method, exhibited cell characteristics, site of delivery; DOU, Diário Oficial da União; EF, ejection fraction; ESSKA, European Society for Sports Traumatology, Knee Surgery and Arthroscopy; EU, European Union; FDA, Food and Drug Administration; FTC, Federal Trade Commission; GVHD, graft-versus-host disease; HA, hyaluronic acid; HCPCS, Healthcare Common Procedure Coding System; HCT/P, human cells, tissues and cellular and tissue-based products; ICER, incremental cost-effectiveness ratio; ICSH, International Council for Standardization in Haematology; IL-1ra, interleukin-1 receptor antagonist; ISAKOS, International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine; ISCT, International Society for Cell and Gene Therapy;

LCD, local coverage determination; LVEF, left ventricular ejection fraction; MARSPILL, method, activation, red blood cells, spin, platelet number, image guidance, leukocyte, light activation; MCID, minimal clinically important difference; MHRA, Medicines and Healthcare products Regulatory Agency; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics; MNC, mononuclear cell; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cell; NNH, number needed to harm; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; ONFH, osteonecrosis of the femoral head; OR, odds ratio; PDGF-BB, platelet-derived growth factor BB; PRP, platelet-rich plasma; QALY, quality-adjusted life year; RCF, relative centrifugal force; RCT, randomised controlled trial; RDC, Resolução da Diretoria Colegiada; RPM, revolutions per minute; RR, relative risk; SoHO, substances of human origin; SSP, same surgical procedure; TGA, Therapeutic Goods Administration; TGF-β1, transforming growth factor beta 1; THR, total hip replacement; TNC, total nucleated cell; USADA, United States Anti-Doping Agency; VAS, visual analogue scale; VEGF, vascular endothelial growth factor; VSEL, very small embryonic-like cell; WADA, World Anti-Doping Agency.

Introduction

Bone marrow has been aspirated for diagnosis since the 1920s and grafted for healing since the middle of the twentieth century. Of the autologous products used in contemporary musculoskeletal practice it is the one with the longest clinical pedigree, the most demanding anatomy, and the widest gap between what the fluid contains and what it is said to contain. The procedure is performed in offices and operating rooms worldwide under the description of a stem cell treatment, yet the cell that gives rise to that description is present at a prevalence of roughly one per thirty thousand nucleated cells in a clinically typical aspirate, and the entire measured effect of point-of-care processing on that population is a concentration step of approximately five-fold [1,2].

This review takes the position that the interesting question is not whether bone marrow aspirate contains useful cells; it demonstrably does, and in some clinical settings a dose–response relationship between those cells and a hard radiographic endpoint has been reported. The interesting question is which of the many distinct clinical activities now performed under the single label of bone marrow aspirate concentrate are supported by evidence that the marrow component, rather than the needle, the arthroscopy, the immobilisation or the passage of time, is doing the work. Answering that question requires holding together five bodies of literature that are usually read separately: the cell biology of the marrow niche, the anatomy and fluid mechanics of aspiration, the physics of density-gradient separation, the clinical trial record judged against minimal clinically important differences rather than p values, and the regulatory and commercial architecture that determines what may lawfully be offered and who pays for it.

Three problems that recur in every section of this review

The first problem is nomenclature. The cells credited with the therapeutic effect have been called mesenchymal stem cells, mesenchymal stromal cells, medicinal signalling cells, skeletal stem cells and connective tissue progenitors, and the choice among these names has repeatedly determined what claims were considered acceptable [3-5]. The second problem is measurement. The variable that determines what a centrifuge actually does to a cell suspension is relative centrifugal force applied for a stated time,

and in a systematic audit of forty-six clinical studies of marrow concentrate this variable was reported in none of them [6]. The third problem is comparison. Almost every positive claim in this field rests on a comparison with a weak comparator; when a marrow product has been compared with a strong comparator in an adequately powered trial, the difference has generally disappeared [7–9].

What this review adds

Three features distinguish this synthesis from the existing secondary literature. First, every quantitative statement is traced to a retrieved primary source, and where a widely repeated figure could not be traced it has been omitted rather than propagated. Second, clinical effect sizes are placed against the published minimal clinically important difference for the same instrument in the same population, so that statistical significance and clinical meaning are visibly separated [10–12]. Third, the review is deliberately unbalanced in favour of the negative literature, because the meta-research on this specific field shows that the secondary literature is not: 67.9% of systematic reviews of marrow concentrate are rated critically low in confidence and 75.0% contain spin in the abstract [13].

Methods

Design and scope

This is a narrative review with structured evidence appraisal, reported in the spirit of the Scale for the Assessment of Narrative Review Articles. It was not registered as a systematic review and makes no claim to exhaustive retrieval. Six independent source-grounded evidence briefs were compiled, each restricted to material retrieved and read during its own construction, covering: marrow cell biology and nomenclature; harvest anatomy, needle mechanics and reporting standards; concentration devices, classification systems and dose–response; musculoskeletal clinical outcomes; non-orthopaedic and systemic administration; and safety, regulation, reimbursement, anti-doping status and evidence quality.

Evidence hierarchy and the handling of effect sizes

Randomised controlled trials, Cochrane reviews and meta-analyses of randomised trials were prioritised, followed by prospective comparative studies, then registries and case series. Regulatory, payer and anti-doping documents were retrieved from the issuing authority rather than from secondary description. For every clinical outcome the point estimate is stated with its confidence interval and then compared with a published minimal clinically important difference for the same instrument. Where a study reported statistical significance without an effect size that can be compared with a threshold of clinical meaning, that limitation is stated explicitly rather than resolved silently in favour of the intervention.

What was deliberately excluded

Three categories of material were excluded. Values that could be found only in aggregator databases or in secondary summaries, without a retrievable primary source, were omitted. Reporting frameworks that could not be located in a retrievable form were omitted rather than described from memory. Marketing materials were used only as evidence of what is being claimed commercially, never as evidence of biological or clinical fact; device instructions for use were the exception, and are cited as manufacturer technical documents [14].

What is Actually in a Bone Marrow Aspirate

The marrow is not a reservoir of stem cells suspended in fluid. It is a densely organized Haematopoietic organ with a vascular, adipocytic, osteoblastic and neural architecture, and aspiration is a destructive sampling of that architecture which necessarily draws sinusoidal blood along with it [15,16]. Every subsequent statement about composition follows from that fact. The clinically relevant consequence is that the composition of an aspirate is not a property of the patient alone; it is a property of the patient, the site, the needle, the volume per needle position and the operator.

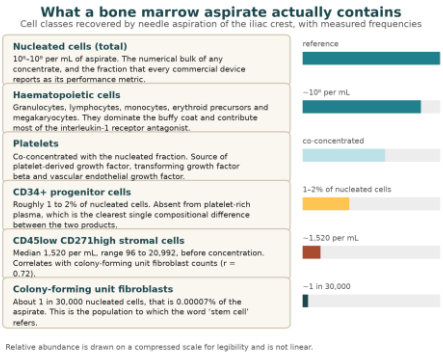

Figure 1: Measured cellular composition of a clinically typical bone marrow aspirate. The nucleated cell fraction is overwhelmingly haematopoietic. Colony-forming fibroblastic progenitors, the population responsible for the skeletal regenerative claims made for this fluid, are present at a prevalence of the order of one per thirty thousand nucleated cells before processing, and the prevalence declines with donor age and with the volume drawn from each needle position.

The cell populations, and which of them are actually rare

Nucleated cells in an aspirate are dominated by granulocytic and erythroid precursors and by lymphocytes and monocytes. Haematopoietic stem and progenitor cells identified by CD34 expression are present at a frequency of roughly one to two percent of nucleated cells. The population credited with skeletal regeneration, variously enumerated as colony-forming unit-fibroblast, connective tissue progenitors or CD45-low CD271-high cells, is two to three orders of magnitude rarer [1,17,18]. Endothelial progenitors, pericytes and a much-debated population of very small embryonic-like cells have all been proposed as contributors; the last of these has been specifically challenged on the grounds that the pluripotency claimed for it could not be reproduced [19,20].

The practical significance of this arithmetic is that the numerator of any dose calculation depends entirely on which assay is used. A total nucleated cell count obtained from a bedside haematology analyser is not interchangeable with a colony-forming unit-fibroblast count obtained after fourteen days of culture, and neither is interchangeable with a flow cytometric CD45-low CD271-high enumeration. Studies that report one and imply another are not comparable, and the audit literature shows this is the norm rather than the exception [6,21].

Cell population	Identification	Typical prevalence in aspirate	Regenerative claim
Granulocytic and erythroid precursors	Morphology; CD45-high	Majority of nucleated cells	None; diluent and source of proteases

Cell population	Identification	Typical prevalence in aspirate	Regenerative claim
Lymphocytes and monocytes	CD45-high; CD3, CD14	Substantial minority	Immunomodulatory and pro-angiogenic paracrine roles
Haematopoietic stem and progenitor cells	CD34-positive	Approximately 1–2% of nucleated cells	Angiogenic support; the basis of transplantation, not of orthobiologics
Connective tissue progenitors / CFU-F	**Adherent fibroblastic colony after 14-day culture**	**Of the order of 1 per 30,000 nucleated cells**	**The population on which all skeletal regenerative claims rest**
CD45-low CD271-high stromal cells	Flow cytometry	Median 1,520 per mL of aspirate in 54 donors	Surrogate for the culture-defined progenitor population
Endothelial progenitors and pericytes	CD31, CD146	Rare	Vascular remodelling; perivascular origin hypothesis
Very small embryonic-like cells	Small CD45-negative Lin- negative fraction	Reported rare; existence contested	Pluripotency claimed but not reproduced in independent work

Table 1: Cell populations in bone marrow aspirate, the assay that defines each, and the claim attached to each. CFU-F, colony-forming unit-fibroblast. Prevalence figures are those reported in the cited primary sources for clinically typical aspiration volumes and are not device-independent constants.

Nomenclature is not a semantic dispute

The International Society for Cellular Therapy defined minimal criteria for multipotent mesenchymal stromal cells in 2006: plastic adherence, a defined surface marker profile, and trilineage differentiation in vitro [22]. In 2019 the same body published a position statement recommending that the term stem be reserved for populations in which stemness has been demonstrated, and that the unqualified abbreviation be avoided [4]. Caplan, who introduced the original term, subsequently proposed medicinal signalling cells on the grounds that the therapeutic mechanism is paracrine rather than structural [3]. A Delphi process among investigators in the field failed to reach consensus on a single name, which is itself an informative result [5].

This matters clinically for two reasons. First, the marker profile that defines the population is a property of cultured cells; it does not identify the corresponding population reliably in a fresh unmanipulated aspirate, so a point-of-care product cannot be characterised by those criteria at the time of injection [18,23]. Second, quality attributes that predict potency are being defined for manufactured products, and none of them is measurable in an office centrifuge [23]. A product that cannot be characterised cannot be standardised, and a product that cannot be standardised cannot be compared across trials.

Donor factors that change the product before any device touches it

Progenitor prevalence and function decline with age. Hernigou and colleagues documented a reduced progenitor pool in the proximal femur of patients with osteonecrosis [24]; Muschler and colleagues quantified age- and sex-related decline in aspirate cellularity and progenitor prevalence [25]; and age-dependent loss of colony-forming capacity has been traced to the demise of specific skeletal stem cell populations [26]. Senescence appears at low passage in culture and is accompanied by loss of immunomodulatory and differentiation capacity [27–29]. Cigarette smoke exposure impairs stromal cell function [30], and the type 2 diabetic microenvironment reduces proliferative and paracrine capacity [31]. Marrow composition also changes with the physiological reconversion of yellow to red marrow, which is why site selection is a biological decision and not only an anatomical one [32,33].

Two consequences follow for trial design. A trial that does not report donor age, smoking status and metabolic status has not characterised its intervention. And a trial that enrols the population most likely to be offered this treatment in practice, namely older patients with degenerative disease and frequent

metabolic comorbidity, is enrolling the population in which the active ingredient is least abundant.

Factor	Direction of effect on progenitor content	Evidence
Increasing donor age	**Marked decline in progenitor prevalence and cellularity**	**Quantified in aspirate series and traced to loss of specific skeletal stem cell populations**
Volume drawn per needle position	Steep decline beyond the first 1–2 mL	Foundational aspiration studies and subsequent small-volume harvest work
Harvest site	Posterior iliac crest yields highest reported counts	Comparative studies across iliac, humeral, tibial, calcaneal and vertebral sites
Osteonecrosis of the femoral head	Reduced progenitor pool in the proximal femur	Direct progenitor enumeration in affected patients
Cigarette smoke exposure	Impaired stromal cell function	Experimental exposure of marrow stromal cells
Type 2 diabetes	Reduced proliferative and paracrine capacity	Comparative characterisation of diabetic versus non-diabetic stromal cells
In vitro passage number	Senescence and loss of immunomodulatory capacity at low passage	Serial passage studies of marrow stromal cells
Marrow fat conversion with age	Site-dependent reduction in haematopoietic marrow	Imaging and anatomical characterisation of red to yellow marrow conversion
Anticoagulant and additive choice	Alters aspirate character; differential cytotoxicity	Direct comparison of anticoagulant formulations

Table 2: Donor and technical factors that change the composition of a bone marrow aspirate before any concentration device is used.

Effect directions are those reported in the cited primary sources; the magnitude of each effect is device- and assay-dependent and the factors are not independent of one another.

Harvest: Anatomy, Fluid Mechanics and the Volume Fallacy

The most consequential decisions in this entire field are made before any device is opened. Where the needle enters, how far it advances, how many separate positions are sampled, and how much fluid is drawn at each position together determine the progenitor content of the aspirate to a degree that no downstream centrifugation protocol can recover.

The volume fallacy

Aspiration draws marrow from a limited volume around the needle tip; once that local reservoir is emptied, continued suction recruits' sinusoidal blood. Muschler and colleagues demonstrated in the foundational work that progenitor density falls steeply as the volume drawn from a single needle position increase, and that multiple small-volume aspirations from separate positions yield far more progenitors than a single large-volume aspiration of the same total volume [17]. Small-volume aspiration has since been shown to be superior for cell therapy manufacture [34], the efficiency of aspiration as a function of technique has been quantified directly [35], and the relationship between draw volume and cell counts has been measured for a lateral-port needle [36]. Reorientation of the needle between draws improves yield [37], as does a systematic multiple-site strategy compared with single-site harvesting [38].

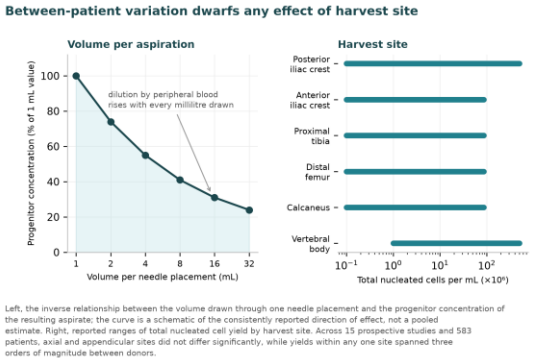

Figure 3: The volume fallacy and the effect of harvest site. Progenitor density falls steeply with the volume drawn from a single needle position, so the total progenitor yield of a given volume depends on how many separate positions were sampled. Reported total nucleated cell ranges differ systematically between the posterior iliac crest, the anterior iliac crest, the proximal humerus, the proximal tibia and the vertebral body.

Site selection

The posterior iliac crest remains the reference site. Hernigou and colleagues mapped the anatomy of the ilium specifically for aspiration and established that trajectory determines both safety and yield [39,40], and the posterior crest has been characterised as the preferred donor site for progenitor-rich marrow [41]. Comparative work has quantified the differences: aspirate from the posterior crest versus the proximal humerus [42-44], axial versus appendicular skeletal sites [45], the effect of age and harvest site on concentrate quality [46], and comparative cell counts across sites in a single-operator series [47]. In the foot and ankle literature, quantitative assessment of aspirate from the calcaneus and the proximal tibia has been reported [48–50]. Vertebral body aspiration during spinal exposure has been described as an efficient source when the surgical corridor is already open [51]. Fluoroscopic and image-guided approaches have been described for the posterior crest [52,53], and a lateral and posterolateral iliac approach has been published more recently [54]. Practical technique guides and device instructions specify entry points and trajectories in operational detail [14,55,56].

Harvest site	Access	Reported advantage	Principal limitation
Posterior iliac crest	Prone or lateral; landmark or image-guided	**Reference site; largest reservoir; highest reported progenitor yields**	Requires repositioning in supine cases; operator-dependent trajectory
Anterior iliac crest	Supine	No repositioning; convenient in supine procedures	Thinner corridor; lower yields reported than posterior crest
Proximal humerus	Same field as shoulder arthroscopy	Avoids a second surgical field in shoulder surgery; sequential aspiration characterised	Smaller reservoir; yields compared unfavourably with posterior crest in some series
Proximal tibia	Supine; same field as knee or foot surgery	Convenient in foot, ankle and knee procedures	Lower nucleated cell counts than iliac crest in quantitative comparisons
Calcaneus	Same field as hindfoot surgery	Avoids a remote incision in hindfoot reconstruction	Small volumes; donor-site morbidity requires specific consent
Vertebral body	Through an open posterior spinal exposure	No additional access when the corridor is already open; efficient for fusion adjuncts	Only available intraoperatively; volume limited by pedicle anatomy
Distal femur	Same field as knee surgery	Convenience in knee reconstruction	Least characterised of the sites in this table

Table 3: Harvest sites, access, reported advantages and limitations.

Yield comparisons between sites are drawn from single-centre comparative studies with differing assays and aspiration protocols and should not be read as device-independent constants.

Needle design, powered devices and anticoagulation

Needle geometry and technique change the product. Comparative analysis of needle techniques has been published for the interventional setting [57], and the effect of draw volume through a lateral-port needle has been quantified [36]. Needle internal diameter and the number of side openings have been specified in technique descriptions from the group that developed the osteonecrosis grafting protocol [58], the influence of anatomical site on the qualitative and quantitative yield of aspiration has been analysed directly [59], and contemporary technique descriptions for orthopaedic harvest have been published in operative form [60]. Contraindications are set out in general reference sources, including severe bleeding diathesis as an absolute contraindication [61]. Powered aspiration and biopsy systems have been compared with manual technique in a randomised comparison and in a systematic review, with reduced procedure time and comparable or improved specimen adequacy [62,63]. Anticoagulant choice is not neutral: the choice of anticoagulant alters the character of the aspirate [64], and differences in cytotoxicity between anticoagulant and additive formulations have been demonstrated directly [65]. Short-term handling and storage conditions have been formally validated for marrow destined for cell processing, which is relevant whenever aspiration and injection are separated in time [66]. Anatomical and computed-tomographic studies define the safe corridor and the structures at risk [67], and pain during aspiration and its modifiable determinants have been characterised, including with pharmacological premedication [68,69].

Reporting standards, and how comprehensively they are ignored

The Minimum Information for Studies Evaluating Biologics in Orthopaedics checklist specifies the variables that must be reported for a marrow-derived product to be interpretable, and the DOSES framework provides a complementary descriptive taxonomy adopted by national bodies [70–72]. Adherence is poor and has been quantified repeatedly. In the audit of forty-six clinical studies of marrow concentrate, relative centrifugal force was reported in none, revolutions per minute in 20%, spin duration in 30%, quantitative composition in 30%, flow cytometry in 15%, a colony-forming assay in 15% and fold increase in 6.5% [6]. Only 42% of the checklist variables were reported in a parallel assessment [21], and comparable deficits have been documented for mesenchymal stromal cell preparation protocols [73], for shoulder marrow concentrate studies [74], and across orthopaedic biologics generally [75].

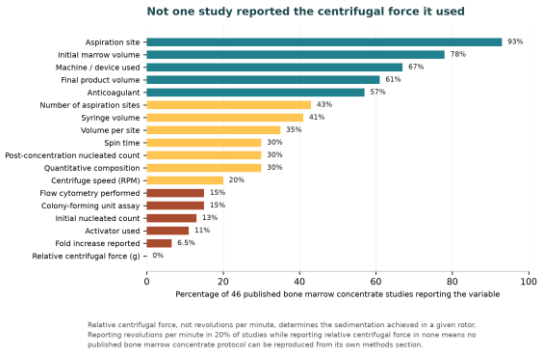

Figure 4: Reporting of processing variables across forty-six clinical studies of bone marrow aspirate concentrate. Relative centrifugal force, the only variable that determines what a centrifuge does to a cell suspension, was reported in none of the studies audited. Revolutions per minute, which is uninterpretable without the rotor radius,

was reported four times more often than the quantity it is used to approximate.

Reported variable	Studies reporting (%)	Why it matters
Relative centrifugal force	**0%**	**The only physically meaningful description of a centrifugation step**
Revolutions per minute	20%	Uninterpretable without rotor radius; not convertible between devices
Spin duration	30%	Determines the extent of separation at a given force
Quantitative cellular composition	30%	Defines the delivered product
Flow cytometry	15%	Only route to a marker-defined stromal enumeration
Colony-forming unit assay	15%	Only functional assay of progenitor content
Fold increase after processing	6.5%	The device's actual claimed effect
MIBO checklist variables overall	42%	Composite adherence across harvest and processing reporting

Table 4: Audited reporting of the variables that define a bone marrow aspirate concentrate product.

MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics. Percentages for individual processing variables are from the audit of forty-six studies; the composite figure is from the parallel checklist assessment.

The cross-domain comparison is instructive because it shows the problem is not confined to marrow. Reporting completeness has been measured at 70.5% for mesenchymal stromal cell randomised trials in the knee, 52.2% with a standard deviation of 12.1 for platelet-rich plasma in epicondylitis, and 42.8% with a standard deviation of 5.2 in foot and ankle biologics [73–75]. The field with the rarest active ingredient has the weakest characterisation of that ingredient.

Concentration: What the Centrifuge Does, and What It Does Not Do

Point-of-care concentration of marrow aspirate is a density-based separation performed on a heterogeneous suspension in a closed disposable. Understanding what it achieves requires separating three distinct claims that are frequently conflated: that the device concentrates nucleated cells, that it concentrates progenitors, and that it concentrates the biologically active soluble mediators. The measured answers are different for each.

The measured enrichment factor

The best-characterised estimate of progenitor enrichment comes from work in which CD45-low CD271-high stromal cells were enumerated by flow cytometry in aspirates from fifty-four donors, giving a median of 1,520 cells per millilitre of aspirate and a concentration factor of approximately five-fold with a 95% confidence interval of 3.6 to 7.2 after point-of-care processing [1]. Density-gradient physics sets the limits of what is achievable: the behaviour of mononuclear cells during density-gradient centrifugation has been characterised directly [76], and controlled concentration of marrow-derived cells has been demonstrated with defined protocols [77]. Because the colony-forming progenitor is present at a prevalence of the order of one per thirty thousand nucleated cells before processing, a five-fold enrichment moves that prevalence to the order of one per six thousand. That is a real biological change and it is not a stem cell preparation; a point made explicitly in the bone-healing literature [2].

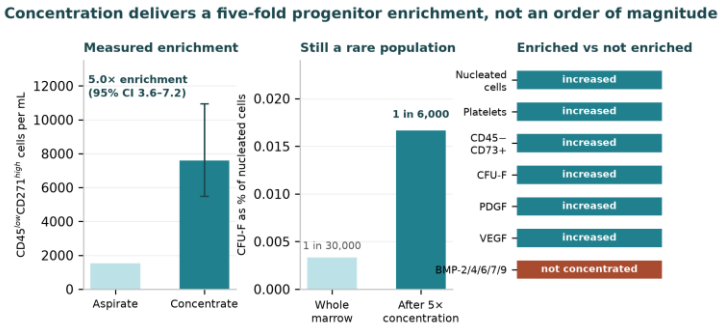

Figure 2: What point-of-care concentration does and does not concentrate. The measured median progenitor enrichment is approximately five-fold, moving the colony-forming progenitor prevalence from the order of one per thirty thousand nucleated cells to the order of one per six thousand. Enrichment of nucleated cells, platelets and specific soluble mediators does not track this figure, and several growth factors are not enriched at all relative to platelet-rich plasma.

Devices differ, and the differences have been measured

Commercially available point-of-care devices have been reviewed systematically [78] and benchmarked against one another for progenitor output [79]. Prospective comparisons of separation systems designed for marrow have shown different nucleated cell and progenitor recoveries from identical input aspirates [80,81], and isolation of clinically relevant cell numbers has been demonstrated for specific protocols [82]. Batch-to-batch consistency and composition of commercially available preparations have been evaluated directly and found variable [83]. The consequence is that device identity is part of the intervention description, and a meta-analysis that pools across devices without stratifying by them is pooling different interventions.

Processing approach	Physical principle	Reported effect on progenitors	Practical caveat
Buffy-coat point-of-care concentration	**Single- or double-spin density separation in a closed disposable**	**Median approximately five-fold progenitor enrichment**	**Enrichment factor is device-specific and rarely reported**
Density-gradient separation (laboratory)	Continuous or discontinuous gradient	Higher purity mononuclear fraction achievable	Not a point-of-care procedure; regulatory status differs in most jurisdictions
Selective retention / matrix enrichment	Progenitor adherence to an implantable matrix during aspirate passage	Enrichment onto the graft rather than into a syringe	Product is a composite graft, not an injectable
Marrow clot / three-dimensional construct	Endogenous clot formation to retain cells and matrix	Retains cells within a handleable construct	Not injectable; evaluated principally in spinal surgery
Unconcentrated whole aspirate	None	Baseline progenitor prevalence	No randomised trial has compared this with concentrate on a clinical endpoint

Table 5: Processing approaches applied to bone marrow aspirate.

Enrichment figures are drawn from the cited comparative and benchmarking studies and are not interchangeable across devices or assays.

The soluble fraction, and where marrow genuinely differs from platelet-rich plasma

The most robust biochemical distinction between marrow concentrates and platelet-rich plasma is not a growth factor but an inhibitor. Cassano and colleagues measured both products from the same donors

and found interleukin-1 receptor antagonist concentrated 22.8-fold in marrow concentrate relative to platelet-rich plasma with p = 0.0018, and basic fibroblast growth factor 6.3-fold with p < 0.001, while platelet-derived growth factor BB, vascular endothelial growth factor, transforming growth factor beta 1 and bone morphogenetic protein 2 did not differ significantly between the two products [84]. Independent characterisation of growth factors, cytokines and catabolic molecules in marrow concentrate is consistent with this picture [85], quantitation of progenitor populations and growth factors after aspiration has been reported [86], and comparable characterisation exists in the equine model [87]. The secretome and extracellular vesicle signatures of marrow-derived stromal cells have been profiled in detail [88], and systemic biodistribution and homing after intravenous administration have been characterised [89].

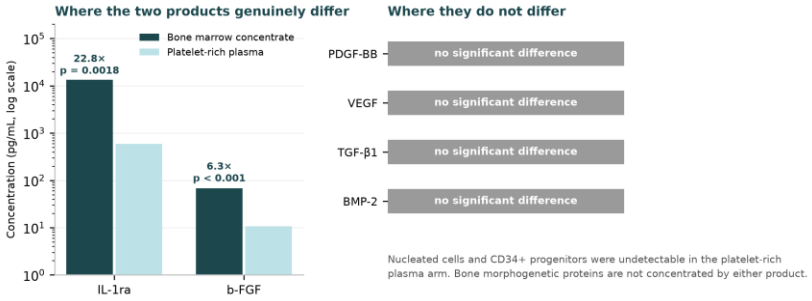

Figure 5: Bone marrow aspirate concentrates versus platelet-rich plasma prepared from the same donors. The distinguishing feature of marrow concentrate is a 22.8-fold enrichment of the anti-inflammatory interleukin-1 receptor antagonist and a 6.3-fold enrichment of basic fibroblast growth factor. Platelet-derived growth factor BB, vascular endothelial growth factor, transforming growth factor beta 1 and bone morphogenetic protein 2 were statistically indistinguishable between the two products.

Mediator	Marrow concentrates versus PRP	Statistical significance	Interpretation
Interleukin-1 receptor antagonist	**22.8-fold higher**	**p = 0.0018**	**The strongest mechanistic rationale for marrow concentrates in an inflamed joint**
Basic fibroblast growth factor	6.3-fold higher	p < 0.001	Mitogenic and angiogenic; supports a distinct biological profile
Platelet-derived growth factor BB	No significant difference	Not significant	Undermines the claim that marrow supplies more anabolic growth factor
Vascular endothelial growth factor	No significant difference	Not significant	Angiogenic claims are not supported by a concentration difference
Transforming growth factor beta 1	No significant difference	Not significant	The canonical chondrogenic cytokine does not distinguish the products
Bone morphogenetic protein 2	No significant difference	Not significant	Osteoinductive claims do not rest on a measured concentration advantage

Table 6: Soluble mediator comparison between bone marrow aspirate concentrates and platelet-rich plasma prepared from the same donors.

PRP, platelet-rich plasma. All values from the same paired-donor study; absolute concentrations depend on the preparation protocol used for each product and are not generalisable across devices.

Classification systems, and why none of them has been adopted

Several classification schemes have been proposed for marrow-derived products, including the MARSPILL system and its successors from the same group [90,91], the DOSES descriptive framework [71], and

consensus and society positions that specify what must be described [92,93]. None has achieved adoption sufficient to make the published literature comparable, for a simple reason: a classification system can only classify variables that investigators measure, and the audit data show that the defining variables are not measured [6,21]. Classification is therefore downstream of the reporting problem, not a solution to it.

Dose: Five Thresholds in Five Units, None Prospectively Validated

If the marrow component is the active ingredient, there must be a dose. The literature contains five separate published thresholds, expressed in five different units, derived from five different clinical settings, and not one has been validated in a prospective trial designed to test it.

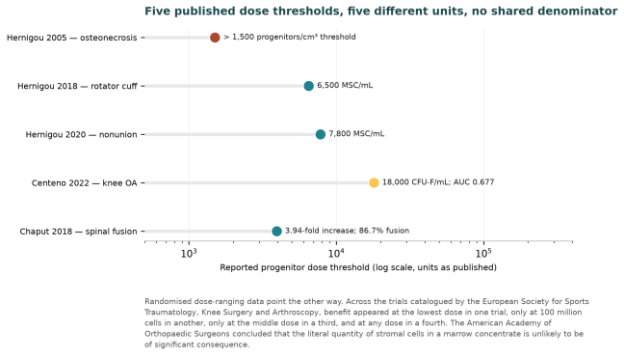

Figure 6: Published dose thresholds for bone marrow-derived products. Each threshold is expressed in different units and derived from a different clinical context, so the thresholds cannot be converted into one another or applied outside the setting in which they were generated. None has been validated in a prospective trial designed for that purpose.

Threshold	Units	Clinical setting	Status
More than 1,500 progenitors per cubic centimetre	**Progenitors per cm³ of graft**	**Percutaneous grafting for femoral head osteonecrosis**	**Retrospective association with survival of the head**
4×10^8 total cells	Total cells injected	Intra-articular knee osteoarthritis, registry dose–response analysis	Observational; derived from a treatment registry
18×10^3 CFU-F per mL	CFU-F per mL of concentrate	Intra-articular knee, registry analysis	Area under the curve 0.677; weak discrimination
3.94-fold nucleated cell increase	Fold increase over baseline	Anterior cervical discectomy and fusion	Associated with 86.7% fusion in a retrospective cohort
No threshold	Not applicable	Concentrated aspirate generally	A society technology overview concluded the literal quantity of stromal cells is unlikely to be of significant consequence

Table 7: Published dose thresholds for bone marrow-derived products, with the setting and evidential status of each.

CFU-F, colony-forming unit-fibroblast. The thresholds are stated in non-interconvertible units and were generated in different tissues with different endpoints; they are presented together to illustrate the absence of a common dose language, not to imply equivalence.

The individual sources deserve to be read on their own terms. Hernigou and colleagues reported that a progenitor dose above roughly 1,500 per cubic centimetre was associated with survival of the femoral head after percutaneous grafting [94]. Centeno and colleagues performed a dose–response analysis in a

treatment registry and identified a total cell threshold of 4×10^8 [95], and subsequently reported that a colony-forming unit-fibroblast dose of 18×10^3 per millilitre discriminated responders with an area under the curve of 0.677 [96]. Chaput and colleagues reported that a 3.94-fold nucleated cell increase was associated with 86.7% fusion after anterior cervical discectomy and fusion [97]. Selective cell retention on a matrix, which raises the delivered progenitor dose without raising the injected volume, has been evaluated in spinal fusion [98,99]. Against all of this, the American Academy of Orthopaedic Surgeons technology overview concluded that the literal quantity of stromal cells in concentrated aspirate is unlikely to be of significant consequence [93,100], and a randomised single-blinded pilot comparison provides no support for a dose effect on clinical outcome [101].

The candid summary is that dose–response in this field is asserted retrospectively in registries and disputed prospectively in trials. The absence of a single randomised comparison of unconcentrated whole aspirate against concentrate on a clinical endpoint means the central premise of the entire concentration industry has never been tested directly [78,102].

Musculoskeletal Clinical Evidence

The musculoskeletal literature is where marrow aspirate is most used and most contested. This section is organised by the strength of the comparator rather than by anatomical region, because the comparator is what determines whether a positive result is informative.

Knee osteoarthritis against weak comparators

Against hyaluronic acid, marrow concentrate is statistically superior. A meta-analysis of eight randomised trials found significant advantages at six months with $p = 0.033$ and at twelve months with $p = 0.011$ [103]. Systematic reviews reach broadly concordant conclusions about statistical superiority over conservative and viscosupplement comparators [104–106], and a randomised comparison with viscosupplementation has been published [107]. Prospective randomised and comparative studies report improvement from baseline [108–111].

The decisive question is not whether these differences are statistically significant but whether they reach the threshold of clinical meaning. The reported point estimates for the Knee Injury and Osteoarthritis Outcome Score pain subscale and for the visual analogue scale were 15.4 and 19.1 respectively, and both lie below the corresponding published minimal clinically important differences for these instruments in knee osteoarthritis populations [10,11,103,112]. A treatment can therefore be simultaneously statistically superior to hyaluronic acid and clinically indistinguishable from it, and that is the most defensible reading of the current knee osteoarthritis evidence.

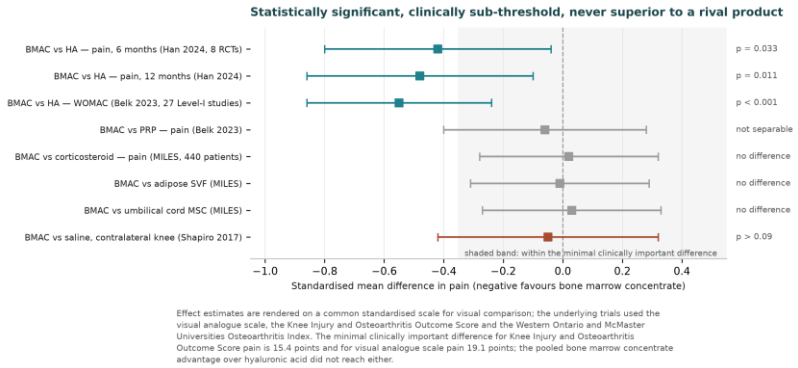

Figure 7: Knee osteoarthritis: pooled and trial-level effect estimates with the minimal clinically important difference band shown. Statistical superiority over hyaluronic acid is reproducible, but the point estimates lie within or below the band of clinical indifference, and the head-to-head comparisons against corticosteroid and against other orthobiologics are null.

Knee osteoarthritis against strong comparators

Three lines of evidence converge. First, the four-arm randomised trial of cell-based injections versus corticosteroid, which randomised 480 patients and analysed 440, found that no orthobiologic arm was superior to corticosteroid or to any other orthobiologic arm [7,113]. Second, a synthesis of twenty-seven Level I studies could not separate marrow concentrate from platelet-rich plasma [8], and a network meta-analysis of orthobiologic arms found marrow concentrate represented only 2.5% of the randomised arms in the entire network, which is itself a comment on the evidential weight behind routine use [114]. Third, and most instructive, a trial using a contralateral intra-articular saline injection as the control within the same patient found no between-knee difference in clinical outcome with all comparisons at P greater than 0.09, and no difference in quantitative T2 magnetic resonance cartilage mapping with all comparisons at P of 0.54 or greater [9]. Comparative trials against adipose-derived products and against culture-expanded stromal cells similarly fail to establish superiority for marrow [115-120].

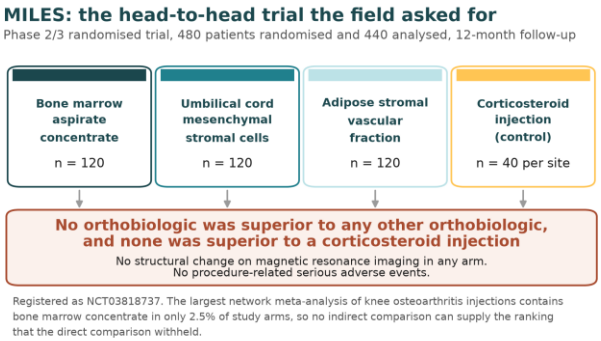

Figure 8: Design and result of the four-arm randomised comparison of cell-based injections against corticosteroid in knee osteoarthritis. Four hundred and eighty patients were randomised and 440 analysed across four arms. No orthobiologic arm was superior to corticosteroid, and no orthobiologic arm was superior to any other.

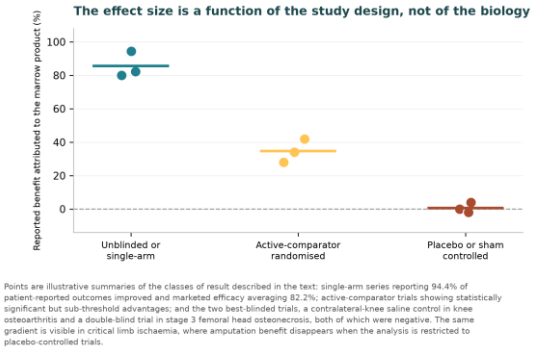

Figure 9: Reported effect size as a function of the strength of the control condition. The apparent efficacy of marrow-derived injection declines monotonically as the comparator strengthens from open-label conservative care, through active viscosupplement comparators, to placebo-controlled and within-patient saline-controlled designs.

Comparison	Design and size	Result	Against MCID
Marrow concentrate versus hyaluronic acid	Meta-analysis of 8 randomised trials	Superior at 6 months (p = 0.033) and 12 months (p = 0.011)	KOOS pain 15.4 and VAS 19.1 lie below published MCID thresholds
Marrow concentrate versus corticosteroid and other orthobiologics	Four-arm randomised trial; 480 randomised, 440 analysed	No arm superior to corticosteroid or to any other arm	Not applicable; null
Marrow concentrate versus platelet-rich plasma	Synthesis of 27 Level I studies	Not separable	Not applicable; null
Marrow concentrate within the orthobiologic network	Network meta-analysis of randomised arms	Marrow concentrate contributed 2.5% of arms	Evidential weight, not effect size
Marrow concentrate versus contralateral saline	Within-patient randomised control with quantitative T2 mapping	No between-knee clinical difference (all P > 0.09); no T2 difference (all P ≥ 0.54)	Not applicable; null
Marrow versus adipose-derived product	Comparative and randomised studies	No consistent superiority for either source	Not applicable; null

Table 8: Knee osteoarthritis: what happens to the marrow concentrate effect as the comparator strengthens.

MCID, minimal clinically important difference; KOOS, Knee Injury and Osteoarthritis Outcome Score; VAS, visual analogue scale. MCID thresholds are those published for the same instruments in knee osteoarthritis populations.

Osteonecrosis of the femoral head: the strongest orthopaedic signal, and its limit

This is the indication with the most coherent biological rationale and the most consistent clinical data. Hernigou and Beaujean established autologous marrow grafting for osteonecrosis [121], reported a progenitor dose–outcome relationship in percutaneous grafting [94], and subsequently documented benefit in the subchondral bone [122]. Ten-year follow-up of a prospective series [123], a network meta-analysis of surgical treatments [124], and reviews of core decompression with concentrate injection [125,126] support the combination of decompression with marrow grafting in early-stage disease.

The limit is equally clear and is rarely quoted alongside the positive data. In a double-blind randomised trial in stage 3 disease, concentration of the marrow product was formally ineffective, with fifteen of twenty-three hips progressing to total hip replacement in both arms [127]. The honest formulation is that marrow grafting is supported in pre-collapse disease and that concentration of the graft has been tested in more advanced disease and failed. An ongoing randomised trial of core decompression with or without autologous marrow is registered and will bear directly on this question [128].

Bone healing, nonunion and spinal fusion

Where the marrow is used as an osteogenic adjunct to a mechanically stabilised construct, the evidence is more favourable and more biologically coherent, because the claim being made is the one the tissue actually supports [2]. Percutaneous marrow grafting for nonunion is long established [94], selective cell retention and cell-matrix composites have been evaluated in spinal fusion [98,99], a truss implant packed with aspirate has been reported for lumbar interbody fusion [129], vertebral marrow clot has been evaluated as a three-dimensional construct with a registered randomised trial in progress [130,131], and the nucleated cell fold-increase association with cervical fusion has been reported [97]. A systematic review of autologous stem cell use in the spine provides the broader appraisal [132], and the general clinical applications review sets the boundaries of what has been attempted [102].

Rotator cuff, labrum, cartilage and tendon

Augmentation of surgical repair is the second most common use after the intra-articular injection. Marrow concentrate augmentation of rotator cuff repair has been evaluated in prospective randomised form [133,134], and augmentation of labral repair is the setting for the only favourable published cost-effectiveness estimate in this field [135,136]. For cartilage lesions, one-step repair with marrow-derived cells on a scaffold has been reported with medium-term follow-up [137,138], and the choice of acellular scaffold has itself been shown to influence outcome, which confounds attribution to the cells [139]. Combined marrow aspirate and platelet-rich plasma on a scaffold [140,141] and hyaluronic acid scaffold constructs have been evaluated. In tendon and muscle, a randomised trial of autologous marrow-derived cells in professional athletes has been published [142], and the ESSKA-ORBIT appraisal provides a European consensus reading of the tendon and joint evidence [92,143]. Ankle and foot applications have been surveyed in a scoping review [144,145].

Spine: intradiscal and subchondral or intraosseous delivery

Intradiscal injection of marrow concentrate for chronic discogenic pain has been reported in prospective series with encouraging uncontrolled results [146–148], and the biological question of whether degenerated discs are a suitable target has been examined directly [149]. These remain uncontrolled data for an intervention delivered into an avascular, hypoxic, acidic compartment. Intraosseous and subchondral delivery has been systematically reviewed for the knee [150,151] and a randomised comparison of intraosseous plus intra-articular plasma rich in growth factors exists for the analogous platelet product [152], together with a single-injection comparative trial [153]. No adequately powered blinded randomised trial supports either route for marrow concentrate, and the appropriate designation for both is research.

Indication	Best available evidence	Direction of effect	Recommended setting
Osteonecrosis, pre-collapse, with core decompression	**Prospective series with 10-year follow-up; network meta-analysis; dose–outcome data**	**Favourable**	**Clinical use, with documented staging**
Osteonecrosis, stage 3	Double-blind randomised trial of concentration	Negative; 15/23 hips to arthroplasty in both arms	Not indicated
Nonunion and spinal fusion adjunct	Comparative series; selective retention studies; fold-increase association	Favourable as a graft adjunct	Clinical use as an adjunct to fixation
Knee osteoarthritis	Meta-analyses; four-arm randomised trial; within-patient saline control	Statistically positive against weak comparators; null against strong ones	Registry or trial
Rotator cuff and labral repair augmentation	Prospective randomised trials	Mixed; the only favourable cost-effectiveness estimate in the field	Registry or trial

Indication	Best available evidence	Direction of effect	Recommended setting
Cartilage lesions with concomitant surgery	One-step repair series; scaffold comparisons	Positive but confounded by the scaffold and the surgery	Registry or trial
Cartilage lesions without concomitant surgery	No adequately powered controlled data	Unknown	Research only
Intradiscal injection	Uncontrolled prospective series	Unknown; biologically unfavourable target	Research only
Intraosseous or subchondral injection	Systematic reviews of small heterogeneous studies	Unknown	Research only

Table 9: Musculoskeletal indications, best available evidence and the setting in which each use can be defended.

Recommended setting reflects the strength of the comparator in the best available study for each indication and the alignment between the claim made and the biology the tissue supports.

Two registered randomised trials will test the two most important open questions directly: whole unconcentrated aspirate against saline in the knee [154] and concentrated aspirate against a sham incision [155], with a further trial comparing marrow against adipose tissue [156]. Until those results are available, the appropriate description of intra-articular marrow concentrate to a patient is that it is statistically better than a weak comparator, has never been shown to be better than a strong one, and has not been shown to be inferior to any competing orthobiologic either.

Beyond the Musculoskeletal System

The non-orthopaedic literature deserves attention from musculoskeletal practitioners for one reason: it is where marrow-derived cell therapy has been tested with the largest sample sizes, the most rigorous blinding and the hardest endpoints, and the pattern of results there is a warning about how the musculoskeletal literature is likely to evolve.

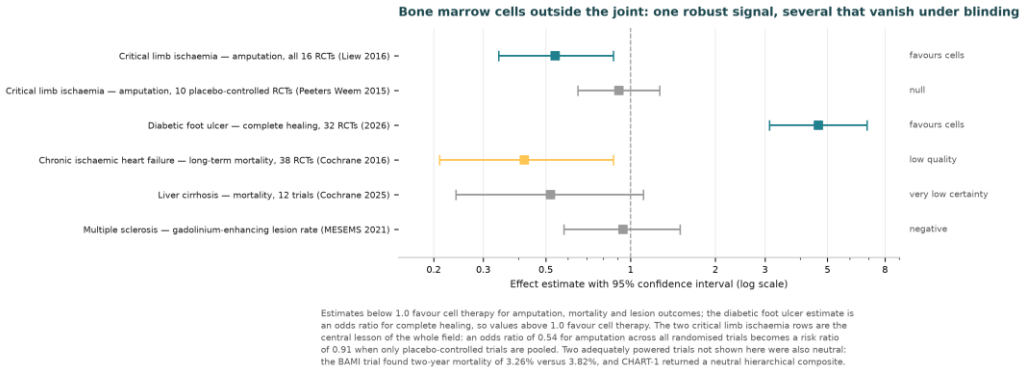

Figure 10: Non-orthopaedic randomised evidence for marrow-derived cell therapy. Effect estimates for amputation in critical limb ischaemia, for mortality in heart failure, for healing in diabetic foot ulceration, for liver disease and for multiple sclerosis, with the point at which restriction to placebo-controlled trials collapses an apparent benefit to the null shown explicitly.

Critical limb ischaemia: the clearest demonstration of what blinding does

A meta-analysis of all randomised trials of autologous cell therapy in critical limb ischaemia found a reduction in amputation with an odds ratio of 0.54 and a 95% confidence interval of 0.34 to 0.87 [157]. When the analysis is restricted to placebo-controlled trials the estimate becomes a relative risk of 0.91

with a 95% confidence interval of 0.65 to 1.27, which crosses one [158]. The Cochrane review of the field is consistent with the conservative reading [159]. This is the single most instructive pair of results in the entire marrow literature: the same intervention in the same indication, positive when unblinded trials are included and null when they are not.

Cardiac disease

Meta-analytic estimates of left ventricular ejection fraction gain after marrow-derived cell therapy for myocardial infarction cluster in the range of two to three percentage points: 2.92% with a 95% confidence interval of 1.91 to 3.92 in one synthesis [160] and 2.55% in another, rising to 5.30% in the subgroup with baseline ejection fraction below 40% [161], with mobilisation strategies reviewed separately [162]. The Cochrane review of chronic ischaemic heart disease and heart failure reported a mortality relative risk of 0.42 with a 95% confidence interval of 0.21 to 0.87 in its primary analysis and an ejection fraction difference of 0.90 percentage points that was not significant [163]. The adequately powered trials, however, were neutral: the trial of intracoronary infusion in 375 patients found 3.26% versus 3.82% [164], and the pivotal cardiopoietic cell trial reported a Finkelstein-Schoenfeld statistic of 0.52 with p = 0.51 [165].

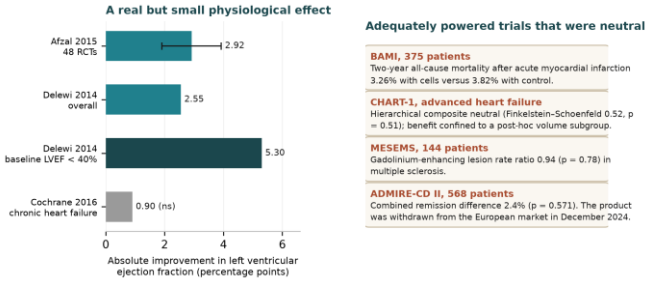

Figure 11: Cardiac outcomes: meta-analytic ejection fraction gains alongside the results of the adequately powered individual trials. Pooled estimates of two to three percentage points of ejection fraction gain coexist with neutral results in the largest and best-controlled individual trials in myocardial infarction, advanced heart failure, perianal fistula and multiple sclerosis.

Diabetic foot ulceration, liver disease, multiple sclerosis and Crohn perianal fistula

Diabetic foot ulceration produces the largest reported effect in the non-orthopaedic literature, with an odds ratio for healing of 4.64 and a 95% confidence interval of 3.11 to 6.90 [166]; the caveat is that wound care trials are among the hardest to blind and the comparator is heterogeneous. The Cochrane review of cell therapy in liver disease found a relative risk of 0.52 with a 95% confidence interval of 0.24 to 1.11, which does not exclude the null [167]. In multiple sclerosis, the mesenchymal stromal cell trial enrolling 144 patients reported an effect estimate of 0.94 with a 95% confidence interval of 0.58 to 1.50 [168]. For Crohn perianal fistula the second pivotal trial of the allogeneic adipose product enrolled 568 patients and reported a difference of 2.4% with p = 0.571 [169]; the product had been authorised in 2018 and its authorisation was subsequently withdrawn [170].

Craniofacial, neurological and ophthalmic applications

Three further fields deserve brief mention because they illustrate both the breadth of the attempts made

and the consistency of the evidential ceiling. In craniofacial and oral reconstruction, marrow concentrate combined with a xenogeneic graft has been evaluated in maxillary sinus augmentation [171], a comparison of two concentrate concentrations in the same procedure has been published [172], and a systematic review with meta-analysis of cell therapy for orofacial bone regeneration provides the pooled appraisal [173]. In stroke, a meta-analysis of randomised trials of mesenchymal stromal cell therapy has been reported [174]. In retinitis pigmentosa, intravitreal administration of marrow-derived cells has been evaluated with quality-of-life endpoints [175]. None of these fields has produced an adequately powered placebo-controlled demonstration of benefit, and all are appropriately described as research.

Where marrow-derived cell therapy is genuinely approved

It is important to distinguish the point-of-care aspirate from manufactured cell products, because the approvals belong entirely to the latter. Haematopoietic transplantation for malignant and non-malignant disease is standard of care [176,177]. A mesenchymal stromal cell product for steroid-refractory acute graft-versus-host disease was approved in December 2024 [178]. A manufactured marrow-derived product has been approved in India [119]. Manufacturing, potency and release testing for such products involve controls that have no counterpart in a point-of-care device [179–185], and extracellular vesicle products remain unapproved and subject to specific regulatory attention [186,187].

Indication	Best evidence	Effect estimate	Reading
Critical limb ischaemia, all randomised trials	**Meta-analysis**	**OR 0.54 (95% CI 0.34–0.87) for amputation**	**Positive**
Critical limb ischaemia, placebo-controlled only	**Meta-analysis**	**RR 0.91 (95% CI 0.65–1.27)**	**Null**
Diabetic foot ulceration	Meta-analysis	OR 4.64 (95% CI 3.11–6.90) for healing	Positive but hard to blind
Chronic heart failure, mortality	Cochrane review	RR 0.42 (95% CI 0.21–0.87)	Positive in pooling; not replicated in large trials
Myocardial infarction, ejection fraction	Meta-analyses	2.92% (95% CI 1.91–3.92); 2.55%, 5.30% if EF < 40%	Small and comparator-dependent
Myocardial infarction, large trial	Randomised trial, 375 patients	3.26% versus 3.82%	Null
Advanced heart failure, pivotal trial	Randomised trial	Finkelstein-Schoenfeld 0.52, p = 0.51	Null
Liver disease	Cochrane review	RR 0.52 (95% CI 0.24–1.11)	Null
Multiple sclerosis	Randomised trial, 144 patients	0.94 (95% CI 0.58–1.50)	Null
Crohn perianal fistula	Randomised trial, 568 patients	2.4% difference, p = 0.571	Null; product authorisation subsequently withdrawn

Table 10: Non-orthopaedic evidence for marrow-derived and related cell therapies.

OR, odds ratio; RR, relative risk; CI, confidence interval; EF, ejection fraction. The first two rows describe the same intervention in the same indication and differ only in whether unblinded trials were included.

Safety: The Harvest is Safe, The Injection is a Separate Question

Safety must be assessed separately for the aspiration and for the delivery, because the risk profiles are entirely different and are commonly reported together in a way that flatters the composite.

Aspiration

The largest safety denominators come from the diagnostic haematology literature. In a surveillance series of 54,890 procedures there were 26 adverse events, a rate of 0.047%, including one death at 0.0018% [188,189], and the international standards body has codified the technical requirements for the procedure [190]. In the orthobiologic setting, a series of 1,252 procedures in Bogotá reported a 6.15% complication

rate consisting almost entirely of pain, a 0.53% rate of non-pain complications, and one death at 0.07% [191,192]. Donor-site morbidity after iliac crest harvest for foot and ankle arthrodesis has been quantified separately [193]. Donor site pain and its determinants have been characterised [68,69], and anatomical and imaging studies define the structures at risk during iliac and vertebral access [56,67]. The reasonable summary is that aspiration by a trained operator through a validated corridor is a low-risk procedure whose dominant adverse effect is transient pain.

Injection and delivery

The comparative data here are more sobering. A matched analysis found adverse event rates of 41.91% after marrow concentrate injection versus 41.25% after the comparator with p = 0.85, a number needed to harm of 152, an effusion rate of 18.26% and no infections [194]. Across forty-eight studies in 1,924 patients the transient adverse event rate was 12.3% [96]. Infection remains the serious concern: septic arthritis has been reported in seven of fourteen patients in a case series of biologic injections, and infectious complications of biologic products have been reviewed [195,196]. Malignancy surveillance in registry data found 12 events among 4,796 patients, a rate of 0.25%, against 6 events among controls [96,197], and the theoretical concerns specific to expanded and karyotypically abnormal products are addressed in regulatory guidance [198,199].

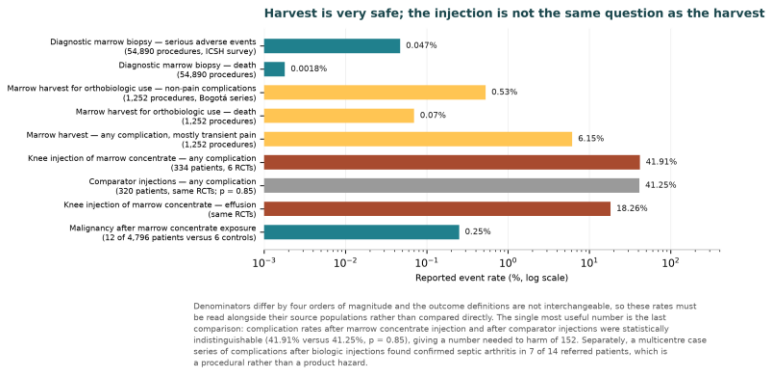

Figure 13: Adverse event rates for marrow aspiration and for marrow-derived injection on a logarithmic scale. Diagnostic aspiration adverse event rates are of the order of one in two thousand procedures, whereas post-injection adverse event rates are of the order of one in ten patients and are statistically indistinguishable from those of the comparator injections.

Event	Rate	Denominator	Source setting
Adverse events after diagnostic aspiration	**0.047%**	**54,890 procedures**	**National haematology surveillance**
Death after diagnostic aspiration	0.0018%	54,890 procedures	National haematology surveillance
Any complication after orthobiologic aspiration	6.15%	1,252 procedures	Single-centre orthobiologic series
Non-pain complication after orthobiologic aspiration	0.53%	1,252 procedures	Single-centre orthobiologic series
Death after orthobiologic aspiration	0.07%	1,252 procedures	Single-centre orthobiologic series
Adverse events after marrow concentrate injection	41.91%	Matched comparison	Versus 41.25% for the comparator, p = 0.85; NNH 152
Effusion after injection	18.26%	Matched comparison	Same series
Transient adverse events	12.3%	48 studies, 1,924 patients	Registry synthesis
Malignancy	0.25%	12 of 4,796 patients	Registry surveillance; 6 events among controls
Infection after injection	Case series	7 of 14 patients with septic arthritis	Reported cluster; not a population rate

Table 11: Reported safety outcomes, separated by whether the event follows the aspiration or the injection.

NNH, number needed to harm. The injection-related rates are not attributable to the marrow product specifically, since they did not differ from the comparator injection; the septic arthritis cluster is a case series and does not support a population rate estimate.

Regulation, Anti-Doping and the Boundary of Lawful Practice

Bone marrow occupies a genuinely unusual regulatory position, and the differences between jurisdictions are large enough that a protocol lawful in one country is prohibited in another.

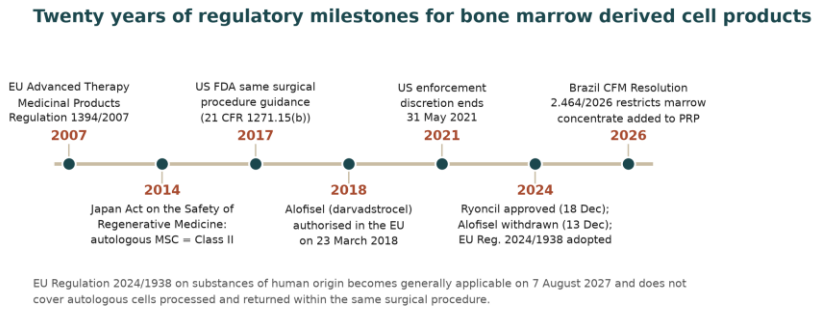

Figure 12: Regulatory timeline, 2007 to 2026. The sequence runs from the European advanced therapy medicinal product regulation, through the United States enforcement discretion period and its expiry, to the Brazilian resolution restricting the combination of marrow concentrate with platelet-rich plasma and the new European regulation whose application date falls in 2027.

United states

Bone marrow is expressly carved out of the definition of structural tissue in 21 CFR 1271.3(d), and the same-surgical-procedure exception in 21 CFR 1271.15(b) permits only rinsing, cleansing, sizing and shaping [200,201]. The period of enforcement discretion for human cells, tissues and cellular and tissue-based products ended on 31 May 2021 [202], and the agency has issued consumer warnings and pursued enforcement actions [203–205]. Adverse events attributable to unapproved products, including bacterial infections traced to a distributed product, have been documented in public health surveillance [206–208]. Extracellular vesicle products are specifically outside the exception [186,187]. The scale of the affected market has been characterised: 1,480 businesses operating 2,754 clinics as of 31 March 2021 [209], with pricing data reported separately [210]. Deceptive marketing has attracted trade regulator action, including a ban and a monetary judgment exceeding US$5.1 million in January 2025 [211,212].

Europe, United Kingdom, Canada, Australia and Japan

The European advanced therapy medicinal product regulation of 2007 establishes the framework for substantially manipulated cell products [213], and the new regulation on substances of human origin, adopted in 2024, applies from 7 August 2027 and excludes same-procedure autologous use from its scope [214]. The United Kingdom operates no hospital exemption equivalent for these products [215]. Canada regulates them as drugs [216]. Australia applies a four-criterion test and prohibits direct consumer advertising [217]. Japan operates a risk-tiered regenerative medicine framework with these products

falling in the intermediate class under legislation implemented on 25 November 2014 [218].

Brazil

Brazilian practitioners face the most specific restriction in the world on a combination that is routine elsewhere. Federal Council of Medicine Resolution 2.464/2026, published in the official gazette on 15 July 2026, prohibits in Article 5 the addition of bone marrow concentrates to platelet-rich plasma outside an approved research protocol [219]. This builds on the earlier opinion designating such use experimental [220] and, on the resolution, governing platelet-rich plasma practice [221], within the national health surveillance framework for cell products [222]. Any Brazilian protocol combining these two products must therefore be conducted and documented as research.

Figure 14: Regulatory status of point-of-care bone marrow products across seven jurisdictions, showing how the same clinical activity moves between the categories of exempt same-procedure practice, regulated medicinal product and expressly prohibited combination depending on the country in which it is performed.

Jurisdiction	Framework	Point-of-care marrow status	Key operational consequence
United States	**21 CFR Part 1271**	**Bone marrow carved out of structural tissue definition; same-procedure exception limited to rinsing, cleansing, sizing, shaping**	**Enforcement discretion ended 31 May 2021; manipulation beyond the exception requires an investigational application**
European Union	Reg. 1394/2007 and Reg. 2024/1938	Substantial manipulation triggers advanced therapy medicinal product status; same-procedure autologous use excluded from the new regulation	New regulation applies from 7 August 2027
United Kingdom	Post-transition national framework	No hospital exemption equivalent for these products	Unlicensed supply routes are narrow
Canada	Food and Drugs Act	Regulated as a drug	Clinical trial application required for non-exempt use
Australia	Therapeutic Goods framework	Four-criterion exclusion test	Direct advertising to consumers prohibited
Japan	Regenerative medicine safety legislation	Intermediate risk class	Legislation implemented 25 November 2014
Brazil	**CFM Res. 2.464/2026 and related instruments**	**Article 5 prohibits adding marrow concentrate to platelet-rich plasma outside research**	**Published in the official gazette 15 July 2026; the combination is a research activity only**

Table 12: Regulatory status of point-of-care bone marrow products by jurisdiction.

CFM, Conselho Federal de Medicina. This table summarises the cited instruments and is not legal advice; practitioners must verify the current text of the applicable instrument in their own jurisdiction.

Anti-doping

The prohibited list for 2026 bans under M3.2 the use of normal or genetically modified cells or cell components with the potential to enhance performance, bans isolated growth factors under S2.3, and restricts blood manipulation exceeding 100 mL per twelve hours under M2.2 [223,224]. The list never names bone marrow explicitly, which places the burden of interpretation on the physician treating a tested athlete; national anti-doping bodies advise case-by-case consultation before any cell-based intervention [225]. For a competing athlete the practical position is that any marrow-derived cellular product should be treated as requiring advance clarification.

Economics, Reimbursement and the Market

The commercial architecture surrounding this procedure is worth stating precisely, because it explains a great deal about the shape of the literature.

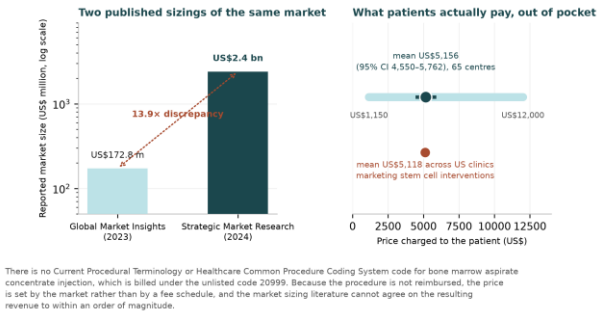

Figure 15: Market sizings and patient-facing prices. Two published sizings of the same procedure category differ by a factor of 13.9, and mean patient-facing pricing sits above five thousand United States dollars with an eleven-fold range between the cheapest and the most expensive advertised price.

Two market research sizings of the same procedure category differ by a factor of 13.9, at US$172.8 million for 2023 in one and US$2.4 billion for 2024 in the other [226,227], while the broader orthobiologics market has been sized at US$6.77 billion for 2024 rising to a projected US$10.34 billion by 2033 [228]. Patient-facing prices in the United States have been surveyed directly, with a mean of US$5,156 and a 95% confidence interval of US$4,550 to US$5,762 across a range of US$1,150 to US$12,000 [210], consistent with the independently reported mean of US$5,118 [209].

Reimbursement

There is no dedicated procedural code, and the service is commonly reported under the unlisted musculoskeletal procedure code [229]. Every major United States payer policy reviewed designates the procedure investigational or not medically necessary [230–233]. Against this, the only favourable published economic evaluation in the field concerns marrow concentrate augmentation of labral repair, with an incremental cost-effectiveness ratio of US$42,935 per quality-adjusted life year in 358 patients gaining 0.233 quality-adjusted life years [135,136].

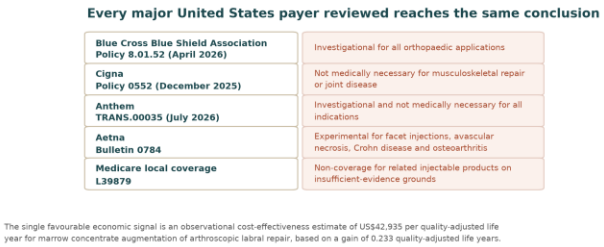

Figure 16: United States payer coverage determinations alongside the only published favourable cost-effectiveness estimate in the field. Every payer policy reviewed designates the procedure investigational, while the labral repair augmentation analysis reports an incremental cost-effectiveness ratio below conventional willingness-to-pay threshold.

Economic parameter	Value	Source type
Market sizing, lower estimate	**US$172.8 million (2023)**	**Market research report**
Market sizing, higher estimate	**US$2.4 billion (2024)**	**Market research report**
Ratio between the two sizings	13.9-fold	Calculated from the two reports
Orthobiologics market, 2024	US$6.77 billion	Market research report
Orthobiologics market, projected 2033	US$10.34 billion	Market research report
Mean patient-facing price	US$5,156 (95% CI 4,550–5,762)	Direct price survey
Range of patient-facing prices	US$1,150 to US$12,000	Direct price survey
Independently reported mean price	US$5,118	Clinic census
Clinics and businesses, 31 March 2021	1,480 businesses; 2,754 clinics	Clinic census
Procedural coding	No dedicated code; unlisted procedure code used	Payer policy
Payer determinations reviewed	All investigational or not medically necessary	Payer policies
Incremental cost-effectiveness ratio, labral augmentation	US$42,935 per QALY; 0.233 QALY in 358 patients	Society economic analysis
Trade regulator action, January 2025	Ban plus judgment exceeding US$5.1 million	Regulatory enforcement

Table 13: Economic and reimbursement parameters.

QALY, quality-adjusted life year; CI, confidence interval. Market research figures are cited as evidence of the range of published commercial estimates and their mutual inconsistency, not as validated measurements of market size.

The Quality of the Secondary Literature Itself

A clinician reading this field is far more likely to encounter a systematic review than a primary trial, which makes the quality of the secondary literature a first-order clinical safety issue rather than an academic curiosity.

A 2026 appraisal screened 156 records and evaluated 28 systematic reviews of marrow concentrate: 67.9% were rated critically low confidence on AMSTAR-2, 17.9% low and only 7.1% high; spin was present in the abstract of 21 of 28 reviews, or 75.0%; funding of the included trials was not reported in 93.5%; and selective outcome reporting was present in 60.7% [13]. An equivalent appraisal of platelet-rich plasma reviews in osteoarthritis found 26 of 31, or 83.8%, critically low and 16.1% low, with included-trial funding unreported in 93.5% [234]. Society positions and technology overviews should be read against this background [92,93,100,143,235,236].

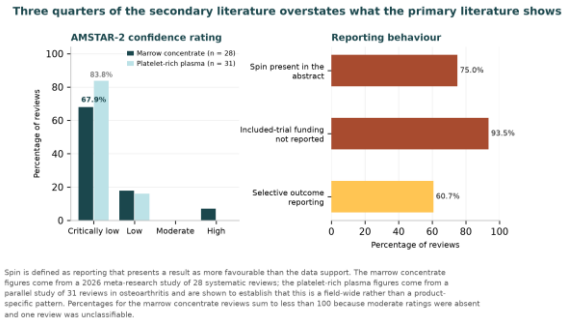

Figure 17: Methodological quality of the systematic reviews in this field. Two thirds of marrow concentrate reviews are rated critically low confidence on AMSTAR-2, three quarters contain spin in the abstract, and more than nine in ten do not report the funding of the trials they include.

Quality indicator	Marrow concentrates reviews	PRP osteoarthritis reviews
Critically low confidence on AMSTAR-2	**67.9%**	**83.8% (26 of 31)**
Low confidence on AMSTAR-2	17.9%	16.1%
High confidence on AMSTAR-2	7.1%	Not reported as a separate category
Spin present in the abstract	75.0% (21 of 28)	Not reported
Funding of included trials not reported	93.5%	93.5%
Selective outcome reporting present	60.7%	Not reported
Records screened	156	Not reported
Reviews appraised	28	31

Table 14: Methodological quality of the secondary literature on marrow concentrates and, for comparison, on platelet-rich plasma in osteoarthritis.

AMSTAR-2, A MeaSurement Tool to Assess systematic Reviews, version 2; PRP, platelet-rich plasma. Spin refers to reporting practices that present results more favourable than the data support.

Discussion

The evidence assembled here supports a small number of conclusions that are firm, a larger number that are provisional, and a set of practices that are currently performed at scale without evidential support. Separating these three groups is the purpose of this section.

What is firm

Bone marrow aspirate contains osteogenic progenitors, and where the clinical task is to add osteogenic capacity to a mechanically stabilised construct the biology and the clinical data align. Percutaneous marrow grafting for pre-collapse osteonecrosis of the femoral head, marrow grafting for nonunion, and marrow as an adjunct to spinal fusion are the uses in which the claim made matches the tissue's documented capability. Harvest by a trained operator through a validated corridor is a low-risk procedure. Point-of-care concentration produces a measurable approximately five-fold enrichment of a rare progenitor population and a genuine biochemical difference from platelet-rich plasma that is dominated by an anti-inflammatory inhibitor rather than by anabolic growth factors.

What is provisional

Intra-articular injection for knee osteoarthritis is statistically superior to hyaluronic acid, indistinguishable from platelet-rich plasma and from corticosteroid, and indistinguishable from contralateral saline in the only within-patient controlled design published. Augmentation of rotator cuff and labral repair has produced mixed randomised results and the only favourable cost-effectiveness estimate in the field. Cartilage repair with marrow-derived cells on a scaffold produces good outcomes that cannot be attributed to the cells, because the scaffold alone changes the result. These uses are defensible inside a registry or a trial with explicit patient disclosure of the evidential status; they are not defensible as established therapy.

What is not supported

Intradiscal injection, intraosseous and subchondral injection, systemic administration for musculoskeletal indications, and any presentation of point-of-care marrow concentrate as a stem cell therapy are research activities or misdescriptions. The non-orthopaedic literature shows what happens to this class of intervention when it is tested at scale with placebo control: an apparent amputation benefit in critical limb ischaemia collapses to the null in placebo-controlled trials alone, and adequately powered trials in myocardial infarction, advanced heart failure, multiple sclerosis and perianal fistula were neutral. There is no reason to expect the musculoskeletal literature to behave differently, and the within-patient saline-controlled knee trial already suggests it does not.

A pathway that follows the evidence

The three-tier structure below is a way of making the evidential status of a given use visible at the point of consent rather than at the point of publication. It assigns each use to clinical practice, to registry or trial conduct, or to research only, and it attaches a non-negotiable reporting minimum to every tier, because the reporting failure documented in this review is the single most correctable defect in the field and costs nothing to correct.

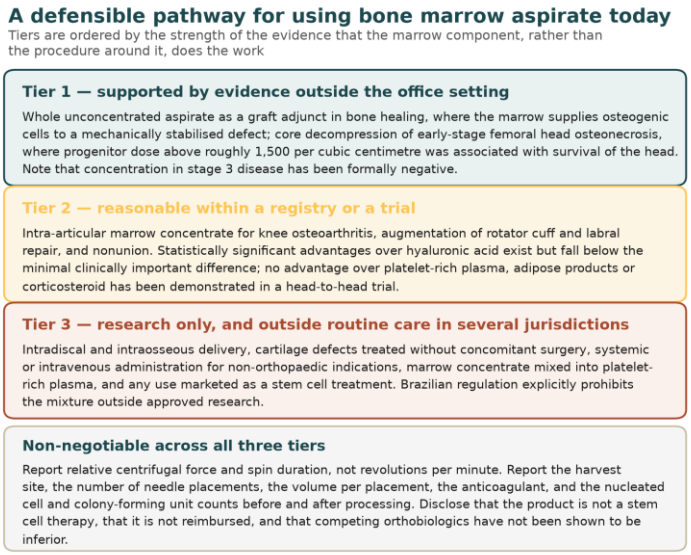

Figure 18: A three-tier pathway for bone marrow aspiration, with the non-negotiable reporting minimum that

applies at every tier. Tier assignment follows the strength of the comparator in the best available study for each use, not the popularity of the use. The reporting box specifies the variables that must accompany any published or registered marrow procedure, headed by relative centrifugal force and spin duration in place of revolutions per minute.

Limitations of this review

This is a narrative review and not a systematic review; retrieval was structured but not exhaustive, and no formal risk-of-bias instrument was applied to individual primary studies. Effect estimates from different meta-analyses are presented side by side although they pool overlapping trial sets, which means they are not statistically independent. Minimal clinically important difference thresholds are themselves population- and method-dependent, so the comparison of a point estimate against a threshold should be read as an aid to interpretation rather than as a formal test. Market research figures are cited to demonstrate the inconsistency of published commercial estimates and should not be treated as measurements. Regulatory instruments change, and the account given here is current only to the dates cited.

A research agenda that would settle the open questions

The questions that matter are answerable with trials that are neither large nor expensive by the standards of other fields, and several are already registered. The agenda below is ordered by the amount of clinical uncertainty each item would remove per unit of effort.

Priority	Question	Design that would answer it	Status
1	**Does concentration add anything to whole aspirate on a clinical endpoint?**	**Randomised trial of unconcentrated aspirate versus concentrates, identical volume, blinded outcome assessment**	**No such trial published; the premise of the concentration industry is untested**
2	Does marrow concentrate outperform saline in the knee?	Placebo-controlled randomised trial with sham needle and blinded assessment	Registered trials of whole aspirate versus saline and of concentrate versus sham incision are in progress
3	Is there a validated progenitor dose threshold?	Prospective trial stratified prospectively on a pre-specified progenitor dose with a hard endpoint	All existing thresholds are retrospective and in non-interconvertible units
4	Does core decompression plus marrow beat core decompression alone?	Randomised trial in pre-collapse osteonecrosis with radiographic progression as the endpoint	Registered and in progress
5	Is intradiscal delivery viable at all?	Dose-finding trial with imaging biomarkers before any efficacy trial	Only uncontrolled series exist; target tissue biology is unfavourable
6	Which device produces which product?	Head-to-head device comparison on identical input aspirate with full reporting of relative centrifugal force and progenitor assays	Partially addressed by benchmarking studies; not standardised
7	What is the true adverse event rate of the injection?	Prospective registry with mandatory reporting and an active comparator	Existing data show no difference from comparator injections

Table 15: Research agenda, ordered by the clinical uncertainty each question would resolve per unit of research effort.

Registered trial identifiers for the items marked as in progress are cited in the corresponding sections of the text.

Conclusion

Bone marrow aspiration is a safe, technically demanding procedure that yields a biologically active fluid whose most abundant components are not the ones invoked to justify its use. The defensible clinical applications today are those in which the marrow acts as an osteogenic graft adjunct to a mechanically stabilised construct, and core decompression with marrow grafting in pre-collapse osteonecrosis of the

femoral head. Intra-articular injection and surgical augmentation are reasonable inside a registry or a trial, with explicit disclosure that superiority over a strong comparator has never been demonstrated. Intradiscal, intraosseous, systemic and stem cell branded uses are research activities, and in Brazil the addition of marrow concentrate to platelet-rich plasma outside approved research is expressly prohibited.

Three commitments would change the trajectory of this field more than any new product. Report relative centrifugal force and spin duration instead of revolutions per minute, and report the harvest and processing variables that existing checklists already specify. Compare against strong comparators, including saline, and publish the result whichever way it falls. And describe the product accurately to patients and to colleagues: a five-fold enrichment of a population present at one per thirty thousand nucleated cells is a legitimate biological intervention and it is not a stem cell treatment. The credibility of orthobiologics depends less on the next trial than on whether this field is willing to describe what it is already doing.

Declarations

Funding

No financial support for this work.

Conflicts of interest

No conflict of interest for any author: including consultancy, speaker fees, equity, royalties and device or biologics industry relationships.

Ethics statement

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

Author contributions

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Data availability

Data availability statement: all data discussed in this review are contained within the cited publications and regulatory documents.

Acknowledgements

None.

Use of artificial intelligence

Use of artificial intelligence-assisted tools in literature organization and comparison tables, with human authors retaining full responsibility for the content.

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38. Oliver KS, Bayes M, Crane D, Pathikonda C. Single- versus multiple-site harvesting techniques for bone marrow concentrate: evaluation of aspirate quality and pain. Orthop J Sports Med. 2017;5(8):2325967117724398. Six bilateral within-patient comparisons showed no difference in any cellular endpoint while six separate cortical entries were significantly more painful during the procedure (p < 0.001) and at 24 hours (p = 0.046).
39. Hernigou J, Alves A, Homma Y, Guissou I, Hernigou P. Anatomy of the ilium for bone marrow aspiration: map of sectors and implication for safe trocar placement. Int Orthop. 2014;38(12):2585–90. Forty-eight iliac wings and ten cadaver pelves; six sectors defined every 4 cm along a crest of mean length 24 cm; sector 6 at the posterior superior iliac spine had the greatest spongiosa thickness (p < 0.001 versus sectors 2 and 3); 114 of 410 trocar placements breached a table, 82 of them the inner table, with nine neurovascular or articular lesions.
40. Hernigou P, Homma Y, Flouzat Lachaniette CH, Poignard A, Allain J, Chevallier N, et al. Benefits of small volume and small syringe for bone marrow aspirations of mesenchymal stem cells. Int Orthop. 2013;37(11):2279–87. In 30 adults aspirated bilaterally, a 10-mL syringe gave on average a 300% higher progenitor concentration than a matched 50-mL syringe (p < 0.01).
41. Pierini M, Di Bella C, Dozza B, Frisoni T, Martella E, Bellotti C, et al. The posterior iliac crest outperforms the anterior iliac crest when obtaining mesenchymal stem cells from bone marrow. J Bone Joint Surg Am. 2013;95(12):1101–07. Posterior connective tissue progenitor yield was 1.6 times anterior in 22 patients with no difference in viability, phenotype or expansion kinetics.
42. Mormone E, et al. Comparison of bone marrow aspirate from the posterior iliac crest and the proximal tibia. J Transl Med. 2024;22:1101. Marrow purity 71 versus 30% (p = 0.002), mononuclear cells 7.10 versus 3.58 x 10^6/mL (p = 0.005) and platelets 189.5 versus 64.5 x 10^6/mL (p < 0.001) in favour of the crest; more than half of tibial samples contained no detectable mesenchymal cells and two of 15 tibial harvests produced non-displaced fractures (13.3%, p < 0.001).
43. Anz AW, Sherman BJ, et al. Bone marrow aspirate from the proximal humerus versus the posterior superior iliac spine. Arthroscopy. 2022;38(4):1110–14. In 12 patients the iliac site gave 55.9 versus 18.7 x 10^6 nucleated cells per mL (3.0-fold, p = 0.014) and 32.5 versus 3.9 colony-forming units per mL (8.3-fold, p = 0.024) with a shorter harvest time (5.6 versus 11.0 min, p = 0.043).
44. Muench LN, Baldino JB, Berthold DP, et al. Proximal humerus bone marrow aspiration: sequential aliquot analysis. BMC Musculoskelet Disord. 2019;20:543. Four consecutive 10-cc aliquots fell from 30.7 plus or minus 23.5 to 3.0 plus or minus 4.3 x 10^6 nucleated cells per cc and from 742.0 plus or minus 885.9 to 39.3 plus or minus 77.9 colony-forming units per cc (p < 0.001) while concentrate volume was unchanged.
45. Dave U, et al. Bone marrow aspirate concentrate harvested in the axial and appendicular skeleton does not differ in progenitor cell count: a systematic review and meta-analysis. J Orthop. 2025;63:216–23. Fifteen prospective studies and 583 patients; pooled axial total nucleated cells 38.3 versus appendicular 20.5 x 10^6/mL and colony-forming units 192.2 versus 204.7 per mL, neither significant, with I-squared 95.41% and 98.94% respectively.
46. Cavallo C, et al. Bone marrow aspirate concentrate quality is affected by age and harvest site. Knee Surg Sports Traumatol Arthrosc. 2023;31:2140–51. Mononuclear cells per mL were 3.8 x 10^7 in young versus 1.2 x 10^7 in older patients (p < 0.0005); iliac crest colony-forming unit-fibroblast at day 10 was 15.9 versus 0.6 for proximal tibia (p = 0.001).
47. Sugaya H, Yoshioka T, Kato T, Taniguchi Y, Kumagai H, Hyodo K, et al. Comparative analysis of cellular and growth factor composition in bone marrow aspirate concentrate and platelet-rich plasma. Bone Marrow Res. 2018;2018:1549826. Colony-forming unit-fibroblast rose from 31.6 to 196 per mL (6.0-fold), basic fibroblast growth factor 67.8 versus 10.7 pg/mL in favour of the marrow product (p < 0.001), while platelet-derived growth factor BB, vascular endothelial growth factor, transforming growth factor beta 1 and bone morphogenetic protein 2 did not differ.
48. Hyer CF, Berlet GC, Bussewitz BW, Hankins T, Ziegler HL, Philbin TM. Quantitative assessment of the yield of osteoblastic connective tissue progenitors in bone marrow aspirate from the iliac crest, tibia and calcaneus. J Bone Joint Surg Am. 2013;95(14):1312–16. Iliac crest exceeded tibia and calcaneus (p < 0.0001); age, sex, tobacco use and diabetes were not predictive.

49. McDaniel JS, Antebi B, Pilia M, Hurtgen BJ, Belenkiy S, Necsoiu C, et al. Quantitative assessment of optimal bone marrow site for the isolation of porcine mesenchymal stem cells. Stem Cells Int. 2017;2017:1836960. Iliac crest yielded 623.7 colony-forming units per mL
50. Encinas R, et al. Calcaneal bone marrow aspiration for orthobiologic harvest: safety and donor-site morbidity. Foot Ankle Spec. In 45 procedures with a mean aspirate volume of 10.3 mL, 32 of 45 patients (71.1%) had no pain at a mean 12.3 months, with no infections, nerve injuries, fractures, haematomas or deaths; a cited series of 548 calcaneal procedures likewise reported no nerve injury, infection or fracture.
51. McLain RF, Fleming JE, Boehm CA, Muschler GF. Aspiration of osteoprogenitor cells for augmenting spinal fusion: comparison of progenitor cell concentrations from the vertebral body and iliac crest. J Bone Joint Surg Am. 2005;87(12):2655–61. In 21 patients with 168 paired aspirations, vertebral nucleated cells were 19.76 versus 16.95 x 10^6/cc (p = 0.05) and progenitor concentration 465.67 versus 356 per cc (p = 0.05).
52. Saluja A, Saluja A, Saluja R. Fluoroscopically guided aspiration of bone marrow from the posterior superior iliac spine: a novel technique. J Orthop Surg Tech. 2024;7(1):572–78. Forty-seven patients followed for at least two years had no vascular injury, nerve injury, persistent pain or haematoma.
53. Shapiro SA, Arthurs JR. Bone marrow aspiration for regenerative orthopaedic intervention: technique with ultrasound guidance for needle placement. Regen Med. 2017;12(8):917–28. All 32 needle passes across eight iliac crests of four cadaver pelves lay in safe zones; insertion should be limited to 4 cm from the posterior superior iliac spine without fluoroscopy or computed tomography, and ultrasound cannot assess depth once the needle has entered bone.
54. Lana JF, Pires L, Macedo A, et al. Lateral and posterolateral iliac crest approach for bone marrow aspirate harvest in regenerative orthopaedic applications. J Orthop Surg Res. 2026;21:162. Sixty-three procedures with a 13-gauge cannula and 4-mL draws under local anaesthesia; correct subendosteal positioning in all cases and no immediate complications; mean posterior-crest-to-sacral-canal distance 18.4 mm and a physiological ceiling of 20 mL per kg body weight.
55. Piuzzi NS, Muschler GF, et al. Bone marrow aspiration technique. JBJS Rev. 2018;6(11):e4 (technique supplement). Beveled 8-gauge 7-inch needle, aspiration sites dispersed 0.5–1 cm apart from a single cortical entry, 1–2 mL per site into a 10-mL syringe preloaded with 1 mL of sodium heparin 1000 IU/mL.
56. Tomasian A, Jennings JW. Bone marrow aspiration and biopsy: techniques and practice implications. Skeletal Radiol. 2021. Complication rates of 0.08–0.12% in two large British surveys, 0.3% immediate complications in 775 fluoroscopy-guided cases, no complications in 981 computed-tomography-guided procedures including 33 with platelets below 20,000 per microlitre, and a dry-tap rate of 2.0–6.6%.
57. Kyriakides PW, Lutz GE, Kyriakides C, et al. Comparative analysis of different needle techniques for bone marrow harvest. J Regen Med. 2024;13(4). Bilateral within-patient design in 29 patients: 5 mL drawn with an 11-gauge multiport needle gave total nucleated cells 46.4 plus or minus 4.6 versus 33.8 plus or minus 4.51 x 10^6/mL (p < 0.001) and colony-forming unit-fibroblast 4469 plus or minus 583 versus 2676 plus or minus 626 per mL (p < 0.0001) against a single-port Jamshidi, with no difference in CD34-positive cells (p = 0.1193); an earlier 10-mL comparison favoured the single-port device.
58. Hernigou P. Bone marrow aspiration technique, concentration methods and applications. 2011. Needle internal diameter 1.5 mm, 2–7 cc per bevel position with 45 degree rotations; maximum 150 cc from the anterior and 250 cc from the posterior iliac crest.
59. Marx RE, Tursun R. A qualitative and quantitative analysis of autologous human multipotent adult stem cells derived from three anatomic areas by marrow aspiration. J Oral Maxillofac Surg. 2013;71(10):1808–13. Anterior and posterior ilium were equivalent with a concentration factor of 6.5 plus or minus 1.0, whereas the tibial plateau gave less than half the nucleated, CD44-positive and CD105-positive counts.
60. Allahabadi S, Chapman RS, Fortier LM, et al. Bone marrow aspirate concentrate harvest techniques for orthopaedic applications. Arthrosc Tech. 2024;13(2):102850.
61. Bone marrow aspiration and biopsy. StatPearls. NCBI Bookshelf; updated 2023. Severe bleeding diatheses are absolute contraindications; retroperitoneal or gluteal haemorrhage may follow internal iliac or superior gluteal artery injury.
62. Bucher CM, Lehmann T, Tichelli A, Tzankov A, Dirnhofer S, Passweg J, et al. Comparison of a powered bone marrow biopsy device with a manual system: results of a prospective randomised controlled trial. J Clin Pathol. 2013;66(1):24–28. Sixty procedures showed no difference in diagnostic cylinders, cylinder length, procedure time or aspirate quality; the only significant advantage was less pain in the unsedated subgroup (median 3 versus 7, p = 0.015).
63. Voigt J, Mosier M. A powered bone marrow biopsy system versus manual methods: a systematic review and meta-analysis of randomised trials. J Clin Pathol. 2013;66(9):792–96. Across five randomised trials powered insertion reduced pain by 6.57 visual analogue points (95% CI -12.93 to -0.22; p = 0.04), shortened the procedure by 85.35 s and lengthened the core by 3.65 mm, with an adverse-event risk ratio of 3.56 (0.59–21.42).
64. Dregalla RC, Herrera JA, Koldewyn LS, Donner EJ. The choice of anticoagulant influences the characteristics of bone marrow aspirate concentrate and mesenchymal stem cell bioactivity in vitro. Stem Cells Int. 2022;2022:8259888. Heparin 100 U/mL versus 15% sodium citrate gave colony-forming unit-fibroblast 1037 plus or minus 153 versus 187 plus or minus 45 per mL (p = 0.0001) and viability 98.50 versus 95.18% (p = 0.0008); heparin 100 U/mL also outperformed 1000 U/mL on nucleated cells (p = 0.0013), viability (p = 0.0091) and colony-forming units (p = 0.0043).

65. Kubrova E, Su M, Galeano-Garces C, Galvan ML, Jerez S, Dietz AB, et al. Differences in cytotoxicity of lidocaine, ropivacaine and bupivacaine on the viability and metabolic activity of human adipose-derived mesenchymal stem cells. Am J Phys Med Rehabil. 2021;100(1):82–91. Lidocaine 8, 5 and 2.5 mg/mL and bupivacaine 2.5, 1.25 and 0.313 mg/mL reduced viability below 50% beyond 6 hours; ropivacaine was the least cytotoxic agent.
66. Kao GS, Kim HT, Daley H, et al. Validation of short-term handling and storage conditions for marrow and peripheral blood stem cell products. Transfusion. 2011;51(1):137–47. Marrow products maintained equivalent viability at 4 and 20 degrees Celsius for up to 72 hours with mean viable CD34-positive recovery above 75% at 4 degrees, and citrate-dextrose anticoagulation was preferred over heparin to limit lactate accumulation.
67. Konda B, Pathak S, Edwin I, et al. Safe and successful bone marrow biopsy: an anatomical and computed-tomography-based cadaver study. Am J Hematol. 2014;89(10):943–46. A trajectory reoriented laterally toward the ipsilateral anterior superior iliac spine caused less neurovascular damage and avoided the sacroiliac joint compared with a perpendicular path.
68. Gendron N, Zia Chahabi S, Poenou G, et al. Pain assessment and factors influencing pain during bone marrow aspiration: a prospective study. PLoS One. 2019;14(8):e0221534. Among 448 patients and 461 procedures the median numerical pain rating was 3.5 for sternal versus 2.5 for iliac crest aspiration ($p < 0.0001$); lidocaine infiltration reduced the score by 1.06 points (95% CI -1.92 to -0.20; $p = 0.0158$) whereas anaesthetic cream alone did not, and anxiety was the dominant determinant.
69. Cerchione C, Martinelli G, Picardi M, et al. Combined oral fentanyl citrate and midazolam as premedication for bone marrow aspiration and biopsy in patients with haematological malignancies: a randomised, controlled, patient-blinded clinical trial. J Clin Med. 2020;9(2):395. Sedoanalgesia did not improve the aspiration phase itself (3.54 versus 3.63) and benefited only the trephine and recovery phases.
70. Murray IR, Geeslin AG, Goudie EB, Petrigliano FA, LaPrade RF. Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. J Bone Joint Surg Am. 2017;99(10):809–19. Delphi process with 23 of 24 experts completing three rounds, producing a 23-statement platelet-rich plasma checklist and a 25-statement mesenchymal stromal cell checklist.
71. Murray IR, Chahla J, Safran MR, Krych AJ, Saris DBF, Caplan AI, LaPrade RF. International expert consensus on a cell therapy communication tool: DOSES. J Bone Joint Surg Am. 2019;101(10):904–11. Thirty-four of 36 invited experts; all 27 final items reached consensus; donor, origin and site of delivery reached 100, 100 and 97% agreement and exhibited cell characteristics 85%.
72. British Orthopaedic Association. Orthobiologics: scientific background. Adopts the DOSES framework and states that the term stem cell is now discouraged in the orthobiologics setting.
73. Piuzzi NS, et al. Reporting of mesenchymal stem cell preparation protocols and composition: a systematic review of the clinical orthopaedic literature. Am J Sports Med. 2019. Studies reported only 52% (range 30–80%) of the variables that may critically influence outcome.
74. Hedbany D, et al. Adherence of bone marrow aspirate concentrate studies of the shoulder to Minimum Information for Studies Evaluating Biologics in Orthopaedics guidelines. Clin Shoulder Elb. 2025;29(1):105–14. Mean adherence 52.2 plus or minus 12.1% (range 30.4–76.1%), no category reaching 80%, and no improvement after 2017 ($p = 0.074$).
75. Butler JJ, et al. Adherence to Minimum Information for Studies Evaluating Biologics in Orthopaedics guidelines in bone marrow aspirate concentrate studies of the foot and ankle. Foot Ankle Surg. 2024. Nine studies and 356 patients; adherence 42.8 plus or minus 5.2% with no study reaching 50%.
76. Pösel C, Moller K, Fröhlich W, Schulz I, Boltze J, Wagner DC. Density gradient centrifugation compromises bone marrow mononuclear cell yield. PLoS One. 2012;7(12):e50293. Mononuclear recovery was 25.6 plus or minus 5.8% for Ficoll, 51.5 plus or minus 2.3% for Percoll and 72.3 plus or minus 6.7% for immunomagnetic granulocyte depletion; colony-forming unit-fibroblast frequency in lysed whole marrow was 0.00007 plus or minus 0.00002% and no colony-forming unit-fibroblast was detected in any gradient-separated fraction; approximately 30% of haematopoietic and 55% of mesenchymal progenitors are lost during mononuclear isolation.
77. Hermann PC, Huber SL, Herrler T, von Hesler C, Andrassy J, Kevy SV, et al. Concentration of bone marrow total nucleated cells by a point-of-care device provides a high yield and preserves their functional activity. Cell Transplant. 2008;17(9):1059–69. Nucleated cell yield was 2.4 times higher than Ficoll (range 2.1–3.0), platelet retention 74.3 plus or minus 14.9% versus below 0.5% for Ficoll, bedside processing time 15 minutes, migratory activity 164 plus or minus 66% of Ficoll cells ($p = 0.007$) and murine hindlimb perfusion 0.64 plus or minus 0.16 versus 0.46 plus or minus 0.15 ($p = 0.003$).
78. Gaul F, Bugbee WD, Hoenecke HR, D'Lima DD. A review of commercially available point-of-care devices to concentrate bone marrow for the treatment of osteoarthritis and focal cartilage lesions. Cartilage. 2019;10(4):387–94. Nucleated cell recovery ranged from 32.6 plus or minus 13.7% (Magellan) to 80% (Celling) and connective tissue progenitors per square centimetre from 0.4 to 2.3; no independent peer-reviewed haematocrit or red-cell-reduction data and no device costs were available for any system.
79. Scillia AJ, et al. Benchmark comparison of bone marrow aspiration systems: increased progenitor cell concentrations achieved without centrifugation using a novel filtration design with high surface area. Cureus. 2026;18(6):e110747. Five donors gave nucleated cells 102.2 plus or minus 66.0 x 10^6/mL, colony-forming unit-fibroblast 15,145 plus or minus 15,131 per mL and viability 96.9 plus or minus 1.4%; the study was descriptive, industry-funded and unrandomised.
80. Hegde V, Shonuga O, Burch S, Besho R, Chojnowski D, Bostrom MP, et al. A prospective comparison of three approved systems for

autologous bone marrow concentration demonstrated non-equivalency in progenitor cell number and concentration. J Orthop Trauma. 2014;28(10):591–98. Forty patients underwent bilateral iliac aspiration with randomised device allocation; the three commercial systems were declared non-equivalent for connective tissue progenitor number, concentration and percentage yield.

81. Degen RM, Bernard JA, Oliver KS, Dines JS. Commercial separation systems designed for preparation of platelet-rich plasma yield differences in cellular composition. HSS J. 2017;13(1):75–80. Platelet concentration ranged from 1,129 plus or minus 264 to 2,310 plus or minus 524 x 10^3 per microlitre and haematocrit from 1.1 plus or minus 0.4% to 28.9 plus or minus 4.4% across six commercial systems processing the same donor blood.
82. Scarpone M, Kuebler D, Chambers A, De Filippo CM, Amatuzio M, Ichim TE, et al. Isolation of clinically relevant concentrations of bone marrow mesenchymal stem cells without centrifugation. J Transl Med. 2019;17:10. An aspiration-only lateral-port system yielded fewer nucleated cells than a centrifuged comparator (31.5 plus or minus 15.5 versus 66.1 plus or minus 20.5 x 10^6/mL, p = 0.0001) but more colony-forming unit-fibroblast (1583 plus or minus 858 versus 797 plus or minus 509 per mL, p = 0.0346); a 30-patient series gave 2885 plus or minus 1716 colony-forming units per mL with an inverse correlation with age (r = -0.4689, p = 0.009).
83. Dragoo JL, Guzman RA. Evaluation of the consistency and composition of commercially available bone marrow aspirate concentrate systems. Orthop J Sports Med. 2020;8(1):2325967119893634. Percentage colony-forming unit-fibroblast recovery was 25.8, 47.4 and 82.4 for three devices (p < 0.001) while fold concentration did not differ (p = 0.689).
84. Cassano JM, Kennedy JG, Ross KA, Fraser EJ, Goodale MB, Fortier LA. Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration. Knee Surg Sports Traumatol Arthrosc. 2018;26(1):333–42. Interleukin 1 receptor antagonist was 13,432 pg/mL in marrow concentrate versus 588 pg/mL in platelet-rich plasma (p = 0.0018) in 29 patients, while transforming growth factor beta 1, platelet-derived growth factor and platelet counts did not differ.
85. Ziegler CG, et al. Characterisation of growth factors, cytokines and catabolic molecules in bone marrow aspirate, bone marrow concentrate, leukocyte-rich and leukocyte-poor platelet-rich plasma. Orthop J Sports Med. 2019;7(7 suppl 5):2325967119S00284. Median interleukin 1 receptor antagonist was 143 in whole blood, 48.9 in leukocyte-poor and 257.8 in leukocyte-rich platelet-rich plasma, 463 in aspirate and 796.6 in marrow concentrate, with marrow concentrate exceeding all others (p < 0.0009).
86. Schäfer R, et al. Quantitation of progenitor cell populations and growth factors after bone marrow aspirate concentration. J Transl Med. 2019;17:115. Nucleated cells were concentrated approximately tenfold, red cells were depleted, CD34-positive cells were not concentrated at all (0.809-fold, p = 0.71 and 1.088-fold, p = 0.93) and colony-forming unit-fibroblast enrichment ranged from 4.4- to 41.2-fold across donors.
87. Long S, Maleas G, Belacic ZA, Quam VG, Durgam S. Equine bone marrow aspirate and bone marrow aspirate concentrate are enriched with interleukin 1 receptor antagonist protein. Am J Vet Res. 2025;86(5):ajvr.24.12.0380. Donor-matched interleukin 1 receptor antagonist was 21 times higher in concentrate than aspirate (P < 0.0005) and 117 times higher than in leukocyte-rich platelet-rich plasma (P < 0.0001), and tracked leukocyte count (R = 0.673).
88. Ragni E, de Girolamo L, Grieco G, Piccolo S. Secretome and extracellular vesicle signatures in bone marrow-derived mesenchymal stromal cells after expansion in standard and next-generation media. Extracell Vesicles Circ Nucl Acids. 2025;6:195–215. Ninety-eight soluble proteins were common to all three media; hepatocyte growth factor differed 208-fold between conditions while identity markers were unchanged.
89. Leibacher J, Henschler R. Biodistribution, migration and homing of systemically applied mesenchymal stem and stromal cells. Stem Cell Res Ther. 2016;7:7. Up to 80% of injected cells are trapped in the lungs within minutes with a pulmonary half-life of approximately 24 hours; intra-arterial delivery to inflamed joints leaves 15% at one month and 1.5% beyond six months.
90. Lana JFSD, Purita J, Paulus C, Huber SC, Rodrigues BL, Rodrigues AA, et al. Contributions for classification of platelet-rich plasma: proposal of a new classification, MARSPILL. Regen Med. 2017;12(5):565–74. The eight axes describe method, activation, red cells, spin, platelet fold-increase, image guidance, leukocytes and light activation, all defined for platelet products; no bone marrow data are presented, so application to marrow concentrate is an extrapolation.
91. Purita J, Lana JFSD, Kolber M, Rodrigues BL, Mosaner T, Santos GS, et al. Bone marrow-derived products: a classification proposal: bone marrow aspirate, bone marrow aspirate concentrate or hybrid? World J Stem Cells. 2020;12(4):241–50. Aspirate, concentrate or hybrid is combined with eight escalating levels of characterisation from collection description to functional assay, written for example as C1-3;5; the authors note that no study defines the optimal centrifugal force and time for bone marrow.
92. de Girolamo L, Laver L, Andriolo L, Andia I, Nehrer S, Kon E, et al. ESSKA Orthobiologic Initiative (ORBIT) Part 2: bone marrow and adipose tissue-derived products for the treatment of knee osteoarthritis. Complete consensus report, 2024. Fifty-one experts from 21 countries and 36 peer-review delegates from 20 societies; aspirations above 2 mL and syringes above 10 mL increase peripheral blood contamination (Q18, Grade C, agreement 8.3 plus or minus 0.7); a properly harvested aspirate approximates single-spin concentrate and double-spin concentrate is recommended for knee osteoarthritis (Q13, Grade D); MIBO is endorsed for characterisation (Q16, Grade D); combination with platelet-rich plasma is not recommended (Q23, Grade C); no consensus was reached on dose (Q19, Grade C).
93. American Academy of Orthopaedic Surgeons. Technology overview: concentrated bone marrow aspirate for knee osteoarthritis. Adopted 3 December 2021. Twelve articles were included from 47 full texts; no single standardised processing device, centrifuge brand or processing protocol could be identified across studies, no study identifies an optimal cell dose, and the document argues that the

literal quantity of mesenchymal cells in concentrated aspirate is unlikely to be of significant consequence.

94. Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions: influence of the number and concentration of progenitor cells. J Bone Joint Surg Am. 2005;87(7):1430–37. Sixty atrophic tibial nonunions received about 20 cm3 of concentrate; union occurred in 53 of 60 patients whose graft contained more than 1500 progenitors per cm3 and averaged 54,962 plus or minus 17,431 total progenitors, whereas the 7 failures received 634 plus or minus 187 per cm3 (p = 0.001) and 19,324 plus or minus 6843 total (p < 0.01).
95. Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman MD. A dose response analysis of a specific bone marrow concentrate treatment protocol for knee osteoarthritis. BMC Musculoskelet Disord. 2015;16:258. In 373 patients and 424 knees a threshold of 4 x 10^8 total cells separated a numeric pain score of 1.6 above threshold from 3.2 below.
96. Centeno CJ, et al. The influence of bone marrow concentrate colony-forming unit-fibroblast dose on outcomes after intra-articular knee injection. Int Orthop. 2022. A threshold near 18 x 10^3 colony-forming unit-fibroblast per mL was identified in 65 patients and 72 knees with a receiver-operating-characteristic area under the curve of 0.677, indicating weak discrimination.
97. Chaput CD, et al. Colony-forming unit-fibroblast dose and fusion after anterior cervical discectomy and fusion with bone marrow aspirate concentrate. PLoS One. 2018. Twenty-four patients and 31 levels achieved 86.7% fusion with a 3.94-fold concentration and a colony frequency window of 3.0 x 10^-6 to 5.83 x 10^-5 per mononuclear cell.
98. Muschler GF, Nitto H, Matsukura Y, Boehm C, Valdevit A, Kambic H, et al. Spine fusion using cell matrix composites enriched in bone marrow-derived cells: selective cell retention. Preparation increased nucleated cells 2.3 plus or minus 0.5-fold and connective tissue progenitors 5.6 plus or minus 3.9-fold with a progenitor attachment efficiency of 61 plus or minus 14%; in 12 dogs and 36 fusion sites the union rate was 67% for enriched matrix, 50% for matrix plus unprocessed aspirate and 17% for matrix alone (p = 0.018).
99. Muschler GF, Nitto H, Matsukura Y, et al. Spine fusion using cell matrix composites enriched in bone marrow-derived cells. Clin Orthop Relat Res. 2003;(407):102–18. An enriched bone-matrix composite combined with a bone marrow clot was superior to enriched matrix alone in union score, fusion volume and fusion area.
100. American Academy of Orthopaedic Surgeons. Technology overview: concentrated bone marrow aspirate for knee osteoarthritis. Studies comparing concentrated bone marrow aspirate with placebo did not identify statistically significant improved outcomes beyond one week, and two high-quality studies found concentrated bone marrow aspirate with platelet-poor plasma no better than placebo saline for function, magnetic resonance cartilage appearance or pain; a reasonable estimate of equipment cost is on the order of more than US$1,000 per episode and the treatment is not covered by insurance.
101. Ruane JJ, Ross A, Zigmont V, McClure D, Gascon G. A single-blinded randomised controlled pilot study of the effects of bone marrow aspirate concentrate and platelet-rich plasma versus hyaluronic acid for knee osteoarthritis. J Stem Cells Regen Med. 2021;17(1):3–17. Thirty patients treated; numerical pain rating fell by 3.13 versus 1.56 points, between-group difference -1.57 (95% CI -2.89 to -0.25; p = 0.02), while the 12-month Knee Injury and Osteoarthritis Outcome Score difference did not reach significance; the trial reported no centrifugal force, spin time, nucleated cell count, colony count or viability.
102. Imam MA, Holton J, Ernstbrunner L, et al. A systematic review of the clinical applications and complications of bone marrow aspirate concentrate in the management of bone defects and nonunions. Int Orthop. 2017;41(11):2213–20.
103. Han S, et al. Bone marrow aspirate concentrate injections for the treatment of knee osteoarthritis: a systematic review of randomised controlled trials. Orthop J Sports Med. 2024. Eight randomised trials with 937 patients gave pooled pain mean differences versus hyaluronic acid of 0.28 (95% CI -0.07 to 0.63) at 3 months, 0.38 (0.03 to 0.72) at 6 months and 0.48 (0.11 to 0.84) at 12 months, all below the authors' minimal clinically important thresholds of 15.4 points for knee osteoarthritis outcome score pain and 19.1 for visual analogue pain.
104. Keeling LE, Belk JW, Kraeutler MJ, Kallner AC, Lindsay A, McCarty EC, et al. Bone marrow aspirate concentrate for the treatment of knee osteoarthritis: a systematic review. Am J Sports Med. 2022;50(8):2315–23. Eight studies and 299 knees followed for a mean 12.9 months showed significant improvement in 34 of 36 patient-reported outcomes but no superiority over platelet-rich plasma, microfragmented adipose tissue or placebo.
105. Chandrashekar S, Jeyaraman M, Mounissamy P, Jeyaraman N, Khanna M, Gupta A. Safety and efficacy of bone-marrow aspirate concentrate in hip osteoarthritis: a systematic review. 2024. Five studies with 182 participants and follow-up of 3 to 12 months were identified, all case series or cohorts; no placebo-controlled randomised trial of marrow concentrate in hip osteoarthritis exists.
106. Systematic review of bone marrow aspirate concentrate for knee osteoarthritis. Br Med Bull. 2025;153(1):ldae016. The superiority of bone marrow aspirate concentrate over other orthobiological treatments cannot be assessed because of conflicting results, and given its higher morbidity and cost it is not worthwhile to prefer it to other conservative treatments.
107. Randomised comparison of bone marrow aspirate concentrate and viscosupplementation for knee osteoarthritis at 24 months. Bone marrow aspirate concentrate did not demonstrate clinically significant short-term superiority, with comparable clinical scores, failures, adverse events, radiographic evaluation, minimal clinically important difference achievement and patient treatment judgement.
108. Anz AW, Hubbard R, Rendos NK, Everts PA, Andrews JR, Hackel JG. Bone marrow aspirate concentrate is equivalent to platelet-rich plasma for the treatment of knee osteoarthritis at 1 year. Orthop J Sports Med. 2020;8(2):2325967119900958. Ninety patients were randomised and 84 analysed; the International Knee Documentation Committee score rose from 45.0 to 64.3 with concentrate and 47.4 to 63.7 with leucocyte-rich platelet-rich plasma, with a significant time effect (p < 0.001) and no between-group difference.

109. Boffa A, Di Martino A, Andriolo L, De Filippis R, Poggi A, Cenacchi A, et al. Bone marrow aspirate concentrate injections provide similar results versus viscosupplementation up to 24 months of follow-up in patients with symptomatic knee osteoarthritis: a randomised controlled trial. Knee Surg Sports Traumatol Arthrosc. 2022;30(12):3958–67. Visual analogue improvement was 2.2 plus or minus 2.6 versus 1.4 plus or minus 2.8 at 24 months (p = 0.002), a between-group difference of about 0.8 points confined to Kellgren-Lawrence grades 1 to 2, with failures 10.7% versus 12.5%.
110. Dulic O, Rasovic P, Lalic I, Kecojevic V, Gavrilovic G, Abazovic D, et al. Bone marrow aspirate concentrate versus platelet-rich plasma or hyaluronic acid for the treatment of knee osteoarthritis. Medicina (Kaunas). 2021;57(11):1193. In 175 patients the concentrate exceeded hyaluronic acid on knee osteoarthritis outcome score pain (mean difference 15.3; p = 0.002) and International Knee Documentation Committee score (15.2; p = 0.002) but did not differ from platelet-rich plasma.
111. Jin QH, Chung YW, Na SM, Ahn HW, Jung DM, Seon JK. Bone marrow aspirate concentration provided better results in cartilage regeneration to microfracture in knee of osteoarthritic patients. Knee Surg Sports Traumatol Arthrosc. 2021;29(4):1090–97. Forty-three microfracture cases were compared with 48 microfracture plus concentrate cases; the International Cartilage Repair Society repair assessment score favoured concentrate (p = 0.035) while pain, function and Western Ontario and McMaster scores did not differ.
112. McCormack J, Underwood F, Slaven E, Cappaert T. The minimum clinically important difference on the Victorian Institute of Sport Assessment-Achilles and Lower Extremity Functional Scale for patients with insertional Achilles tendinopathy. In 15 patients the minimal clinically important difference was 6.5 points for the Victorian Institute of Sport Assessment-Achilles scale and 12 points for the Lower Extremity Functional Scale; the very small sample and insertional phenotype limit generalisation.
113. Mautner K, Gottschalk M, Boden SD, et al. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. Nat Med. 2023;29(12):3120–6. In the MILES trial, 480 patients were randomised to bone marrow aspirate concentrate, umbilical cord mesenchymal stromal cells, adipose stromal vascular fraction or corticosteroid; no orthobiologic was superior to another or to corticosteroid at 12 months, with no magnetic resonance structural change.
114. Jawanda H, Khan ZA, Warrier AA, et al. Platelet-rich plasma, bone marrow aspirate concentrate and hyaluronic acid injections outperform corticosteroids in pain and function scores at a minimum of 6 months as intra-articular injections for knee osteoarthritis: a systematic review and network meta-analysis. Arthroscopy. 2024;40(5):1623–36.e1. Across 48 studies and 9338 knees the surface under the cumulative ranking curve was 91.54 for platelet-rich plasma, 76.46 for marrow concentrate, 53.12 for hyaluronic acid, 15.18 for corticosteroid and 13.70 for placebo, with marrow concentrate contributing only about 2.5% of included studies.
115. Vitali M, et al. Bone marrow versus adipose-derived cell therapy for knee osteoarthritis: an exploratory comparative study with CD34+ quantification. Indian J Orthop. 2025;59(12):2119–25. Both groups improved (p < 0.01) with no between-group difference at six months and no correlation between mesenchymal stromal cell quantity and efficacy; 30 of 30 marrow aspirates versus 2 adipose samples reached the culture threshold.
116. Mohamed-Ahmed S, Fristad I, Lie SA, et al. Adipose-derived and bone marrow mesenchymal stem cells: a donor-matched comparison. Stem Cell Res Ther. 2018;9(1):168. Adipose-derived cells showed greater proliferation and adipogenic capacity, whereas bone marrow cells showed greater osteogenic and chondrogenic differentiation.
117. Awad ME, et al. Efficacy and safety of mesenchymal stem cell therapy for knee osteoarthritis: a systematic review and meta-analysis of 28 randomised controlled trials. Clin Rheumatol. 2026;45(5):2905–42. Visual analogue scale mean difference was −1.67 (p = 0.007) and Knee Injury and Osteoarthritis Outcome Score pain +15.37 (p = 0.03), while Western Ontario and McMaster Universities Osteoarthritis Index and Whole-Organ Magnetic Resonance Imaging Score outcomes were non-significant; injection-site pain risk ratio was 2.04 (p = 0.0005).
118. Kim SH, Djaja YP, Park YB, Park JG, Ko YB, Ha CW. Intra-articular injection of culture-expanded mesenchymal stem cells without adjuvant surgery in knee osteoarthritis: a systematic review and meta-analysis. Am J Sports Med. 2020;48(11):2839–49. Across six randomised trials the visual analogue scale mean difference was −13.55 (95% confidence interval −22.19 to −4.9) with no demonstrated cartilage benefit.
119. Gupta PK, Maheshwari S, Cherian JJ, et al. Efficacy and safety of stempeucel in osteoarthritis of the knee: a phase 3 randomized, double-blind, multicentre, placebo-controlled study. Am J Sports Med. 2023;51(9):2254–66. In 146 patients, pooled allogeneic bone marrow mesenchymal stromal cells with hyaluronic acid reduced total Western Ontario and McMaster Universities Osteoarthritis Index score by 45.60% at 12 months (95% confidence interval −55.97 to −35.23, p < 0.001), with no worsening of deep medial femorotibial cartilage on T2 mapping.
120. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: four-year follow-up of a multicenter randomized controlled clinical trial. J Transl Med. 2018;16(1):213. Visual analogue scale improvement was significant at four years for both the 10 million and 100 million cell doses (p = 0.01 and p = 0.004).
121. Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. Clin Orthop Relat Res. 2002;(405):14–23. Among 116 patients and 189 hips followed 5 to 10 years, only 9 of 145 pre-collapse hips progressed to arthroplasty compared with 25 of 44 post-collapse hips, and outcome correlated with the number of progenitors transplanted.
122. Hernigou P, Bouthors C, Bastard C, Flouzat Lachaniette CH, Rouard H, Dubory A. Subchondral bone or intra-articular injection of bone

marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomised study. Int Orthop. 2021;45(2):391–99. In 60 patients and 120 knees a 40 mL concentrate averaging 5727 colony-forming units per mL was split between subchondral and intra-articular delivery; at a mean 15 years arthroplasty incidence was 1.3% versus 4.6% per knee-year (p = 0.01) and total knee arthroplasty was performed in 20% versus 70% of knees.

123. Li M, Ma Y, Fu G, Zhang Z, Zhao Q, Zhou Y, et al. Ten-year follow-up results of the prospective, double-blinded, randomised, controlled study on autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of the femoral head. Stem Cell Res Ther. 2020;11:287. Mean survival was 78.1 versus 102.3 months (log-rank p = 0.029), the hazard ratio for buffy-coat treatment was 0.332 (p = 0.042) and for Ficat stage 3.283 (p = 0.028); at 120 months visual analogue score was 3.5 versus 1 (p = 0.001).
124. Hu L, et al. Network meta-analysis of surgical treatments for osteonecrosis of the femoral head. Eighteen randomised trials and 11 treatments were compared; autologous bone graft plus marrow concentrate versus core decompression alone gave an odds ratio of 0.019 (95% CI 0.0012 to 0.25) for disease progression and ranked first by surface under the cumulative ranking curve, without a difference in arthroplasty conversion.
125. Pawar N, Vaish A, Vaishya R. Core decompression and bone marrow aspirate concentrate injection for osteonecrosis of the femoral head: a scoping review. J Clin Orthop Trauma. 2021;24:101691. Across 612 hips of mean age 38.3 years followed 2 to 12 years, radiographic progression occurred in 23.5% and conversion to arthroplasty in 14.9%, with cell doses from 2 x 10^6 to 3.46 x 10^9.
126. Pepke W, Kasten P, Beckmann NA, Janicki P, Egermann M. Core decompression and autologous bone marrow concentrate for treatment of femoral head osteonecrosis: a randomized prospective study. Orthop Rev (Pavia). 2016;8(1):6162. Centrifugation increased colony-forming unit counts without translating into a clinical difference. https://pubmed.ncbi.nlm.nih.gov/27114808/
127. Hauzeur JP, De Maertelaer V, Baudoux E, Malaise M, Beguin Y, Gangji V. Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial. Int Orthop. 2018;42(7):1429–35. Fifteen of 23 hips progressed to total hip replacement in both arms.
128. ClinicalTrials.gov identifier NCT06123481. Core decompression with or without autologous bone marrow aspirate in early osteonecrosis of the femoral head: randomised double-blind trial of 192 participants, Johns Hopkins University.
129. Chatterjee S, et al. Lumbar interbody fusion using a truss implant packed with bone marrow aspirate clot versus crushed cancellous homologous bone: a randomised trial. Int J Spine Surg. 2020;14(6):924–35. Endpoints included Oswestry Disability Index, visual analogue scales, EuroQol-5D, reoperations and independently assessed fusion on computed tomography at three months.
130. Salamanna F, Barbanti Brodano G, Griffoni C, et al. Vertebral bone marrow clot as a three-dimensional multifunctional bioscaffold in instrumented posterior lumbar fusion: a prospective clinical pilot. Front Endocrinol (Lausanne). 2023;14:1245344. Ten consecutive patients were followed with visual analogue scale, Oswestry Disability Index and EuroQol at baseline, three and 12 months; the approach was safe and feasible.
131. ClinicalTrials.gov identifier NCT05947175. Vertebral bone marrow clot in spinal surgery: randomised trial of 96 participants, Istituto Ortopedico Rizzoli.
132. Buser Z, Hsieh P, Meisel HJ, Skelly AC, Brodt ED, Brodke DS, et al. Use of autologous stem cells in lumbar spinal fusion: a systematic review of current clinical evidence. Global Spine J. 2021. Unconcentrated aspirate did not improve fusion in three comparative studies, whereas the Hart randomised trial of concentrated aspirate with allograft chips gave computed-tomography fusion of 80% versus 40% at 24 months (relative risk 2.0, 95% CI 1.3 to 3.0; p = 0.01) and radiographic fusion of 35% versus 10% (p = 0.01); in revision fusion aspirate plus allograft achieved 78% versus 100% for autograft or recombinant bone morphogenetic protein 2 (p = 0.005).
133. Cole BJ, Kaiser JT, Wagner KR, Sivasundaram L, Otte RS, Tauro TM, et al. Prospective randomised trial of biologic augmentation with bone marrow aspirate concentrate in patients undergoing arthroscopic rotator cuff repair. Am J Sports Med. 2023;51(5):1234–42. Ninety-one patients with isolated 1 to 3 cm supraspinatus tears were randomised to concentrate or sham incision; retear on 1-year magnetic resonance imaging was 57% in controls versus 18% with concentrate (p < 0.001), yet treatment failure and all functional indices were equivalent at 2 years.
134. Park JY, Ng Hing Cheung JA, Todorov D, Park SY, Lim H, Shin E, et al. Biological augmentation of anterior cruciate ligament reconstruction with bone marrow aspirate concentrate: a systematic review and meta-analysis of randomised controlled trials. Int Orthop. 2025;49(1):35–43. Five randomised trials with 221 patients gave International Knee Documentation Committee mean differences of 2.56 (95% CI -0.19 to 5.32) at 12 months and 5.34 (0.21 to 10.46) at 24 months, judged by the authors to be below clinical significance; three of five trials were at high risk of bias.
135. Whitney KE, Briggs KK, Chamness C, Bolia IK, Huard J, Philippon MJ, et al. Bone marrow concentrate injection treatment improves short-term outcomes in symptomatic hip osteoarthritis patients: a pilot study. Orthop J Sports Med. 2020;8(12):2325967120966162. In 18 hips of 16 patients, numeric pain at rest fell from 5 to 1 (p < 0.001), Western Ontario and McMaster index from 31 to 16 (p = 0.006) and modified Harris hip score rose from 63 to 80 (p = 0.004), with 2 of 18 hips converting to arthroplasty.
136. Lee MS, et al. Cost-effectiveness of bone marrow aspirate concentrate augmentation of arthroscopic acetabular labral repair. ISAKOS 2025 abstract 20403. Among 358 patients under 50 years with at least two years of follow-up, 124 received bone marrow aspirate concentrate at an all-inclusive out-of-pocket cost of US$10,000; quality-adjusted life years were 6.162 versus 5.929, giving a gain of 0.233 and an incremental cost-effectiveness ratio of US$42,935 per quality-adjusted life year.

137. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. Cartilage. 2011;2(3):286–99. Fifteen patients with grade 4 lesions averaging 9.2 cm2 received 60 mL of aspirate concentrated four- to six-fold (3904 plus or minus 1232 colony-forming units per mL) under a collagen matrix; visual analogue score fell from 5.1 to 0.7 (p = 0.001) and complete defect filling was seen in 12 of 15 knees.
138. Whyte GP, Bizzoco L, Gobbi A. One-step cartilage repair of full-thickness knee chondral lesions using a hyaluronic acid-based scaffold embedded with bone marrow aspirate concentrate: long-term outcomes after mean follow-up duration of 14 years. Am J Sports Med. 2024;52(14). Twenty-six patients with a median lesion of 6.6 cm2 were followed a mean 14.0 years; median visual analogue score fell from 5.0 to 0.6 (p < 0.001) with three treatment failures.
139. Ow ZGW, Cheang HLX, Koh JH, Koh JZE, Lim KKL, Wang D, et al. Does the choice of acellular scaffold and augmentation with bone marrow aspirate concentrate affect short-term outcomes in cartilage repair? A systematic review and meta-analysis. Am J Sports Med. 2023. Concentrate augmentation improved visual analogue scores for single-layered scaffolds (weighted mean difference -4.88, 95% CI -5.38 to -4.37, versus -4.08 without; p = 0.01) and reduced incomplete defect filling, but all significant improvements fell below their respective minimal clinically important differences.
140. Hede K, Christensen BB, Olesen ML, et al. Combined bone marrow aspirate and platelet-rich plasma for cartilage repair: two-year clinical results. Cartilage. 2021;13(1_suppl):937S–47S. In 10 patients, biopsy histology showed 58% fibrous tissue and 40% fibrocartilage, indicating that repair tissue was predominantly not hyaline. https://pubmed.ncbi.nlm.nih.gov/31538811/
141. Lind M, et al. Bone marrow aspirate concentrate on a hyaluronic acid scaffold with intra-articular platelet-rich plasma for cartilage lesions in 165 patients. Cartilage. 2026. Outcomes were excellent in 50%, good in 28% and poor in 22%, with a mean Magnetic Resonance Observation of Cartilage Repair Tissue 2.0 score of 71
142. Rodas G, Soler-Rich R, Rius-Tarruella J, Alomar X, Balius R, Orozco L, et al. Effect of autologous expanded bone marrow mesenchymal stem cells or leucocyte-poor platelet-rich plasma in chronic patellar tendinopathy with gap greater than 3 mm: preliminary outcomes after 6 months of a double-blind randomised prospective study. Am J Sports Med. 2021. Twenty athletes received 20 x 10^6 expanded marrow cells or two platelet injections; the Victorian Institute of Sport Assessment patellar score improved in both arms without between-group difference (p = 0.6776), while only the cell arm reduced the intratendinous gap area from 15.06 to 3.38 mm2 (between-group p = 0.0159) and improved the composite magnetic resonance score (between-group p = 0.0041).
143. de Girolamo L, Filardo G, Abat F, Barfod KW, Bastos R, Cugat R, et al.; ESSKA-ORBIT Group. The use of injectable orthobiologics for knee osteoarthritis: a formal ESSKA-ORBIT consensus. Part 2, cell-based therapy. Knee Surg Sports Traumatol Arthrosc. 2025;33(11):4079–95. Twenty-seven statements averaged 8.2 plus or minus 0.3 of 9; point-of-care cell therapy is supported as a treatment option (Grade B) but not as first-line, platelet-rich plasma is recommended first and cell therapy second (Grade D), there is no sufficient direct evidence of disease modification (Grade C), double-spin concentrate is recommended for knee osteoarthritis (Grade D) and harvest should use multiple punctures of 2 to 5 mL with a 10 mL syringe (Grade C).
144. Scoping review of cell-based therapy for ankle osteoarthritis and osteochondral lesions. Bioengineering (Basel). 2026;13(7):843. In nine of 11 included studies cells were co-administered with a surgical procedure, making the independent cell effect uninterpretable.
145. Louwerens JKG, van den Bekerom MPJ, van Royen BJ, Eygendaal D, van Noort A, Sierevelt IN. Quantifying the minimal and substantial clinical benefit of the Constant-Murley score and the Disabilities of the Arm, Shoulder and Hand score in patients with calcific tendinitis of the rotator cuff. JSES Int. 2020;4(3):606–11. The minimal clinically important difference was 9.8 points (95% CI 3.7 to 15.9) for the Constant-Murley score and -8.2 for the Disabilities of the Arm, Shoulder and Hand score.
146. Pettine KA, Suzuki RK, Sand TT, Murphy MB. Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up. Int Orthop. 2017;41(10):2097–103. Twenty-six fusion candidates received 2 mL of concentrate into the nucleus pulposus; 20 avoided surgery at 36 months with Oswestry index falling from 56.7 to 17.5 and visual analogue score from 82.1 to 21.9, and patients receiving more than 2000 colony-forming units and 2 million CD34-positive cells per mL improved more.
147. Levi D, Tyszko S, Horn S, Pham N, Levin J. Bone marrow concentrate intradiscal injection for chronic discogenic low back pain: a double-blind randomised sham-controlled trial. Interv Pain Med. 2025;4(3):100611. Among 63 patients, at least 50% pain relief was achieved by 40% of concentrate and 33% of sham patients at 3 months and 44% versus 56% at 12 months, with no significant difference at any timepoint; the authors concluded that intradiscal concentrate was equivalent to a sham procedure.
148. El-Kadiry AE, Lumbao C, Rafei M, Shammaa R. Autologous BMAC therapy improves spinal degenerative joint disease in lower back pain patients. BMC Musculoskelet Disord. 2022;23(1):23. In a retrospective comparison, bone marrow aspirate concentrate outperformed platelet-rich plasma on visual analogue scale (29.38% improvement, p < 0.002), Knee Injury and Osteoarthritis Outcome Score (53.89%, p < 0.01) and Western Ontario and McMaster Universities Osteoarthritis Index (51.71%, p < 0.011).
149. Herger N, Bermudez-Lekerika P, Farshad M, et al. Should degenerated intervertebral discs of patients with Modic type 1 changes be treated with mesenchymal stem cells? Stem Cell Res Ther. 2024;15(1):65. Pro-inflammatory cytokine priming and three-dimensional culture both enhanced bone marrow mesenchymal stromal cell T-cell suppression, but the effect faded when cells returned to standard two-dimensional culture.
150. Abu Salem M, et al. Subchondral injections in knee osteoarthritis: a systematic review of 24 studies and 1,109 patients. Cartilage. 2026.

Conversion to total knee arthroplasty after calcium phosphate injection ranged from 1.3% to 45%, and cell-based subchondral treatment showed the best long-term profile.

151. Di Matteo B, Polignano A, Onorato F, et al. Knee intraosseous injections: a systematic review of clinical evidence of different treatment alternatives. Cartilage. 2021;13(1_suppl):1165S–77S. Of 12 studies and 459 patients receiving intraosseous treatment, only two used bone marrow concentrate.
152. Sanchez Santiuste M, et al. Intraosseous plus intra-articular plasma rich in growth factors versus intra-articular treatment alone in advanced knee osteoarthritis: a randomised controlled trial. J Clin Med. 2025;14(22):8075. Among 86 patients with Kellgren-Lawrence grade III–IV disease, the intraosseous arm was superior on nearly all Knee Injury and Osteoarthritis Outcome Score and Western Ontario and McMaster Universities Osteoarthritis Index domains at 3, 6 and 12 months ($p < 0.05$).
153. Barman A, Prakash S, Sahoo J, Mukherjee S, Maiti R, Roy SS. Single intra-articular injection with or without intraosseous injection of platelet-rich plasma in knee osteoarthritis: a randomised trial. Injury. 2022;53(3):1247–53. The visual analogue scale difference between combined intraosseous plus intra-articular and intra-articular alone was not significant at six months ($p = 0.422$).
154. ClinicalTrials.gov identifier NCT05517434. Autologous bone marrow aspirate versus saline for knee osteoarthritis: a quadruple-blind randomised phase 2/3 trial of 148 participants, University Health Network, Toronto.
155. ClinicalTrials.gov identifier NCT06311513. Concentrated bone marrow aspirate versus sham incision in revision anterior cruciate ligament reconstruction: randomised phase 4 trial of 40 participants, Hospital for Special Surgery.
156. ClinicalTrials.gov identifier NCT06040957. Bone marrow versus adipose tissue for knee osteoarthritis: randomised trial of 204 participants, Istituto Ortopedico Rizzoli.
157. Liew A, Bhattacharya V, Shaw J, Stansby G. Cell therapy for critical limb ischemia: a meta-analysis of randomized controlled trials. Angiology. 2016;67(5):444–55. Across 16 randomised trials, cell therapy reduced amputation (odds ratio 0.54, 95% confidence interval 0.34–0.87), but the effect was null when analysis was restricted to placebo-controlled trials.
158. Peeters Weem SM, Teraa M, de Borst GJ, Verhaar MC, Moll FL. Bone marrow derived cell therapy in critical limb ischemia: a meta-analysis of randomized placebo controlled trials. Eur J Vasc Endovasc Surg. 2015;50(6):775–83. Ten placebo-controlled trials gave a risk ratio for amputation of 0.91 (95% confidence interval 0.65–1.27), with mean differences of 0.11 for ankle-brachial index and 11.88 mmHg for transcutaneous oxygen tension.
159. Abdul Wahid SF, Ismail NA, Wan Jamaludin WF, et al. Autologous cells derived from different sources and administered using different regimens for no-option critical lower limb ischaemia patients. Cochrane Database Syst Rev. 2018;8:CD010747. The review found no evidence supporting routine autologous cell therapy in no-option critical limb ischaemia.
160. Afzal MR, Samanta A, Shah ZI, et al. Adult bone marrow cell therapy for ischemic heart disease: evidence and insights from randomized controlled trials. Circ Res. 2015;117(6):558–75. Pooled analysis of 48 randomised trials showed an improvement in left ventricular ejection fraction of 2.92% (95% confidence interval 1.91–3.92).
161. Delewi R, Andriessen A, Tijssen JG, Zijlstra F, Piek JJ, Hirsch A. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. Eur Heart J. 2014;35(15):989–98. Left ventricular ejection fraction improved by 2.55% overall and by 5.30% in patients with baseline ejection fraction below 40%.
162. Powell RJ, Marston WA, Berceli SA, et al. Cellular therapy with Ixmyelocel-T to treat critical limb ischemia: the randomized, double-blind, placebo-controlled RESTORE-CLI trial and the MOBILE experience with bone marrow aspirate concentrate. Among 152 patients treated with a point-of-care marrow concentrate, one-year amputation-free survival was 80%.
163. Fisher SA, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst Rev. 2016;12:CD007888. Across 38 randomised trials, long-term mortality risk ratio was 0.42 (95% confidence interval 0.21–0.87) on low-quality evidence, while left ventricular ejection fraction showed a non-significant mean difference of −1.60.
164. Mathur A, Fernandez-Aviles F, Bartunek J, et al. The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: the BAMI trial. Eur Heart J. 2020;41(38):3702–10. In 375 patients, two-year all-cause mortality was 3.26% with cell therapy versus 3.82% with control, a non-significant difference.
165. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the CHART-1 randomised controlled trial. Eur Heart J. 2017;38(9):648–60. The primary hierarchical composite was neutral (Finkelstein-Schoenfeld 0.52, $p = 0.51$), with benefit confined to a subgroup defined by baseline left ventricular end-diastolic volume.
166. Zhang Y, et al. Efficacy and safety of stem cell therapy for diabetic foot ulcer: a systematic review and meta-analysis of randomised controlled trials. Front Endocrinol (Lausanne). 2026. Thirty-two randomised trials with 2,059 participants gave an odds ratio for complete healing of 4.64 (95% confidence interval 3.11–6.90) and for amputation of 0.29; the bone-marrow mesenchymal stromal cell subgroup odds ratio was 8.33. No dedicated trial of bone marrow aspirate concentrate in diabetic foot ulcer was identified.
167. Mesenchymal stromal cell therapy for liver cirrhosis. Cochrane Database Syst Rev. 2025. Across 12 trials, mortality risk ratio was 0.52 (95% confidence interval 0.24–1.11) on very low certainty evidence. https://pubmed.ncbi.nlm.nih.gov/40371762/
168. Uccelli A, Laroni A, Ali R, et al. Safety, tolerability, and activity of mesenchymal stem cells versus placebo in multiple sclerosis (MESEMS): a phase 2, randomised, double-blind crossover trial. Lancet Neurol. 2021;20(11):917–29. In 144 patients the gadolinium-enhancing lesion rate ratio was 0.94 (95% confidence interval 0.58–1.50, $p = 0.78$), a definitively negative result.

169. Panes J, et al. Long-term efficacy and safety of darvadstrocel for complex perianal fistulas in Crohn disease: the ADMIRE-CD II randomised trial. Gastroenterology. 2026. In 568 patients the treatment difference for combined remission was 2.4% (95% confidence interval −5.8 to 10.6, p = 0.571); the product was subsequently withdrawn from the European market.
170. European Medicines Agency. Alofisel (darvadstrocel): withdrawal of the marketing authorisation in the European Union, 13 December 2024. Marketing authorisation had been granted on 23 March 2018.
171. Pasquali PJ, Teixeira ML, de Oliveira TA, de Macedo LG, Aloise AC, Pelegrine AA. Maxillary sinus augmentation combining bio-oss with the bone marrow aspirate concentrate: a histomorphometric study in humans. Int J Biomater. 2015;2015:121286. Vital mineralised tissue was 55.15 ± 20.91% with bone marrow aspirate concentrate plus anorganic bovine bone versus 27.30 ± 5.55% in controls (p < 0.05).
172. Comparison of single and double bone marrow aspirate concentrate concentrations in maxillary sinus augmentation. Int J Oral Maxillofac Implants. 2016;31(1):216–22. Vital mineralised tissue was 38.44 ± 12.34% with single concentration, 34.63 ± 9.84% with double concentration and 27.30 ± 5.55% in controls, with no significant dose effect. https://pubmed.ncbi.nlm.nih.gov/26800181/
173. Shanbhag S, Pandis N, Mustafa K, Nyengaard JR, Stavropoulos A. Cell therapy for orofacial bone regeneration: a systematic review and meta-analysis. J Clin Periodontol. 2019;46(Suppl 21):162–82. Across 47 clinical and 57 preclinical studies, whole bone marrow with a scaffold was superior to scaffold alone in sinus and ridge augmentation and comparable to autograft in cleft repair.
174. Tang Y, et al. Efficacy of mesenchymal stem cell therapy for stroke: a meta-analysis of randomised controlled trials. Across six randomised trials, the three-month National Institutes of Health Stroke Scale standardised mean difference was −0.34 (95% confidence interval −0.57 to −0.11, p = 0.004), with a null result at six months.
175. Siqueira RC, Messias A, Messias K, et al. Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells. Stem Cell Res Ther. 2015;6:29. Quality-of-life gains observed at three months were no longer present at 12 months.
176. Kebriaei P, Hayes J, Daly A, et al. A phase 3 randomized study of remestemcel-L versus placebo added to second-line therapy in patients with steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant. 2020;26(5):835–44. In 260 patients durable complete response was 35% versus 30% (p = 0.42), with benefit confined to the grade C/D subgroup (58% versus 37%, p = 0.03).
177. Kurtzberg J, Prockop S, Chaudhury S, et al. Study 275: updated expanded access program for remestemcel-L in steroid-refractory acute graft-versus-host disease in children. Biol Blood Marrow Transplant. 2020;26(5):845–54. In 54 children, day-28 overall response was 70.4% against a protocol-specified control rate of 45% (p = 0.0003), with day-100 survival of 74.1%.
178. United States Food and Drug Administration. FDA approves first mesenchymal stromal cell therapy to treat steroid-refractory acute graft-versus-host disease. Press announcement, 18 December 2024. Ryoncil (remestemcel-L-rknd), an allogeneic bone marrow-derived mesenchymal stromal cell product, was approved for children aged two months and older. https://www.fda.gov/news-events/press-announcements/fda-approves-first-mesenchymal-stromal-cell-therapy-treat-steroid-refractory-acute-graft-versus-host
179. Lechanteur C, Briquet A, Giet O, Delloye O, Baudoux E, Beguin Y. Clinical-scale expansion of mesenchymal stromal cells: a large banking experience. J Transl Med. 2016;14(1):145. Sixty-eight clinical-grade cultures from 59 validated donors produced a mean final yield of 886 million cells per culture and 464 cryopreserved aliquots at a mean 132.8 million cells per bag.
180. Oja S, Kaartinen T, Ahti M, Korhonen M, Laitinen A, Nystedt J. The utilization of freezing steps in mesenchymal stromal cell manufacturing: potential impact on quality and cell functionality attributes. Front Immunol. 2019;10:1627. A validated single-freeze protocol preserved viability, phenotype and differentiation but thawed cells showed an approximately 50% reduction in in-vitro immunosuppressive capacity; four or more freezing steps may induce earlier senescence.
181. Wiese DM, Wood CA, Ford BN, Braid LR. Cytokine activation reveals tissue-imprinted gene profiles of mesenchymal stromal cells. Proc Natl Acad Sci U S A. 2021;118(35). Interferon-gamma licensing generated heterogeneous rather than uniform mesenchymal stromal cell responses, a central manufacturing problem.
182. Jakl V, Popp T, Haupt J, et al. Effect of different preparation methods on the properties of small extracellular vesicles from bone marrow mesenchymal stromal cells. Front Bioeng Biotechnol. 2023;11:1107055. Isolation method produced considerable variability in vesicle quantity, purity and characteristics; cross-flow filtration with ultracentrifugation approximated the differential-centrifugation standard whereas polyethylene glycol precipitation did not.
183. Morata-Tarifa C, Macias-Sanchez MDM, Gutierrez-Pizarraya A, Sanchez-Pernaute R. Mesenchymal stromal cells for the prophylaxis and treatment of graft-versus-host disease: a meta-analysis. Stem Cell Res Ther. 2020;11(1):64. Prophylaxis increased overall survival by 17% (95% confidence interval 1.02–1.33) and reduced grade IV acute disease (risk ratio 0.22, 95% confidence interval 0.06–0.81); in acute disease, survival correlated with cell dose (p = 0.0214).
184. Fernandez-Garza LE, Barrera-Barrera SA, Barrera-Saldana HA. Mesenchymal stem cell therapies approved by regulatory agencies around the world. Pharmaceuticals (Basel). 2023;16(9):1334. Twelve mesenchymal stromal cell products had been approved worldwide, nine of them in Asia and the Republic of Korea leading, against 1,120 registered mesenchymal stromal cell clinical trials as of April 2023.
185. Patel AN, Henry TD, Quyyumi AA, et al. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial (ixCELL-DCM). Lancet. 2016;387(10036):2412–21. The composite of death, cardiovascular hospitalisation and unplanned clinic visits was reduced with a risk ratio of 0.63 (95% confidence interval 0.42–0.97, p = 0.0344).

186. Sengupta V, Sengupta S, Lazo A, Woods P, Nolan A, Bremer N. Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. Stem Cells Dev. 2020;29(12):747–54. In 24 patients, a single 15 mL intravenous dose was followed by an average 192% rise in the ratio of arterial oxygen tension to inspired oxygen fraction ($p < 0.001$), with 83% survival and no adverse events within 72 hours.
187. Lightner AL, Sengupta V, Qian S, et al. Bone marrow mesenchymal stem cell-derived extracellular vesicle infusion for the treatment of respiratory failure from COVID-19: a randomized, placebo-controlled dosing clinical trial. Chest. 2023;164(6):1444–53. Among 102 patients the primary endpoint of 60-day all-cause mortality was not met ($p = 0.1343$); post-hoc analysis of the 15 mL arm gave a relative risk of 0.385 (95% confidence interval 0.159–0.931, $p = 0.0340$).
188. Bain BJ. Bone marrow biopsy morbidity and mortality. Br J Haematol. 2003;121(6):949–51. Twenty-six adverse events including one death among an estimated 54,890 biopsies; haemorrhage in 14 patients, transfusion required in 6.
189. Bain BJ. Morbidity associated with bone marrow aspiration and trephine biopsy: a review of UK data for 2004. Haematologica. 2006;91(9):1293–94. Fifteen adverse events among 20,323 procedures, mainly haemorrhagic.
190. Lee SH, Erber WN, Porwit A, Tomonaga M, Peterson LC; International Council for Standardization in Haematology. ICSH guidelines for the standardization of bone marrow specimens and reports. Int J Lab Hematol. 2008;30(5):349–64. Progressive dilution with peripheral blood accompanies increasing aspirate volume; a 10- or 20-mL syringe is required for adequate negative pressure; sternal aspiration should be performed only by experienced operators aware of the risk of cardiac tamponade.
191. Sanabria-de la Torre R, Quinones-Vico MI, Fernandez-Gonzalez A, et al. Alloreactive immune response associated to human mesenchymal stromal cells treatment: a systematic review. J Clin Med. 2021;10(13):2991. Among 356 patients receiving allogeneic cells, a mean 11.51% developed donor-specific antibodies, without correlation to safety, tolerability, dose number or degree of human leucocyte antigen mismatch.
192. Patino JA, et al. Morbidity and mortality associated with performing bone marrow aspiration and biopsy. Int Phys Med Rehab J. Among 1,252 procedures in 914 patients there were 77 complications (6.15%), of which all reported pain and only seven were non-pain events (0.53%); major bleeding occurred in three (0.2%), infection in two (0.15%), and one patient died of retroperitoneal haematoma (0.07%). The same report cites a British Society of Haematology national survey of 54,890 biopsies with 26 adverse events (0.047%) and one death.
193. Elattar O, et al. Donor-site morbidity after iliac crest bone marrow aspirate concentrate harvest for foot and ankle arthrodesis. Foot Ankle Int. 2021. Among 55 patients, 50% reported immediate postoperative harvest-site pain, two had non-limiting pain persisting to six months, and three had persistent complications or dissatisfaction beyond six months; good-to-excellent results were achieved in 52 of 55 (94.5%).
194. Fucaloro SP, et al. Complication rates of bone marrow aspirate concentrate injections versus other injectable therapies for knee osteoarthritis: a systematic review and meta-analysis. J Orthop. 2025;62:36–42. Across six randomised trials, complications occurred in 140 of 334 bone marrow aspirate concentrate patients (41.91%) versus 217 of 526 comparators (41.25%), $p = 0.85$, absolute risk increase 0.66%, number needed to harm 152; effusion occurred in 18.26% and infection in none.
195. Complications following biologic therapeutic injections: a multicenter case series. Arthroscopy. 2021. Among 14 patients from six United States institutions, seven (50.0%) had culture- or pathology-confirmed septic arthritis and six (42.9%) a suspected sterile inflammatory response; mean time from injection to presentation was 8.9 days, the seven infections required a mean 3.6 operations, and 12 of 14 index injections had been performed at outside clinics.
196. Complications of stem cell-based injections for knee osteoarthritis: a systematic review. 2024. Of 427 studies screened, 48 were included with 1,924 patients; the overall transient adverse-event rate was 12.3%, rising to 51.7% for umbilical cord-derived products and 29.5% for cultured adipose-derived cells, with no infection, fat embolism, sepsis, neoplasm, embolism or death across the dataset.
197. Prodromos C, Rumschlag T, Finkle S. Mesenchymal stem cell treatment does not result in tumor formation: a systematic review. Among 217 articles and 4,796 mesenchymal stromal cell-treated patients with a mean follow-up of 13.92 months, 12 malignancies (0.25%) were reported versus six in controls
198. Barkholt L, Flory E, Jekerle V, et al. Risk of tumorigenicity in mesenchymal stromal cell-based therapies: bridging scientific observations and regulatory viewpoints. Extensive in-vitro expansion increases the risk that genetically abnormal cells arise and are propagated; chromosomal abnormalities exist at early passages and can be clonally propagated, yet there are no reports of malignant transformation in clinically used mesenchymal stromal cells and the tumourigenic potential remains unresolved.
199. Wang Y, Yi H, Song Y. The safety of mesenchymal stromal cell transplantation: a 15-year meta-analysis. Stem Cell Res Ther. 2021. Across 62 trials and 3,546 participants, transient fever odds ratio was 3.65 (95% confidence interval 2.05–6.49) and administration-site adverse events 1.98 (1.01–3.87), while death (0.99) and infection (1.03) were unchanged; no pooled malignancy estimate was possible and the authors found no direct evidence of tumourigenicity.
200. United States Food and Drug Administration, Center for Biologics Evaluation and Research. Same surgical procedure exception under 21 CFR 1271.15(b): questions and answers regarding the scope of the exception. Guidance for industry, November 2017. Minimally manipulated bone marrow for homologous use, not combined with another article, is not considered a human cell, tissue or cellular and tissue-based product under 21 CFR 1271.3(d); permitted processing under the exception is limited to rinsing, cleansing, sizing and shaping, with centrifugation or filtration allowed only to remove debris.

201. United States Food and Drug Administration. Questions and answers regarding the end of the compliance and enforcement policy for certain human cells, tissues, or cellular or tissue-based products. Enforcement discretion regarding investigational new drug and premarket approval requirements ended on 31 May 2021; every establishment manufacturing products regulated as drugs or biologics is expected to hold an approved biologics licence application or an investigational new drug application in effect.
202. United States Food and Drug Administration, Center for Biologics Evaluation and Research. Enforcement actions: biologics internet surveillance and other. The listing includes 18 untitled-letter entries plus one affiliate letter covering 19 named stem-cell or regenerative-medicine firms between 2018 and 2023.
203. United States Food and Drug Administration. Important patient and consumer information about regenerative medicine therapies. The agency lists ectopic tissue formation, tumour formation, immune reactions and cross-contamination among the risks of unapproved products and states that it has received reports of blindness, tumour formation and infections.
204. United States v. US Stem Cell Clinic, LLC, 998 F.3d 1302 (11th Cir. 2021). The Eleventh Circuit affirmed a permanent injunction after the district court held on 3 June 2019 that the clinic's stromal vascular fraction product was an adulterated and misbranded drug.
205. AABB. Supreme Court declines stem cell case, upholding FDA oversight of cell therapies, 15 October 2025. The Ninth Circuit's September 2024 ruling reversed the district court and rejected the argument that same-day stromal vascular fraction treatments qualify for the same-surgical-procedure exception; the Supreme Court's refusal of certiorari left that holding in place.
206. Kuriyan AE, Albini TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous adipose tissue-derived stem cells for age-related macular degeneration. N Engl J Med. 2017;376(11):1047–53. Three patients with pre-injection acuity of 20/30 to 20/200 declined to 20/200 to no light perception at one year, with retinal detachment, vitreous haemorrhage and lens dislocation.
207. Perkins KM, Spoto S, Rankin DA, et al. Notes from the field: infections after receipt of bacterially contaminated umbilical cord blood products for non-hematopoietic indications. MMWR Morb Mortal Wkly Rep. 2018;67(50):1397–9. Twelve patients across three states were hospitalised with bloodstream infections, joint infections and epidural abscesses caused by Enterobacter cloacae, Citrobacter freundii, Escherichia coli, Enterococcus faecalis and Proteus mirabilis; 11 of 12 had been treated for pain or orthopaedic conditions.
208. Berkowitz AL, Miller MB, Mir SA, et al. Glioproliferative lesion of the spinal cord as a complication of stem-cell tourism. N Engl J Med. 2016;375(2):196–8. A 66-year-old man developed paraplegia from an intradural mass after intrathecal infusions abroad; short tandem repeat fingerprinting showed the lesion was composed predominantly of non-host cells, and a 309-gene panel found no cancer-associated aberrations.
209. Turner LG. ISSCR's guidelines for stem cell research and clinical translation in the context of unproven stem cell-based interventions. Cell Stem Cell. 2021. As of 31 March 2021, 1,480 United States businesses operated 2,754 clinics marketing purported stem cell interventions, up more than fourfold from 351 businesses and 570 clinics in 2016; 1,262 (85.27%) advertised treatment of painful symptoms and 689 (46.55%) orthopaedic conditions, and among the 56 businesses (3.78%) publishing prices the mean was US$5,118 and the median US$4,000 (range US$1,200–28,000).
210. Piuzzi NS, Ng M, Chughtai M, et al. The stem-cell market for the treatment of knee osteoarthritis: a patient perspective. J Knee Surg. Across 65 centres the mean price was US$5,156 (standard deviation US$2,446; 95% confidence interval US$4,550–5,762) with a range of US$1,150–12,000, and marketed efficacy averaged 82.2% (range 55–100%).
211. United States Federal Trade Commission. Stem Cell Institute of America co-founders and companies banned from marketing stem cell treatments and ordered to pay more than US$5.1 million, January 2025. Summary judgment was granted in March 2024 on all counts, with relief orders issued on 26 December 2024 comprising US$3,310,146 in refunds and US$1,845,000 in civil penalties and a permanent ban on marketing any regenerative medicine treatment.
212. United States Federal Trade Commission. FTC stops deceptive health claims by a stem cell therapy clinic, 18 October 2018. The defendants earned at least US$3.31 million between 2014 and 2017 advertising that amniotic stem cell therapy could treat Parkinson disease, autism, macular degeneration, cerebral palsy, multiple sclerosis and heart attacks; the settlement imposed a partially suspended US$3.31 million judgment and prohibited unsupported claims including for osteoarthritis
213. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. OJ L 324, 10 December 2007, pp. 121–137.
214. 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. OJ L, 17 July 2024. General application begins 7 August 2027; the Regulation does not apply to autologous substances that are neither processed nor stored before application, but does apply to bedside processing using devices whose quality, safety and effectiveness were not demonstrated for that specific purpose as part of CE marking.
215. Medicines and Healthcare products Regulatory Agency (United Kingdom). Advanced therapy medicinal products: regulation and licensing in the UK. Supply of unlicensed advanced therapy medicinal products is possible only through the hospital exemption for non-routine preparation or the specials scheme, and a manufacturer's licence from the agency is required for either route; no minimal-manipulation exemption is published.
216. Health Canada. Policy position paper: autologous cell therapy products. Autologous cell therapy products meet the definition of a drug under the Food and Drugs Act and require a new drug submission or a clinical trial application under Division 5, Part C of the Food and Drug Regulations; the only exception is minimally manipulated lympho-haematopoietic cells for homologous use in transplantation,

and a medical device licence for processing equipment does not constitute review of the cell therapy output.

217. Therapeutic Goods Administration (Australia). Exempt autologous human cells and tissues, version 1.0, July 2018. Exemption under Schedules 5 and 7 of the Therapeutic Goods Regulations requires that the product be collected from a patient under the clinical care of a registered medical or dental practitioner, manufactured and used by or under the supervision of that practitioner, for a single indication in a single clinical procedure, and minimally manipulated for homologous use; exempt products must not be advertised to consumers and criminal penalties may apply.
218. Regulatory framework for regenerative medicine in Japan under the Act on the Safety of Regenerative Medicine. Implemented 25 November 2014, the Act assigns autologous mesenchymal stromal cells and autologous somatic cells not for homologous use to Class II, requiring a provision plan reviewed by an accredited Certified Committee for Regenerative Medicine and notified to the Minister of Health, Labour and Welfare; an amendment promulgated 14 June 2024 extends the Act to gene therapy, genome editing and messenger RNA products, while exosomes remain outside its scope.
219. Conselho Federal de Medicina (Brazil). Resolucao CFM no 2.464, de 2 de julho de 2026. Diario Oficial da Uniao, 15 July 2026, Edicao 131, Secao 1, p. 70. Platelet-rich plasma is regulated as an adjuvant medical procedure for knee osteoarthritis, lumbar discopathy, lateral elbow epicondylitis and meniscal repair; Article 5 prohibits adding medicines, biologically active substances, cell products, stem cells, bone marrow concentrate, stromal vascular fraction, microfragmented fat or recombinant growth factors to platelet-rich plasma outside formally approved clinical research, and Article 13 prohibits promises of cure, guarantees of result, assured tissue regeneration or claims of substitution for indicated surgery. The resolution revokes Resolucao CFM 2.128/2015.
220. Conselho Federal de Medicina (Brazil). Parecer CFM no 43/2016, 28 October 2016. The use of bone marrow aspirate for the treatment of orthopaedic lesions is an experimental procedure and may be performed only within research protocols approved under the national research ethics system.
221. Conselho Federal de Medicina (Brazil). Resolucao CFM no 2.336, de 13 de julho de 2023, on medical advertising and publicity. Diario Oficial da Uniao, 13 September 2023, Edicao 175, Secao 1, p. 312. Article 11 prohibits attributing privileged capacity to equipment, advertising equipment or medicines without national health agency registration, promoting methods or techniques not recognised by the Council, and guaranteeing, promising or insinuating good treatment results; Paragraph 5 defines untruthful content as advertising of revolutionary or miraculous practices or new procedures not approved for medical use by the Council.
222. Agencia Nacional de Vigilancia Sanitaria (Brazil). Resolucao da Diretoria Colegiada RDC no 505, de 27 de maio de 2021, on the registration of advanced therapy products. Class I comprises minimally manipulated products with non-homologous function and Class II extensive manipulation, tissue engineering and gene therapy; the resolution entered into force on 1 July 2021.
223. World Anti-Doping Agency. The 2026 Prohibited List, international standard, effective 1 January 2026. Section S2.3 prohibits growth factors and growth factor modulators at all times, including platelet-derived growth factor, insulin-like growth factor 1, vascular endothelial growth factor and thymosin-beta 4; M1 prohibits reintroduction of blood into the circulatory system; M2.2 prohibits intravenous infusions or injections exceeding 100 mL per 12-hour period outside hospital treatment; and M3.2 prohibits the use of normal or genetically modified cells or cell components.
224. World Anti-Doping Agency. Athlete and athlete support personnel guide to the 2026 Prohibited List. The guide confirms that the use of normal or genetically modified cells or cell components, including nuclei, mitochondria and ribosomes, is banned, describing an expanded scope encompassing the complete cell structure and key functional organelles.
225. United States Anti-Doping Agency. Orthobiologics: what athletes need to know about platelet-rich plasma. The agency states that platelet-rich plasma is not prohibited under World Anti-Doping Agency regulations, that it becomes prohibited if altered to enhance performance, that the only expected result is restoration of pre-injury function, and that individual growth factors remain prohibited when given separately as purified substances; bone marrow aspirate concentrate is not addressed.
226. Global Market Insights. Bone marrow aspirate concentrates market size, share and forecast. The market was valued at US$172.8 million in 2023, with North America at US$70 million and hospitals and clinics holding a 35.3% share, and is projected to grow at more than 5.4% annually to 2032.
227. Strategic Market Research. Bone marrow aspirate concentrates market report. The market is valued at US$2.4 billion in 2024 and projected to reach US$5.13 billion by 2030 at a compound annual growth rate of 13.5%, with aspiration kits holding a 60% share.
228. Grand View Research. Orthobiologics market size, share and trends analysis report. The global orthobiologics market was US$6.77 billion in 2024 and is projected to reach US$10.34 billion by 2033 at a compound annual growth rate of 4.74%, with viscosupplementation the largest product segment at 42.21%, spinal fusion the largest application at 48.29%, and North America 46.03% of the global market.
229. Blue Cross Blue Shield Association. Medical policy 8.01.52: orthopedic applications of stem cell therapy. Effective 1 April 2026; last revised 23 March 2026. Mesenchymal stem cell therapy is considered investigational for all orthopaedic applications, as are allograft products containing viable stem cells and graft substitutes that must be combined with autologous blood or bone marrow; demineralised bone matrix products designed to be mixed with marrow are cleared through the 510(k) pathway under product code MQV, and transplantation codes 38205 to 38241 are not appropriate for orthopaedic stem cell billing.
230. Cigna. Coverage policy 0552: stem cell therapy for orthopedic applications, effective 15 December 2025. Stem cell therapy is considered not medically necessary for regeneration or repair of musculoskeletal tissue, joint disease, osteoarthritis of the knee, hip,

ankle or shoulder, fracture repair including long-bone nonunion, and osteonecrosis repair; the Medicare table records no national coverage determination and no local coverage determination.

231. Anthem. Medical policy TRANS.00035: therapeutic use of stem cells, blood and bone marrow products, published 1 July 2026, last reviewed 14 May 2026. Use of bone marrow aspirate concentrate is considered investigational and not medically necessary for all indications, including critical limb ischaemia; mesenchymal stromal cell therapy, autologous bone marrow mononuclear cell therapy and platelet-rich plasma are likewise investigational for all indications.
232. Aetna. Clinical policy bulletin 0784: blood and adipose tissue derived products for selected indications. Bone marrow-derived mesenchymal stromal cell administration for facet joint injections, avascular necrosis of the shoulder, Crohn disease and osteoarthritis, and bone marrow plasma injection for tendinopathies of the elbow, heel, knee and shoulder, are considered experimental, investigational or unproven
233. Centers for Medicare and Medicaid Services. Local coverage determination L39879: amniotic and placental-derived product injections and/or applications for musculoskeletal indications, non-wound. The determination is a non-coverage policy on the basis that there is insufficient evidence-based literature to support coverage and that Medicare reasonable and necessary requirements have not been met; the current effective period began 12 January 2024.
234. Onuki TS, Sa KMM, Alves N, de Souza SI, Santos EM, Martimbianco ALC. Methodological quality of systematic reviews on platelet-rich plasma therapy for osteoarthritis: a meta-research study. Rev Bras Ortop (Sao Paulo). 2025;60(1). Of 31 systematic reviews, 26 (83.8%) were of critically low and five (16.13%) of low AMSTAR-2 quality with none moderate or high; only six (19.35%) applied the GRADE approach, 93.5% did not report the funding sources of included trials, and all 31 failed to report reasons for excluding trials.
235. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology and Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip and knee. Arthritis Rheumatol. 2020;72(2):220–33. Stem cell injections and platelet-rich plasma are strongly recommended against in knee and hip osteoarthritis, citing heterogeneity and lack of standardisation, while intra-articular glucocorticoid is strongly recommended
236. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27:1578–89. Intra-articular stem cell therapy and platelet-rich plasma were strongly recommended against because the supporting evidence is of extremely low quality and the formulations are not standardised.