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A Three-Tier Framework for Orthobiologic Use in Arthrosis and Lumbar Degeneration: Separating What Is Proven Safe and Effective from What Is Merely Proven Safe

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Abstract

Background: Orthobiologic injections are offered to patients with arthrosis and degenerative lumbar disease on the strength of a large and reassuring safety literature. Safety and efficacy are, however, different claims resting on different evidence, and the two are routinely conflated in clinical conversation, in marketing and occasionally in review articles. We set out to separate them formally and to determine which product–indication pairs are currently supported by both.

Methods: Working from a three-stream evidence base of 82 randomised controlled trials in arthrosis (460 outcome rows), 24 clinical studies in lumbar degeneration (92 rows) and 63 systematic reviews and network meta-analyses (192 pooled estimates), we defined four pre-specified, operationally explicit criteria: (A) safety established in controlled comparative data on at least 300 exposed patients with no excess of serious adverse events; (B) a pooled effect against a non-inert (active) comparator whose 95% confidence interval excludes the null; (C) that effect surviving every leave-one-out iteration; and (D) at least five controlled comparisons. Tier 1 requires A, B, C and D together; Tier 2 requires A and B; everything else falls to Tier 3. Effects were expressed as Hedges g with negative values favouring the orthobiologic and pooled by DerSimonian–Laird random effects with one pain-preferred estimate per study.

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Results: Eight product–indication pairs were assessable. Criterion A was met by 6 of 8, criterion B by 5, criterion D by 4 and criterion C by 0. No pair therefore reached Tier 1. Four pairs reached Tier 2 — PRP in knee osteoarthritis (g = -0.34 (-0.63, -0.05), k = 18), adipose-derived products in knee osteoarthritis (-0.44 (-0.86, -0.01), k = 7), orthobiologic injection in non-knee joints (-0.55 (-0.98, -0.13), k = 7) and the PRP family in lumbar degeneration (-1.77 (-3.31, -0.22), k = 4) — and four fell to Tier 3. Robustness was the universal failure point. The pooled class-level estimate against active comparators was stable (k = 33, g = -0.33 (-0.53, -0.14), p = 0.00093; leave-one-out range -0.38 to -0.28), but every product-specific estimate was fragile. PRP alone versus hyaluronic acid was not significant (k = 7, g = -0.29 (-0.63, +0.06), p = 0.1022), with 6 of 7 single-trial omissions abolishing any signal. Effects were strongly comparator-dependent: pooled g was -0.97 (-1.54, -0.41) against saline or sham (k = 10) versus -0.33 (-0.53, -0.14) against active comparators (k = 33), so 66% of the apparent benefit was not reproduced when the control arm received an injection — closely matching the 63% attributed to contextual effects by an independent analysis [1].

Conclusions: Under a strict product-specific standard the top tier of the orthobiologic evidence base is currently empty. This is not an argument for abandoning these treatments; it is an argument for describing them accurately. Safety is genuinely established for several products, class-level symptomatic benefit is genuinely established, and product-specific superiority over an active injection is not. The framework makes that distinction operational, states for every pair what evidence would promote it, and shows that for most pairs the required trial is small enough to be feasible.

Keywords

Orthobiologics; Platelet-rich plasma; Mesenchymal stromal cells; Evidence tiering; Osteoarthritis; Lumbar degeneration; Comparator dependence; Contextual effects; Informed consent.

Introduction

Two different claims, one sentence

A clinician who tells a patient that an orthobiologic injection is “safe and effective” is making two claims that rest on entirely different bodies of evidence, that were generated by different study designs, and that currently have very different levels of support. The safety claim is supported by large pooled series, by network meta-analyses of adverse events and by regulatory pharmacovigilance; it is, for several products, one of the better-evidenced statements in musculoskeletal medicine. The efficacy claim is supported by a body of randomised trials that is heterogeneous, dominated by inert comparators, rarely blinded to the degree required for a subjective outcome, and almost never powered to detect the modest effect that is actually present. Conflating the two is the single most consequential communication error in this field.

The companion synthesis to this article quantified the aggregate effect of orthobiologic injection across arthrosis and lumbar degeneration. It found a moderate, durable, statistically robust class-level benefit in arthrosis — g = -0.47 (-0.66 to -0.27) at 6 months across 43 controlled comparisons — that did not decay by 12 months (-0.53 (-0.78 to -0.27)), was largest against inert controls, was not demonstrably superior to corticosteroid, and was unaccompanied by any structural benefit on imaging [2,3,4]. That result is reassuring at the level of the class and unhelpful at the level of the consultation, because no patient is offered “a class”. They are offered a specific product, prepared in a specific way, for a specific joint or spinal level.

Why an explicit tier is necessary

Existing evidence appraisals in this field mostly grade the certainty of a body of evidence, in the manner of GRADE, or issue directional recommendations, in the manner of clinical practice guidelines. Both are valuable and neither answers the question a clinician actually faces, which is closer to: for this product, in this indication, do I have evidence that it works better than the injection I would otherwise give, and separately, do I have evidence that it will not harm the patient? Guideline positions diverge sharply on precisely this point. The American Academy of Orthopaedic Surgeons rates PRP in knee osteoarthritis as limited-strength evidence [5], several interventional-pain societies grade selected biologic applications as Level II to III with moderate recommendation strength [6,7], and a Cochrane review of cell therapy for knee osteoarthritis concluded that benefits were uncertain and that the certainty of the evidence was low to very low [8]. These are not contradictory readings of the same data so much as different questions asked of it.

We therefore constructed a framework with a deliberately narrow purpose: to sort product–indication pairs into three tiers using criteria that are pre-specified, arithmetically checkable, and phrased so that every pair carries an explicit statement of what evidence would move it up. A tier that cannot be promoted is a verdict; a tier that states its own promotion condition is a research agenda.

Objectives

- To define four operationally explicit criteria that separate established safety from established comparative efficacy.
- To apply them to every product–indication pair in the arthrosis and lumbar evidence base for which a pooled controlled estimate can be computed.
- To quantify how much of the apparent benefit of orthobiologic injection is contingent on the choice of control arm.
- To distinguish class-level conclusions, which are robust, from product-level conclusions, which are not.
- To state, for each pair, the specific trial that would change its tier, together with the sample size that trial would require.

Methods

Evidence base

Three streams were used. Stream 1 comprised arm-level continuous outcomes extracted from 82 randomised controlled trials of orthobiologic injection in arthrosis, yielding 460 outcome rows across the knee (69 trials), hip (6) and other joints. Stream 2 comprised 92 outcome rows from 24 clinical studies of orthobiologics in lumbar degeneration, of which 10 were randomised controlled trials. Stream 3 was an umbrella layer of 63 systematic reviews and network meta-analyses contributing 192 pooled estimates, used for safety accounting and for triangulation rather than for pooling. Every extracted value was bound to the URL of the document from which it was read.

Effect measure and pooling

Continuous pain and function outcomes were converted to Hedges g with the sign oriented so that

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negative values favour the orthobiologic arm. Where a study reported several eligible outcomes at the same timepoint, one estimate per study was retained, preferring pain over function and, within pain, the most frequently reported instrument. Pooling used DerSimonian–Laird random effects with Q, τ^2 and I^2 reported; 95% confidence intervals are Wald intervals on the pooled estimate. The 6-month timepoint was pre-specified as the primary anchor for tiering because it is the most densely reported and because it post-dates the period in which a procedural placebo effect is at its largest.

Comparator classification

Every controlled comparison was classified as inert or active. Inert comparators were saline injection, dry needling and sham procedure. Active comparators were hyaluronic acid, corticosteroid, structured exercise or conservative care delivered as the trial's control arm, and any other injectable given with therapeutic intent. This distinction is the analytical hinge of the framework: an effect measured against saline conflates the biological action of the product with the procedural and contextual effects of receiving an injection, whereas an effect measured against an active injection isolates the increment attributable to the product itself.

The four criteria

Criteria were specified before the tier assignments were computed and each was given a threshold that can be checked arithmetically from the data tables. They are set out in Table 2 and summarized here.

- **Criterion A:** safety established. Controlled comparative safety data covering at least 300 patients exposed to the product in the relevant indication, with no excess of serious adverse events relative to the comparator. Uncontrolled case series were not counted, because they cannot establish the absence of an excess.
- **Criterion B:** efficacy against a non-inert comparator. A pooled Hedges g at 6 months against active comparators whose 95% confidence interval excludes zero.
- **Criterion C:** robustness. That pooled estimate retains statistical significance in every leave-one-out iteration. A result that depends on the presence of any single trial is not a stable basis for a routine-care recommendation.
- **Criterion D:** volume. At least five controlled comparisons contribute to the pooled estimate, so that heterogeneity can be estimated with some stability and a single small trial cannot dominate the weight.

Tier 1 requires all four criteria. Tier 2 requires A and B, that is, established safety together with a pooled effect against an active comparator, whether or not that effect is robust or well replicated. Everything else, including products with excellent safety data but no demonstrated incremental efficacy, falls to Tier 3.

Sensitivity, fragility and promotion arithmetic

Three additional analyses support the tiering. First, a fragility analysis recorded, for each pooled estimate, the leave-one-out range and the identity of every trial whose removal abolished statistical significance. Second, a blinding-restricted sensitivity analysis repeated the active-comparator pools using double-blind trials only. Third, a promotion analysis computed, for each product, the total sample size that a single new

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two-arm trial would require to detect the currently observed active-comparator effect with 80% power at a two-sided α of 0.05, together with the sample size required to detect a minimum clinically important standardised effect of 0.30 irrespective of the observed point estimate.

Reporting and reproducibility

The analysis was performed in Python. All pooled estimates, subgroup pools, leave-one-out sequences and power calculations reported here were computed from the extracted data rather than transcribed from published reviews; where a published review is cited for a number, that number is attributed to the review and not presented as an independent result. Figures were generated directly from the same computed objects, so that no figure can disagree with the text.

Tier	Definition	What the clinician can honestly say	How the treatment should be offered
Tier 1	**Proven safe and proven effective. Criteria A, B, C and D all satisfied.**	This product has been shown to relieve symptoms better than the injection you would otherwise be offered, and its safety is established.	As routine care, within the indication studied, with standard consent.
Tier 2	**Proven safe, efficacy partly established. Criteria A and B satisfied; C or D not satisfied.**	This product is well tolerated and, taken across the published trials, performs somewhat better than an active comparator — but that finding is not yet stable.	After explicit consent naming the uncertainty; dose recorded; patient entered into a registry where one exists.
Tier 3	**Proven safe only, or not characterised. Criterion A or B not satisfied.**	This product appears to be well tolerated, but it has not been shown to work better than the alternatives — or it has not been tested adequately at all.	Inside a trial or a registry protocol. It should not be presented as an established treatment.

Table 1: The three tiers. Tiers are assigned to product–indication pairs, not to products in the abstract. The same product may occupy different tiers in different joints or spinal levels.

Criterion	Question it answers	Operational threshold	Why this threshold	Pairs meeting it
A. Safety established	Is there controlled evidence that this product does not cause more serious harm than the alternative?	Controlled comparative safety data on ≥300 exposed patients in the relevant indication, with no excess of serious adverse events.	300 exposures give roughly 80% probability of observing at least one event with a true incidence of 1%; uncontrolled series cannot demonstrate the absence of an excess.	**6 of 8**
B. Effect versus an active comparator	Does it outperform the injection the patient would otherwise receive?	Pooled Hedges g at 6 months against active comparators with a 95% confidence interval excluding zero.	Saline-controlled effects conflate product action with procedural and contextual effects; only an active control isolates the increment.	**5 of 8**
C. Robustness	Does that effect depend on any single trial?	Statistical significance retained in every leave-one-out iteration.	A recommendation for routine care should not be reversible by the removal of one study, particularly in a literature with strong small-study asymmetry.	**0 of 8**
D. Volume	Is there enough replication to estimate heterogeneity?	≥5 controlled comparisons contributing to the pooled estimate.	Below five studies τ^2 is estimated so imprecisely that the random-effects interval is not interpretable.	**4 of 8**

Table 2: The four criteria and their operational thresholds. Thresholds were fixed before tier assignment. Each is checkable from the data tables without recourse to judgement.

Criterion C is evaluated on the same pooled estimate used for criterion B.

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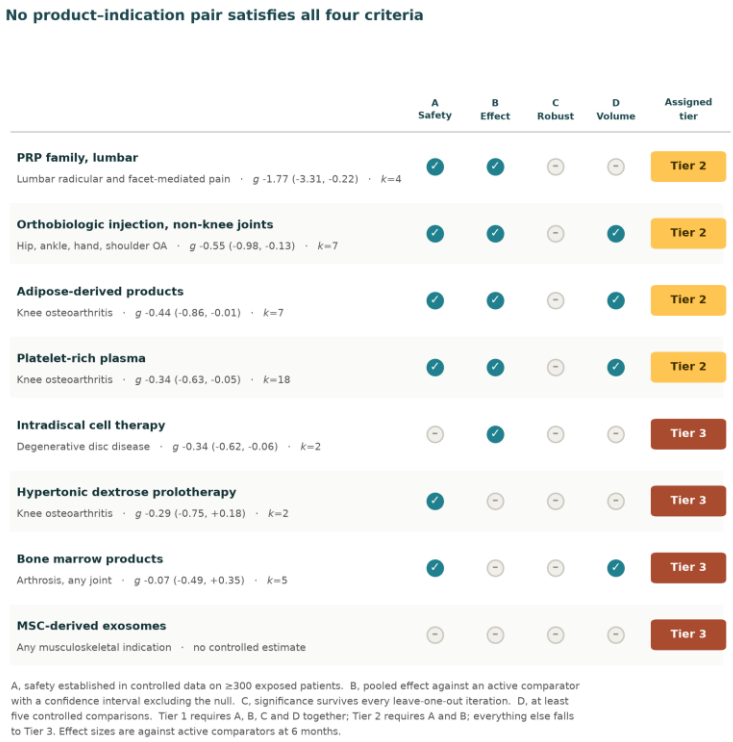

Figure 1: Criterion satisfaction and resulting tier for all eight product–indication pairs. Filled markers indicate a satisfied criterion. Criterion C is unsatisfied for every pair, which is why Tier 1 is empty. Effect sizes shown are against active comparators at 6 months.

Results

The evidence base to which the framework was applied

At the 6-month anchor the arthrosis stream contributed 43 controlled comparisons enrolling 2,833 patients. Of these, 33 comparisons (76.7%) used an active comparator and 10 (23.3%) used saline or sham; by enrolment the split was 2,342 patients (83%) against active controls and 491 (17%) against inert controls. PRP dominates the field, accounting for 1,505 of those patients, followed by adipose-derived products (689), bone marrow products (404), umbilical cord or amniotic products (98) and hypertonic dextrose (46). The lumbar stream contributed only 8 poolable controlled comparisons at 6 months and a single one at 12 months [9].

Eight product–indication pairs could be assessed. Four are knee-specific product families, one aggregates orthobiologic injection in non-knee joints, two are lumbar applications and one — MSC-derived exosomes — is included precisely because it has no poolable controlled human estimate at all and is nonetheless offered commercially.

Criterion A: safety is the best-supported claim in the field

Six of the eight pairs satisfied criterion A. The supporting data are set out in Table 3. For PRP the largest controlled safety comparison pools 11 randomised trials and 1,023 patients [10]. For bone marrow aspirate concentrate a meta-analysis of six randomised trials and 860 patients found complication rates of 41.91% versus 41.25% for comparator injections ($p = 0.85$), corresponding to a number needed to harm of 152 [11]. For cell-based products in the knee, a Cochrane review reported a risk ratio for serious adverse

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events of 0.72 (0.20 to 2.64) with $I^2 = 0\%$ across seven trials and 461 patients [8], while a separate synthesis of 16 trials and 807 patients reported a risk ratio of 2.67 (1.19 to 5.99) for any adverse event at low certainty [12]. A network meta-analysis of 16 randomised trials and 1,005 patients ranked placebo most favourably on safety (P-score 74.9) and adipose-derived MSC least favourably (13.3) [13]. Hypertonic dextrose accumulated 319 patients across five studies with no severe product-related adverse events [14], and lumbar PRP accumulated 416 patients with none [6].

Two pairs failed criterion A. Intradiscal cell therapy has a favourable safety signal — the DREAM trial recorded four adverse events in the cell arm against three in the sham arm with no ectopic tissue growth [15] — but total controlled exposure remains below the 300-patient threshold. MSC-derived exosomes have no controlled human safety dataset of any size; the pooled evidence is animal-model [16,17]. It is worth stating plainly that the criterion failure for exosomes is an absence of data, not a signal of harm; the two are distinguishable and should be described differently to patients.

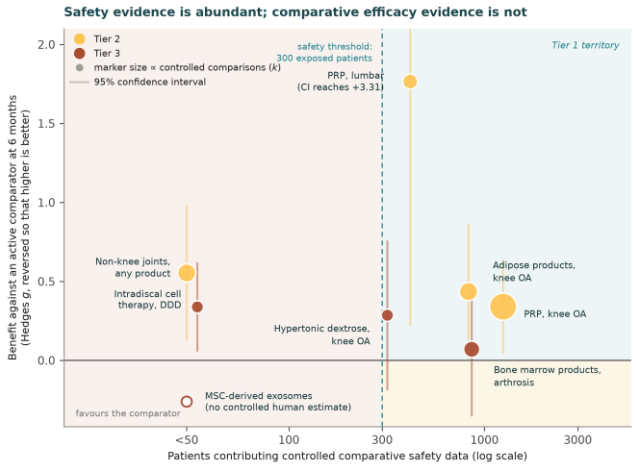

Figure 2: The safety–efficacy plane. Horizontal position is the number of patients contributing controlled comparative safety data; vertical position is the benefit against an active comparator at 6 months, reversed so that higher is better. Marker area is proportional to the number of controlled comparisons and vertical bars are 95% confidence intervals. Tier 1 territory is the upper-right region: adequate safety exposure together with a confidence interval clear of the null. Confidence intervals reach it; point estimates with stable intervals do not.

Product family	Indication	Controlled exposure (patients)	Criterion A met	Principal controlled safety evidence
Platelet-rich plasma (all leukocyte grades)	Knee osteoarthritis	1,023	Yes	11 RCTs, 1023 patients; RR 0.41 (0.35 to 0.48) for adverse events with PRP+HA versus PRP alone [10]
Adipose-derived products (AD-MSC, SVF, MFAT)	Knee osteoarthritis	1,005	Yes	Network meta-analysis of 16 RCTs, 1005 patients; ranked least favourably of the injectables on adverse events [13]
Bone marrow products (BMAC, culture-expanded BM-MSC)	Arthrosis, any joint	860	Yes	6 RCTs, 860 patients; complication rate 41.91% versus 41.25% for comparators, NNH 152 [11]
Hypertonic dextrose prolotherapy	Knee osteoarthritis	319	Yes	5 studies, 319 patients; no severe dextrose-related adverse events reported [14]

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Orthobiologic injection, non-knee joints	Hip, ankle, hand, shoulder OA	—	Yes	No distinct safety signal identified; safety inferred from the knee literature
PRP family, lumbar	Lumbar radicular and facet-mediated pain	416	Yes	No severe adverse events across 416 patients in the interventional-pain guideline syntheses [6]
Intradiscal cell therapy (BM-MSC, BMAC)	Degenerative disc disease	—	No	No excess serious adverse events versus sham, but exposure is below the 300-patient threshold [15]
MSC-derived exosomes	Any musculoskeletal indication	—	No	Human safety data insufficient to characterise [16,17]

Table 3: Safety ledger. Controlled exposure counts only patients in comparative studies with a control arm; uncontrolled series are excluded because they cannot demonstrate the absence of an excess of events.

Exposure figures are the largest controlled safety synthesis identified for each family and are not additive across rows, since the underlying trials overlap.

Criterion B: the effect exists, but it is smaller than advertised

Five of the eight pairs satisfied criterion B. Against active comparators, PRP in knee osteoarthritis returned g = -0.34 (-0.63, -0.05) (k = 18, p = 0.0221, I^2 = 83%), adipose-derived products -0.44 (-0.86, -0.01) (k = 7, p = 0.0431, I^2 = 82%), orthobiologic injection in non-knee joints -0.55 (-0.98, -0.13) (k = 7, I^2 = 65%), the PRP family in lumbar degeneration -1.77 (-3.31, -0.22) (k = 4, p = 0.0250, I^2 = 93%) and intradiscal cell therapy -0.34 (-0.62, -0.06) (k = 2, p = 0.0168, I^2 = 10%). Two pairs failed on a null estimate rather than on absent data: bone marrow products returned -0.07 (-0.49, +0.35) (k = 5, p = 0.7396), an estimate centred almost exactly on no difference with an interval narrow enough to exclude a moderate effect, and hypertonic dextrose returned -0.29 (-0.75, +0.18) on only 2 poolable comparisons. Dextrose is the single exception to the 6-month anchor: only one controlled dextrose comparison reports at 6 months, so the 3-month pool of two comparisons is carried forward for this pair and is flagged as such wherever it appears.

The magnitude deserves emphasis. Pooled across all products and all active comparators the effect is g = -0.33 (-0.53, -0.14) (k = 33, p = 0.00093, I^2 = 80%). On a 0–100 pain scale with a typical between-patient standard deviation of 20 points this corresponds to roughly 6.7 points — real, reproducible at the level of the class, and below most published thresholds for a minimum clinically important difference in osteoarthritis pain.

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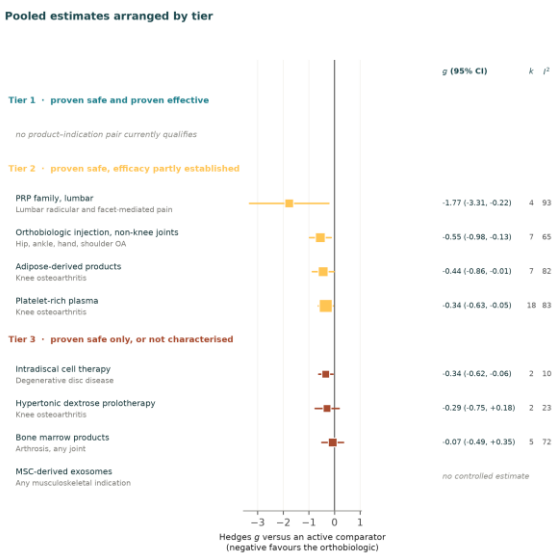

Figure 3: Pooled estimates arranged by tier. All estimates are against active comparators at 6 months, pooled by DerSimonian–Laird random effects with one estimate per study. Marker area is proportional to the number of contributing comparisons. The Tier 1 band is empty.

Product family	Indication	k	Hedges g (95% CI)	p	I^2 (%)	A B C D	Tier
PRP family, lumbar	Lumbar radicular and facet-mediated pain	4	-1.77 (-3.31, -0.22)	0.025	93	●●○○	**2**
Orthobiologic injection, non-knee joints	Hip, ankle, hand, shoulder OA	7	-0.55 (-0.98, -0.13)	0.0102	65	●●○●	**2**
Adipose-derived products (AD-MSC, SVF, MFAT)	Knee osteoarthritis	7	-0.44 (-0.86, -0.01)	0.0431	82	●●○●	**2**
Platelet-rich plasma (all leukocyte grades)	Knee osteoarthritis	18	-0.34 (-0.63, -0.05)	0.0221	83	●●○●	**2**
Intradiscal cell therapy (BM-MSC, BMAC)	Degenerative disc disease	2	-0.34 (-0.62, -0.06)	0.0168	10	○●○○	**3**
Hypertonic dextrose prolotherapy	Knee osteoarthritis	2	-0.29 (-0.75, +0.18)	0.2314	23	●○○○	**3**
Bone marrow products (BMAC, culture-expanded BM-MSC)	Arthrosis, any joint	5	-0.07 (-0.49, +0.35)	0.7396	72	●○○●	**3**
MSC-derived exosomes	Any musculoskeletal indication	—	no estimate	—	—	○○○○	**3**

Table 4: Tier assignments with supporting statistics. Effect sizes are against active comparators at 6 months. Filled circles denote satisfied criteria in the order A, B, C, D.

Negative Hedges g favours the orthobiologic. No pair satisfies all four criteria, so no pair is assigned to Tier 1. The hypertonic dextrose row is the one exception to the 6-month anchor: its estimate is the 3-month pool of two controlled comparisons, because only one dextrose comparison reports at 6 months (g = -0.57, 95% CI -1.16 to +0.02; Table 9).

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Criterion C: robustness is where every product fails

Not one of the eight pairs satisfied criterion C, and this single finding is what empties the top tier. The contrast between class-level and product-level stability is stark. Pooled across all products and all active comparators, the estimate survives every leave-one-out iteration with a range of -0.38 to -0.28 and no omission abolishing significance. Pooled across all products against hyaluronic acid specifically it is equally stable: k = 12, g = -0.36 (-0.60, -0.12), p = 0.0030, I^2 = 64%, leave-one-out range -0.42 to -0.28 with no losses.

Restrict the same comparison to PRP alone, however, and it collapses: k = 7, g = -0.29 (-0.63, +0.06), p = 0.1022, I^2 = 69% — not statistically significant, with 6 of the 7 single-trial omissions leaving no signal at all — specifically Du 2020 [18], Nouri 2022 [19], Kraeutler 2021 [20], Raeissadat 2020 [21], Filardo 2012 [22], Arliani 2021 [23]. This is an important correction to a widely repeated claim. The frequently quoted result that PRP outperforms hyaluronic acid derives from pools that mix PRP with adipose and other products; the PRP-specific cell does not reach significance in these data.

The same pattern recurs across families. PRP against all active comparators has a leave-one-out range of -0.43 to -0.28 with 4 of 18 omissions losing significance; adipose products lose it in 4 of 7; bone marrow products never attain it. Restricting to double-blind trials removes the effect entirely for both leading families: PRP k = 9, g = -0.29 (-0.62, +0.04), p = 0.0875; adipose k = 3, g = -0.87 (-2.00, +0.26), p = 0.1303. The class-level signal is real; the product-level signal is currently an artefact of which trials happen to be in the pool.

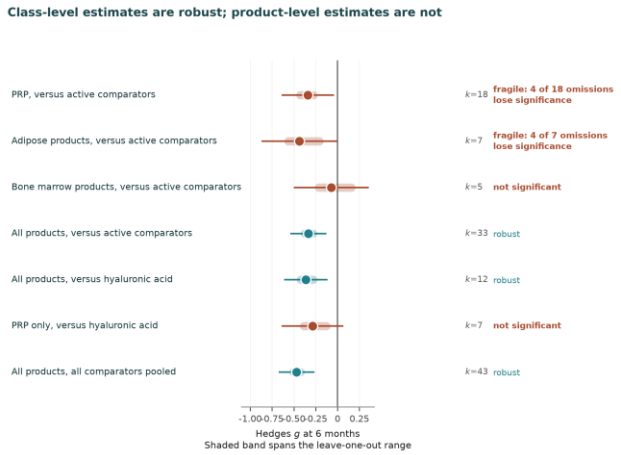

Figure 4: Fragility of pooled estimates. Points are pooled Hedges g at 6 months; horizontal lines are 95% confidence intervals; the shaded band spans the leave-one-out range. Estimates aggregated at the level of the class survive every omission; estimates specific to one product family do not.

Pooled estimate	k	Hedges g (95% CI)	p	Leave-one-out range	Verdict	Trials whose removal abolishes significance
All products, all comparators pooled	43	-0.47 (-0.66, -0.27)	< 0.0001	-0.50 to -0.43	**robust**	none
All products, versus	33	-0.33 (-0.53, -0.14)	0.00093	-0.38 to -0.28	**robust**	none

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active comparators						
All products, versus hyaluronic acid	12	-0.36 (-0.60, -0.12)	0.003	-0.42 to -0.28	**robust**	none
PRP only, versus hyaluronic acid	7	-0.29 (-0.63, +0.06)	0.1022	-0.39 to -0.13	not significant	—
PRP, versus active comparators	18	-0.34 (-0.63, -0.05)	0.0221	-0.43 to -0.28	fragile (4/18)	Abbadi 2022 [24], Elksnins-Finogejevs 2020 [25], Du 2020 [18], Patel 2024 [26]
Adipose, versus active comparators	7	-0.44 (-0.86, -0.01)	0.0431	-0.56 to -0.21	fragile (4/7)	Lu 2025 [27], Jing 2026 [28], Lu 2019 [29], Wu 2023 [30]
Bone marrow, versus active comparators	5	-0.07 (-0.49, +0.35)	0.7396	-0.21 to +0.16	not significant	—
PRP family, lumbar, versus active comparators	4	-1.77 (-3.31, -0.22)	0.025	-2.27 to -0.74	fragile (2/4)	Wongjarupong 2023, Wang 2025

Table 5: Fragility and leave-one-out ledger. An estimate is called robust when it retains statistical significance in every leave-one-out iteration, and fragile when at least one omission abolishes it.

All estimates are at 6 months. Class-level pools are robust; every product-specific pool is fragile or null.

Criterion D and the shape of the evidence base

Four pairs met the volume threshold. The shortfalls are informative rather than incidental. Hypertonic dextrose — an inexpensive, widely available, exceptionally well-tolerated agent — has only 2 poolable controlled comparisons at 3 months and one at 6 months, despite 319 patients of controlled safety data. Intradiscal cell therapy has 2. The lumbar PRP family has 4. In other words, the evidence base is not merely small in places; it is unevenly distributed in a way that tracks commercial interest more closely than clinical need. PRP accounts for 53% of all randomised patients at 6 months, while the two lumbar applications together contribute fewer controlled comparisons than a single well-conducted trial programme would.

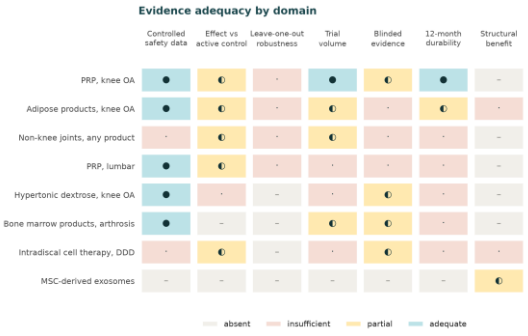

Figure 5: Evidence adequacy by domain for each product–indication pair. Each cell grades the evidence available in one domain as absent, insufficient, partial or adequate. Adequacy is reached only for controlled safety data and,

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for PRP in knee osteoarthritis, for trial volume and 12-month durability. Leave-one-out robustness is inadequate for every pair, and a structural benefit is absent or insufficient throughout; the single partial cell in that column reflects animal-model data for exosomes rather than human evidence.

Tier assignments: the top tier is empty

Applying the criteria yields 4 pairs in Tier 2, 4 in Tier 3 and 0 in Tier 1 (Table 4, Figures 1 and 3). Tier 2 comprises PRP in knee osteoarthritis, adipose-derived products in knee osteoarthritis, orthobiologic injection in non-knee joints and the PRP family in lumbar degeneration. Each has adequate controlled safety exposure and a pooled effect against an active comparator whose interval excludes the null, and each fails robustness. Tier 3 comprises bone marrow products in arthrosis (safe, well replicated, and null), hypertonic dextrose (safe, promising point estimate, too few controlled comparisons), intradiscal cell therapy (significant but with controlled exposure below the safety threshold and only two poolable comparisons) and MSC-derived exosomes (no controlled human efficacy or safety data).

The reader should note what this result is not. It is not a finding that orthobiologics do not work. The class-level effect is real, replicated and durable. It is a finding that, for every individual product–indication pair, the demonstration of incremental benefit over an active injection currently rests on a pool that one trial can overturn.

How much of the effect is the injection rather than the product

The gap between inert-controlled and active-controlled estimates is the quantitative core of the framework. Pooled across all products, g was -0.97 (-1.54, -0.41) against saline or sham (k = 10) and -0.33 (-0.53, -0.14) against active comparators (k = 33). The ratio implies that 65.8% of the effect observed against an inert control is not reproduced when the control arm also receives an injection. Within families the same pattern holds and is larger for adipose products: PRP -0.87 against inert (k = 6) versus -0.34 against active (k = 18), a 60.8% shortfall; adipose -2.00 versus -0.44, a 78.1% shortfall.

This is a computation performed on our own extracted data, and it converges closely with an independently derived estimate: a 2025 analysis attributed 63% of the pain benefit and 61% of the function benefit of intra-articular injection in knee osteoarthritis to contextual effects [1]. Two different datasets and two different analytical routes arriving within three percentage points of one another is about as much corroboration as this literature permits. The practical implication is direct: most of what a patient experiences after an orthobiologic injection would also have been experienced after a different injection.

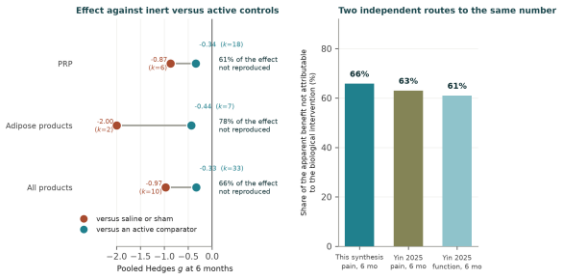

Figure 6: Comparator dependence of the pooled effect. Left, pooled Hedges g against inert and active comparators for all products and for the two largest families. Right, the proportion of the inert-controlled effect that is not reproduced against an active comparator, with the independently derived contextual-effect estimate shown for comparison.

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Product family	k (inert)	g vs inert	k (active)	g vs active	Difference	Effect not reproduced vs an active comparator
All products pooled	10	-0.97	33	-0.33	-0.64	**65.80%**
Platelet-rich plasma	6	-0.87	18	-0.34	-0.53	**60.80%**
Adipose-derived products	2	-2	7	-0.44	-1.56	**78.10%**

Table 6: Comparator dependence of the pooled effect at 6 months. The final column is the proportion of the inert-controlled effect that disappears when the control arm receives an active injection.

An independent analysis of contextual effects in intra-articular injection for knee osteoarthritis attributed 63% of the pain benefit and 61% of the function benefit to context, closely matching the all-products figure computed here.

What would change each tier

Because the criteria are arithmetic, the promotion condition for each pair can be stated as a specific trial with a specific size. A two-arm trial with 80% power at a two-sided α of 0.05 to detect the currently observed active-comparator effect would require 272 patients in total for PRP, 166 for adipose-derived products, 96 for hypertonic dextrose and 54 for umbilical cord or amniotic products. For bone marrow products the corresponding figure is 6,190, which is a formal way of saying that the observed effect is so close to zero that confirming it is not a realistic undertaking; the appropriate inference is that bone marrow products do not outperform active comparators for symptomatic relief in arthrosis, not that a larger trial is required. To detect a minimum clinically important standardised effect of 0.30 irrespective of the observed estimate would require 350 patients.

These are not large trials. A 272-patient double-blind comparison of PRP against hyaluronic acid in knee osteoarthritis, with a pre-registered protocol, a standardised preparation and a 12-month primary endpoint, would settle the single most commercially consequential question in the field. That such a trial has not been performed after more than a decade and several thousand randomised patients is the most telling observation in this analysis.

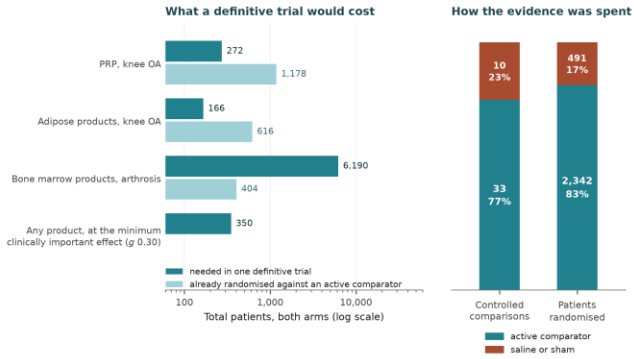

Figure 7: Sample size required to promote each product family. Bars show the total two-arm sample size needed for 80% power at a two-sided α of 0.05 to detect the currently observed active-comparator effect. The bone marrow requirement reflects an effect indistinguishable from zero rather than a feasible trial.

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Product family	Indication	Current tier	Target	Evidence that would change the tier	Trial size (total)
Platelet-rich plasma (all leukocyte grades)	Knee osteoarthritis	**2**	→ 1	Loses significance when any of six individual trials is removed; a single adequately powered PRP versus hyaluronic acid trial would resolve it	272
Adipose-derived products (AD-MSC, SVF, MFAT)	Knee osteoarthritis	**2**	→ 1	Active-comparator estimate rests on 7 trials with wide intervals; needs replication at 12 months	166
Bone marrow products (BMAC, culture-expanded BM-MSC)	Arthrosis, any joint	**3**	→ 2	A null estimate with a narrow interval; further uncontrolled series will not change the tier	6,190
Hypertonic dextrose prolotherapy	Knee osteoarthritis	**3**	→ 2	Guideline-level support exists but the randomised base is too small to test; needs 3 to 4 further trials	96
Orthobiologic injection, non-knee joints	Hip, ankle, hand, shoulder OA	**2**	→ 1	Joint-specific active-comparator trials are absent outside the knee	—
PRP family, lumbar	Lumbar radicular and facet-mediated pain	**2**	→ 1	Graded Level III with moderate recommendation strength; needs blinded active-comparator trials	—
Intradiscal cell therapy (BM-MSC, BMAC)	Degenerative disc disease	**3**	→ 2	The single controlled 12-month estimate is g -0.29; a confirmatory trial is under way	—
MSC-derived exosomes	Any musculoskeletal indication	**3**	→ 2	Requires dose-finding and controlled human safety data before efficacy testing	—

Table 7: Promotion criteria — what would move each pair up a tier. Trial size is the total two-arm sample required for 80% power at a two-sided α of 0.05 to detect the currently observed active-comparator effect.

A dash indicates that no meaningful power calculation is possible because no controlled effect estimate exists.

Evidence allocation and what is missing

(Table 8) sets out how the randomised evidence at 6 months is distributed. Three features stand out. First, the concentration in PRP: 18 of the 33 active-controlled comparisons and 1,178 of the 2,342 actively controlled patients. Second, the near-absence of controlled data for the products marketed most aggressively as advanced: umbilical cord and amniotic products contribute 2 comparisons and 98 patients, and exosomes contribute none. Third, the systematic under-use of active comparators in exactly the families where the contextual-effect problem is largest: adipose products have 2 inert-controlled comparisons generating the largest effect estimate in the entire dataset (-2.00) against 7 active-controlled comparisons generating -0.44.

Product family	k active	Patients (active)	k inert	Patients (inert)	Total patients	Share of evidence	Actively controlled
PRP	18	1,178	6	327	1,505	53.10%	78%
Adipose	7	616	2	73	689	24.30%	89%
Bone marrow	5	404	—	—	404	14.30%	100%
Dextrose	1	46	—	—	46	1.60%	100%
UC-MSC/amniotic	2	98	—	—	98	3.50%	100%
Other	—	—	2	91	91	3.20%	0%
All families	**33**	**2,342**	**10**	**491**	**2,833**	**100%**	**83%**

Table 8: Allocation of randomised evidence at 6 months. Counts are controlled comparisons and randomised patients contributing to the 6-month pooled analyses.

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"Actively controlled" is the percentage of each family's randomised patients whose control arm received an active intervention rather than saline or sham.

Provenance of the pooled estimates

(Table 9) lists every controlled comparison contributing to the active-comparator pools that underpin criteria B, C and D, so that any reader can reconstruct a pool, repeat a leave-one-out iteration or identify the trial responsible for a fragile result without returning to the parent synthesis.

Product–indication pair	k	Pooled g (95% CI)	Contributing controlled comparisons
Platelet-rich plasma, knee osteoarthritis	18	-0.34 (-0.63, -0.05)	Abbadi 2022 [24], Elksnins-Finogejevs 2020 [25], Du 2020 [18], Patel 2024 [26], Rahimzadeh 2018 [31], Nouri 2022 [19], Kraeutler 2021 [20], Sun 2021 [32], Jubert 2017 [33], Raeissadat 2020 [21], Filardo 2012 [22], Zhou 2023 [34], Romandini 2024 [35], Baria 2022 [36], Pretorius 2022 [37], Arliani 2021 [23], Huang 2022 [38], Karaborklu Argut 2024 [39]
Adipose-derived products, knee osteoarthritis	7	-0.44 (-0.86, -0.01)	Lu 2025 [27], Jing 2026 [28], Lu 2019 [29], Wu 2023 [30], Baria 2024 [40], Molnar 2025 [41], Gobbi 2022 [42]
Bone marrow products, arthrosis	5	-0.07 (-0.49, +0.35)	Dulic 2021 [43], Dwyer 2021 [44], Lamo Espinosa 2020 [45], Lana 2026 [46], Anz 2020 [47]
Hypertonic dextrose, knee osteoarthritis	1	-0.57 (-1.16, +0.02)	Gul 2020 [48]
Umbilical cord or amniotic products, knee osteoarthritis	2	-0.77 (-2.81, +1.27)	Matas 2019 [49], Pill 2025 [50]
PRP family, lumbar degeneration	4	-1.77 (-3.31, -0.22)	Singh 2023, Wongjarupong 2023, Wang 2025, Won 2022

Table 9: Provenance of the active-comparator pools at 6 months. Every trial contributing to the pooled estimates used for criteria B, C and D, listed by first author and year.

Lumbar studies are identified by first author and year; full citations for the lumbar stream are given in the parent synthesis.

Discussion

An empty top tier is a finding, not a failure of the framework

We designed the criteria before computing the assignments and did not revise them when the top tier came out empty. It would have been easy to relax criterion C — dropping robustness would have promoted four pairs immediately — and the temptation to do so is precisely why pre-specification matters. The substantive question is whether robustness is a reasonable requirement for the claim "proven effective". We think it is. In a literature with strong small-study asymmetry (Egger intercept -3.68, SE 1.05, t = -3.51, p = 0.0011; Begg τ = -0.40, z = -3.74, p = 0.00019), an effect that one trial's removal can abolish is an effect one unpublished trial's inclusion might also abolish.

The alternative reading — that our threshold is too strict — should be tested against the sensitivity analyses rather than asserted. Restricting to double-blind trials, which is a different and arguably more

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fundamental restriction than leave-one-out, removes significance for both leading families. Restricting to PRP versus hyaluronic acid, the single most clinically relevant head-to-head, removes it as well. Three independent restrictions all point the same way.

Class-level truth and product-level uncertainty

The most useful distinction to emerge from this analysis is between what can be said about the class and what can be said about a product. Injecting something biologically active into an arthritic joint produces a modest, durable symptomatic benefit that exceeds what an active comparator injection produces, and that conclusion is stable under every sensitivity analysis we applied. Which biologic to inject is a question the current evidence cannot answer, because the differences between products are smaller than the noise between trials.

This has an uncomfortable corollary for the economics of the field. The products differ in cost by more than an order of magnitude — hypertonic dextrose and leukocyte-poor PRP at one end, culture-expanded cells and exosome preparations at the other — while the evidence provides no basis for ranking them. Indeed, the cheapest agent in the dataset returned a point estimate (-0.29 (-0.75, +0.18)) that is not distinguishable from the most expensive, and the product family with the most elaborate laboratory processing (bone marrow, -0.07 (-0.49, +0.35)) returned the least favorable one.

No structural benefit for any product

None of the tier assignments incorporates a structural claim, because no product supports one. A meta-analysis of randomised trials with imaging endpoints reported a standardised mean difference of −0.01 ($p = 0.91$) for cartilage outcomes [2]; a second found $g = 0.079$ ($p = 0.723$) [3]; a third, examining WORMS scores across 16 studies and 875 patients, found no difference between orthobiologic and control [4]. Any consent conversation that describes an orthobiologic injection as regenerating, repairing or rebuilding cartilage is unsupported by the randomised imaging literature, regardless of tier.

Implications for consent and for practice

The framework translates into three concrete changes to the way these treatments should be discussed. For Tier 2 products, the phrase “safe and effective” should be replaced by something closer to: this is well tolerated; averaged across the trials it works somewhat better than the alternative injection; that finding is not yet stable enough for me to promise you it will hold. For Tier 3 products with good safety data and null efficacy data — bone marrow products in arthrosis being the clearest case — the honest statement is that the product is safe and has not been shown to work better than the alternatives. For Tier 3 products with no controlled data at all, including exosomes, the honest statement is that we do not know, and the appropriate setting is a trial.

Guideline bodies have converged on positions broadly compatible with this reading, though they express it differently: limited-strength evidence for PRP in knee osteoarthritis from the orthopaedic surgery side [5], low to very low certainty for cell therapy from Cochrane [8], and graded but qualified support for selected biologic applications from interventional pain medicine [6,7,51]. The tier framework does not overturn any of these; it makes the reason for their divergence visible, which is that they are weighing safety and comparative efficacy in different proportions.

A research agenda that follows from the tiers

Because each tier carries its promotion condition, the research agenda writes itself and is notable mostly

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for how modest it is.

- A double-blind trial of PRP against hyaluronic acid in knee osteoarthritis, 272 patients, standardised preparation, 12-month primary endpoint. This single trial would either promote PRP to Tier 1 or demote it to Tier 3.
- A double-blind trial of an adipose-derived product against an active comparator, 166 patients, with the preparation characterised well enough to be reproduced.
- A trial of hypertonic dextrose against an active comparator, 96 patients — the cheapest question in the field and the one closest to being answered.
- No further uncontrolled case series of any product, and no further saline-controlled trials of products already shown to beat saline; both add exposure without adding information relevant to any criterion.
- Controlled human safety data for exosome preparations before any efficacy trial, and mandatory registry entry for every culture-expanded cell product administered outside a trial.

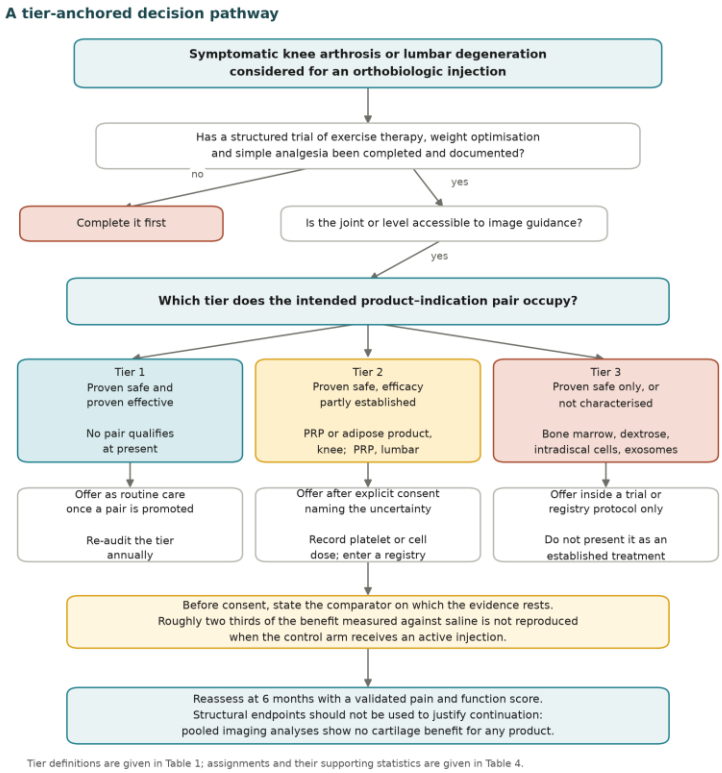

Figure 8: Decision algorithm for applying the framework to a product–indication pair. The algorithm is deliberately sequential: safety is assessed first because a product that fails criterion A cannot be promoted by any amount of efficacy data.

Limitations

The thresholds are defensible but arbitrary at the margin; 300 exposed patients, five comparisons and complete leave-one-out stability are conventions rather than derivations, and reasonable analysts would set them slightly differently. Heterogeneity is extreme throughout (I^2 91–88% for the arthrosis pools), so every pooled point estimate should be read as a summary of a distribution rather than as an estimate of

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a common effect; the prediction interval for the primary arthrosis pool spans -1.64 to +0.71. Products were grouped into families, which conceals real variation in preparation — platelet concentration, leukocyte content, activation method, cell dose and passage number all differ across trials nominally testing the same thing. The lumbar evidence base is thin enough (8 controlled 6-month comparisons, one at 12 months) that its tier assignments should be regarded as provisional. Our contextual-effect computation assumes that inert-controlled and active-controlled trials are otherwise comparable, which is not guaranteed. Finally, this is a secondary analysis of a previously assembled evidence base: it inherits that base's search date, inclusion decisions and extraction errors, and it was not separately registered.

Conclusions

Applying four pre-specified criteria to eight product–indication pairs in arthrosis and lumbar degeneration leaves the top tier empty. Six pairs have established safety, five have a pooled effect against an active comparator, and none has an effect that survives every leave-one-out iteration. Four pairs — PRP and adipose-derived products in knee osteoarthritis, orthobiologic injection in non-knee joints, and the PRP family in lumbar degeneration — are proven safe with partly established efficacy. Four, including the entire bone marrow family and all exosome preparations, are proven safe only or not characterised at all.

Two quantitative findings should shape practice immediately. 66% of the benefit seen against saline is not reproduced against an active injection, a figure that matches an independently derived contextual-effect estimate of 63% [1]. And the class-level conclusion is robust while every product-level conclusion is fragile, which means the honest unit of claim is “injecting a biologic helps a little” rather than “this biologic helps”. The remedy is not more patients treated; it is three modest, double-blind, actively controlled trials totalling fewer than 550 participants. Until they are done, the accurate description of most orthobiologic practice is that it is proven safe and not yet proven better.

Declarations

Not applicable. This study is a secondary analysis of published aggregate data and involved no new human or animal participants.

Consent for publication

Not applicable.

Availability of data and materials

All extracted data tables, the analysis scripts and the figure-generation code are available from the corresponding author on reasonable request. Every extracted value is bound to the URL of its source document.

Competing interests

The authors declare that they have no competing interests. [To be completed by each author before submission.

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Authors' contributions

[MHK, CAPMR] conceived and designed the study. All authors read, revised and approved the final manuscript.

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