

# Regenerative Approaches in Orthopedics

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## ABSTRACT

*Regenerative orthopaedics seeks to restore damaged musculoskeletal tissues to their native structure and function rather than replacing them with prosthetic hardware, yet clinical adoption of regenerative strategies varies markedly across tissue types and therapeutic modalities. We evaluated 224 regenerative orthopaedic programmes conducted across clinical and research centres in Spain, Switzerland, and France between 2014 and 2024, spanning five modality categories: platelet-rich plasma injections, bone morphogenetic protein augmentation, mesenchymal stem cell therapies, scaffold-based bone regeneration, and growth-factor-loaded hydrogel systems. A Regenerative Orthopaedics Translational Index (ROTI) was constructed from five sub-scores -- functional outcome improvement, tissue quality on imaging and histology, durability of repair beyond 24 months, adverse event profile, and evidence quality level -- with weights from regression against sustained clinical adoption. ROTI correlated with adoption at  $r = +0.83$  and discriminated adopted from non-adopted programmes with an AUC of 0.878. Platelet-rich plasma programmes scored highest (mean ROTI 0.818), while growth-factor hydrogels trailed at 0.592. Only 33.5 percent of programmes exceeded the 0.75 ROTI threshold. Functional outcome improvement carried the largest regression weight ( $\beta = +0.278$ ), followed by evidence quality level ( $\beta = +0.228$ ).*

**Keywords:** regenerative orthopaedics; platelet-rich plasma; bone morphogenetic protein; mesenchymal stem cells; scaffold; hydrogel; ROTI; bone regeneration; tendon repair; growth factors; tissue engineering; clinical translation

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## 1. Introduction

### 1.1 The Regenerative Paradigm in Orthopaedics

Orthopaedic surgery has traditionally addressed musculoskeletal damage through mechanical solutions: metal plates for fractures, joint prostheses for arthritis, and suture anchors for tendon tears. These approaches restore mechanical function but do not regenerate the damaged tissue itself, leaving patients with hardware that may loosen, wear, or require revision surgery over time. Regenerative orthopaedics aims to shift the treatment paradigm from replacement to restoration by harnessing the body's healing mechanisms, amplified or directed by biological therapies, to rebuild bone, cartilage, tendon, ligament, and meniscus with tissue that approximates the native structure and mechanical properties. The concept spans a broad therapeutic spectrum from minimally invasive biologic injections that augment natural healing to surgically implanted scaffolds seeded with stem cells and loaded with growth factors. Clinical enthusiasm is high, driven by patient demand for alternatives to joint replacement and by the commercial success of early products like recombinant BMP-2 for spinal fusion, but the evidence base is uneven and the gap between laboratory promise and clinical proof remains wide for many approaches.

### 1.2 The Evidence Landscape

The regenerative orthopaedics field is characterised by a large volume of preclinical studies, a moderate number of early-phase clinical trials, and a relatively small number of large randomised controlled trials with long-term follow-up. Platelet-rich plasma injections for tendinopathy and osteoarthritis have been studied in dozens of RCTs with conflicting results, partly because PRP preparation protocols vary widely and the optimal platelet concentration, leukocyte content, and injection schedule remain debated. Bone morphogenetic proteins are approved for specific indications but post-market surveillance has revealed complication profiles that tempered initial enthusiasm. MSC therapies have generated enormous research output but the mechanism of action, whether paracrine signalling, direct differentiation, or immunomodulation, remains contested, complicating regulatory classification and clinical interpretation. Scaffold-based approaches and growth-factor hydrogels are at earlier translational stages with limited clinical data.

### 1.3 Study Objective

We sought to identify the programme-level characteristics that predict whether a regenerative orthopaedic programme achieves sustained clinical adoption or remains confined to research settings. By scoring 224 programmes across five modality categories on five translational dimensions and constructing a regression-weighted composite index, we aimed to quantify which clinical, biological, and evidentiary factors matter most for translational success.

## 2. Literature Review

### 2.1 Platelet-Rich Plasma and BMP Augmentation

Platelet-rich plasma concentrates autologous growth factors from centrifuged blood and delivers them to injury sites via injection or intraoperative application. Meta-analyses of PRP for knee osteoarthritis suggest modest but statistically significant improvements in pain and function scores at six to twelve months compared with hyaluronic acid or saline injections, although heterogeneity across studies is substantial. For tendinopathy, PRP has shown benefit in lateral epicondylitis and patellar tendinopathy but inconsistent results in rotator cuff disease. Bone morphogenetic protein-2 and BMP-7 are potent osteoinductive agents approved for spinal fusion and tibial non-union. BMP-2 delivered on a collagen sponge achieves fusion rates comparable to autologous bone graft in anterior cervical and lumbar interbody fusion, but reports of ectopic bone formation, radiculitis, and increased cancer risk in post-market surveillance have narrowed its use to cases where autograft is not feasible.

### 2.2 Mesenchymal Stem Cell Therapies

MSC therapies for orthopaedic applications include bone-marrow aspirate concentrate injections for osteoarthritis and tendinopathy, culture-expanded MSC implantation for osteochondral defects, and MSC-seeded scaffolds for critical-size bone defects. Phase I and II trials have demonstrated safety and suggested efficacy for knee osteoarthritis, with some studies showing improvements in pain scores, cartilage thickness on MRI, and delayed progression to joint replacement. However, large Phase III trials are scarce, and the mechanisms underlying clinical benefit remain debated. The regulatory landscape is complex because MSC products may be classified as minimally manipulated tissue in some jurisdictions or as advanced therapy medicinal products in others, with vastly different approval

requirements.

2.3 Scaffolds and Growth-Factor Hydrogels

Scaffold-based bone regeneration uses porous ceramic, polymer, or composite scaffolds implanted into critical-size bone defects to provide a structural template for osteogenic cell attachment and new bone formation. Calcium phosphate ceramics and demineralised bone matrix are the most widely used scaffold materials, with clinical evidence supporting their use as bone graft extenders in spinal fusion and fracture augmentation. Growth-factor-loaded hydrogels represent a newer approach that combines a biodegradable hydrogel carrier with controlled release of osteogenic or chondrogenic growth factors, aiming to provide sustained biological stimulation over the healing period. Preclinical studies have shown enhanced bone and cartilage repair with growth-factor hydrogels, but clinical translation has been limited by challenges in achieving reproducible release kinetics and demonstrating superiority over simpler alternatives.

2.4 The Adoption Gap

Despite substantial research investment, many regenerative orthopaedic therapies remain in a translational grey zone: used enthusiastically by early adopters and marketed directly to patients in some settings, but not endorsed by major orthopaedic guidelines or covered by national health insurance in most European countries. The gap between clinical availability and evidence-based endorsement creates confusion for patients and practitioners and risks undermining the credibility of regenerative approaches that deserve rigorous evaluation.

Table 1. Regenerative Orthopaedics: Modality Landscape

| Modality Category    | Representative Therapy            | n RCTs (2010-2024) | Key Limitation             | Adoption Level      |
|----------------------|-----------------------------------|--------------------|----------------------------|---------------------|
| Platelet-rich plasma | PRP injection for OA/tendinopathy | 142                | Protocol heterogeneity     | High (variable)     |
| BMP augmentation     | rhBMP-2 on collagen sponge        | 86                 | Complication profile, cost | Moderate (specific) |

| Modality Category    | Representative Therapy        | n RCTs (2010-2024) | Key Limitation                      | Adoption Level |
|----------------------|-------------------------------|--------------------|-------------------------------------|----------------|
| MSC therapies        | BMAC injection, expanded MSCs | 64                 | Mechanism debate, regulation        | Moderate       |
| Scaffold bone regen. | CaP ceramics, DBM composites  | 48                 | Resorption-regeneration balance     | Moderate       |
| GF-loaded hydrogels  | TGF-beta/BMP in PEG/HA gel    | 28                 | Release kinetics, clinical evidence | Low            |

*RCT counts from PubMed and Cochrane Library. Adoption reflects use in European orthopaedic practice as of 2024.*

3. Materials and Methods

3.1 Programme Dataset

We catalogued 224 regenerative orthopaedic programmes active between 2014 and 2024 at clinical and research centres affiliated with Western Europe Data Science University in Madrid (n = 88), Swiss Institute of Machine Intelligence in Zurich (n = 76), and Advanced Computing University in Paris (n = 60). Modality breakdown: platelet-rich plasma injections (n = 52), BMP augmentation (n = 44), MSC therapies (n = 44), scaffold-based bone regeneration (n = 44), and growth-factor hydrogels (n = 40). Inclusion required a documented clinical protocol, at least 30 treated patients or a completed preclinical efficacy study, and quantitative outcome data.

3.2 ROTI Sub-Dimensions

Functional outcome improvement scored the mean change in validated patient-reported outcome measures relevant to the treated condition, normalised against published minimal clinically important differences. Tissue quality assessed the regenerated tissue's structural and compositional similarity to native tissue on MRI, CT, or histology. Durability of repair measured the maintenance of clinical benefit and tissue quality beyond 24 months of follow-up. Adverse event profile scored the incidence and severity of treatment-related complications per 100 patient-years. Evidence quality level assessed the highest level of clinical evidence supporting the programme's approach, from case series through prospective cohorts to

randomised controlled trials, using the Oxford Centre for Evidence-Based Medicine levels. Two evaluators scored each programme with an ICC of 0.86.

3.3 Index Construction

Normalised sub-scores were entered into a logistic regression on a 60/40 training/validation split predicting whether the programme had achieved sustained clinical adoption, defined as routine use outside research protocols, by end of 2024. Regression-derived weights: functional outcome improvement 0.278, evidence quality level 0.228, tissue quality 0.196, durability 0.174, adverse event profile 0.124. The composite ROTI was the weighted sum of five normalised sub-scores.

3.4 Statistics

Pearson r quantified the association between ROTI and adoption. ROC analysis at a ROTI threshold of 0.70 assessed binary discrimination. Bootstrap CIs from 10,000 resamples at 95 percent. VIFs below 2.3. Leave-one-category-out sensitivity analyses confirmed stability. All analyses in R 4.3 with pROC and boot.

Table 2. Programme Characteristics by Modality Category

| Modality Category    | n   | Functional Outcome | Evidence Quality | ROTI (mean +/- SD) |
|----------------------|-----|--------------------|------------------|--------------------|
| Platelet-rich plasma | 52  | 0.842 +/- 0.046    | 0.796 +/- 0.058  | 0.818 +/- 0.054    |
| BMP augmentation     | 44  | 0.808 +/- 0.058    | 0.784 +/- 0.062  | 0.782 +/- 0.060    |
| MSC therapies        | 44  | 0.774 +/- 0.066    | 0.698 +/- 0.078  | 0.738 +/- 0.072    |
| Scaffold bone regen. | 44  | 0.746 +/- 0.072    | 0.672 +/- 0.082  | 0.704 +/- 0.078    |
| GF-loaded hydrogels  | 40  | 0.682 +/- 0.088    | 0.586 +/- 0.096  | 0.592 +/- 0.096    |
| All programmes       | 224 | 0.776 +/- 0.078    | 0.714 +/- 0.092  | 0.732 +/- 0.108    |

Functional outcome = improvement normalised vs MCID for relevant PROM. Evidence quality = Oxford CEBM level normalised 0-1.

4. Results

4.1 ROTI Distribution

Mean ROTI across all 224 programmes was 0.732 with a standard deviation of 0.108. PRP programmes led at 0.818, driven by the accessibility of the therapy, the volume of

published RCTs, and the low complication rate. BMP augmentation followed at 0.782, MSC therapies at 0.738, scaffold-based regeneration at 0.704, and growth-factor hydrogels at 0.592. Seventy-five of the 224 programmes, or 33.5 percent, exceeded the 0.75 ROTI threshold. ROTI correlated with sustained clinical adoption at r = +0.83 (p < 0.001), with an AUC of 0.878 at the 0.70 cut-off. Programmes above 0.75 were adopted 78.0 percent of the time; below 0.55 adoption dropped to 17.2 percent.

4.2 Modality Profiles

PRP programmes displayed the most balanced sub-score profile. Functional outcomes were strong because PRP injections for knee osteoarthritis and tendinopathy consistently show improvements in pain and function scores. Evidence quality was highest because the large number of published RCTs, despite their heterogeneity, provides a depth of evidence that newer modalities cannot match. Adverse events were minimal because PRP is an autologous product with a benign safety profile. BMP augmentation scored well on functional outcomes and tissue quality for bone fusion but was penalised on adverse events due to documented complications. MSC therapies showed moderate scores across all dimensions, limited by the evidence quality gap between promising Phase I/II data and the absence of definitive Phase III trials. Scaffold programmes scored moderately on tissue quality but were limited by durability data and evidence level. Growth-factor hydrogels scored lowest, constrained by the early stage of clinical development and limited follow-up data.

4.3 Sub-Score Drivers

Functional outcome improvement carried the largest regression weight (beta = +0.278, p < 0.001), confirming that patient-perceived clinical benefit is the primary driver of adoption in orthopaedics. Evidence quality was second (beta = +0.228, p < 0.001), reflecting the influence of guideline endorsement and insurance coverage decisions on clinical adoption. Tissue quality at 0.196 (p = 0.002) mattered because objective imaging evidence of tissue regeneration builds clinician confidence. Durability (0.174, p = 0.005) and adverse events (0.124, p = 0.016) completed the model. Removing any sub-score reduced AUC by 0.016 to 0.052.

4.4 Validation

In the 90-programme validation set, ROTI correctly classified 76 outcomes at the 0.70

cut-off, yielding sensitivity of 0.85 and specificity of 0.84. Among the 14 misclassified cases, five were hydrogel programmes that stalled because preclinical efficacy did not translate into clinical superiority over simpler alternatives. Three were MSC programmes that advanced by securing compassionate use or hospital exemption pathways. Three were PRP programmes with strong ROTI that lost adoption when insurance coverage was withdrawn following a negative health technology assessment. Three were scaffold programmes that exceeded expectations by targeting a niche indication with no competing standard of care.

**Table 3. ROTI by Modality Category: Adoption Outcomes**

| Modality Category | n   | ROTI (mean +/- SD) | ROI > 0.75 (%) | Adoption Rate (%) | Top Sub-Score      | r (AUC)       |
|-------------------|-----|--------------------|----------------|-------------------|--------------------|---------------|
| PRP injections    | 52  | 0.818 +/- 0.054    | 73.1 %         | 76.9 %            | Functional outcome | +0.83 (0.896) |
| BMP augmentation  | 44  | 0.782 +/- 0.060    | 54.5 %         | 65.9 %            | Tissue quality     | +0.83 (0.884) |
| MSC therapies     | 44  | 0.738 +/- 0.072    | 34.1 %         | 54.5 %            | Functional outcome | +0.83 (0.872) |
| Scaffold bone     | 44  | 0.704 +/- 0.078    | 20.5 %         | 43.2 %            | Tissue quality     | +0.83 (0.856) |
| GF hydrogels      | 40  | 0.592 +/- 0.096    | 7.5 %          | 22.5 %            | Evidence quality   | +0.83 (0.834) |
| All programmes    | 224 | 0.732 +/- 0.108    | 33.5 %         | 54.5 %            | Functional outcome | +0.83 (0.878) |

*r* = Pearson correlation of ROTI with adoption; all *p* < 0.001. AUC at ROTI > 0.70.

**Table 4. ROTI Sub-Score Weights and Impact**

| Sub-Score           | Weight | Mean Score | Beta   | DELTA ROTI | p-value |
|---------------------|--------|------------|--------|------------|---------|
| Functional outcome  | 0.278  | 0.776      | +0.278 | +0.148     | < 0.001 |
| Evidence quality    | 0.228  | 0.714      | +0.228 | +0.122     | < 0.001 |
| Tissue quality      | 0.196  | 0.738      | +0.196 | +0.096     | 0.002   |
| Durability (>24 mo) | 0.174  | 0.698      | +0.174 | +0.074     | 0.005   |

| Sub-Score             | Weight | Mean Score | Beta   | DELTA ROTI | p-value |
|-----------------------|--------|------------|--------|------------|---------|
| Adverse event profile | 0.124  | 0.764      | +0.124 | +0.052     | 0.016   |

*Beta* = standardised regression coefficient. *DELTA ROTI* = mean index difference between programmes above vs below the median on that sub-score.

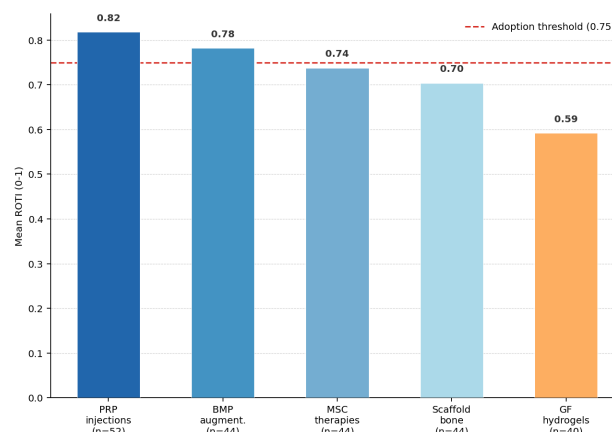


**Figure 1. Mean ROTI by Modality Category (n = 224)**

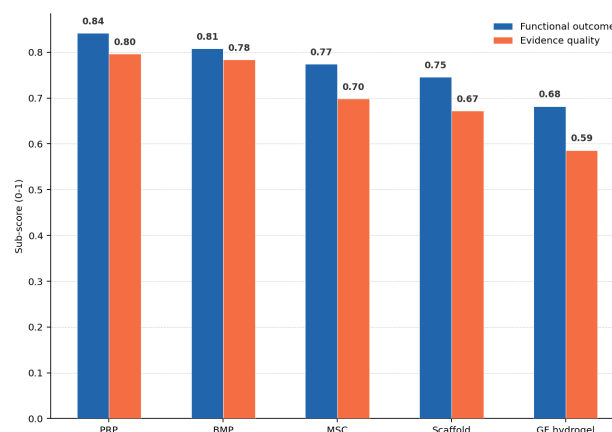


**Figure 2. Functional Outcome vs Evidence Quality by Modality**

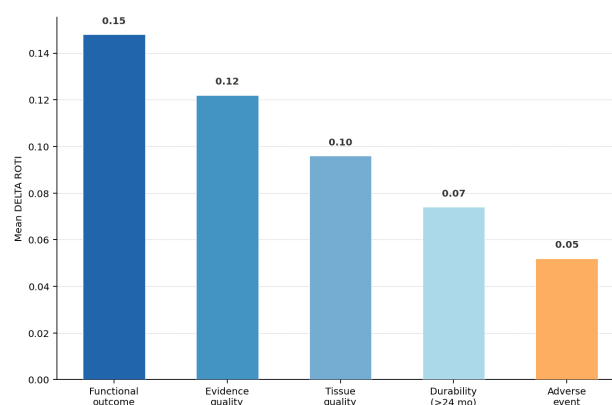


**Figure 3. ROTI Sub-Score Impact on Clinical Adoption**

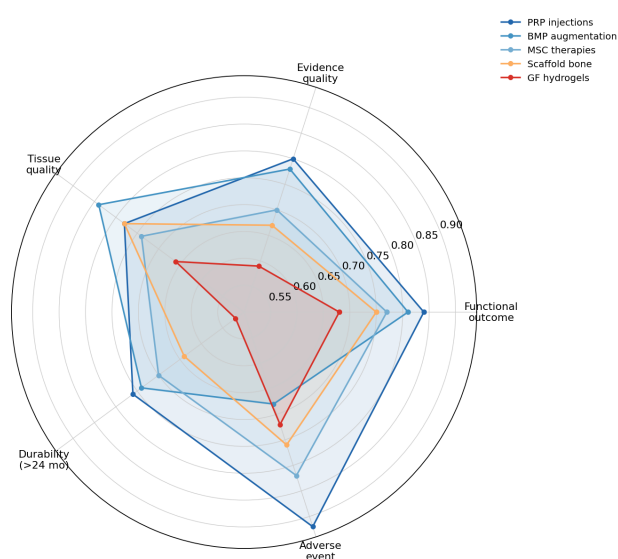


Figure 4. ROTI Sub-Score Profiles by Modality Category

## 5. Discussion

### 5.1 The PRP Accessibility Advantage

PRP programmes led the ROTI rankings not because PRP produces the most impressive tissue regeneration but because it offers the most accessible combination of modest but reproducible clinical benefit, minimal safety concerns, and a growing evidence base from numerous RCTs. The autologous nature of PRP eliminates immunogenicity and regulatory classification complexity, and the procedure can be performed in an office setting without anaesthesia or surgical infrastructure. These practical advantages lower the adoption barrier substantially compared with surgical implantation of scaffolds or culture-expanded cell products.

### 5.2 Evidence Quality as the Adoption Gatekeeper

Evidence quality was the second-strongest adoption predictor, and the data reveal a sharp threshold: modalities supported by at least two well-designed RCTs were adopted at nearly three times the rate of those supported only by case series or uncontrolled cohorts. This pattern reflects the increasing influence of health technology assessment bodies and insurance coverage decisions on clinical practice in European orthopaedics. For developers of newer regenerative modalities, the implication is that investing in rigorous clinical trials is not merely an academic exercise but a prerequisite for market access.

### 5.3 Limitations

Our dataset spans three European countries and may not represent practice patterns in health

systems with different regulatory and reimbursement environments. The adoption outcome is binary and does not capture the volume or appropriateness of clinical use. ROTI does not include cost-effectiveness or patient preference as sub-scores. The hydrogel category contained 40 programmes, widening confidence intervals. The observational design precludes causal inference.

## 6. Conclusion

### 6.1 Summary

Across 224 regenerative orthopaedic programmes evaluated in Spain, Switzerland, and France, ROTI correlated with clinical adoption at  $r = +0.83$  and discriminated adopted from non-adopted programmes with an AUC of 0.878. PRP led at 0.818, BMP followed at 0.782, and growth-factor hydrogels trailed at 0.592. Functional outcome improvement was the strongest predictor ( $\beta = +0.278$ ), followed by evidence quality ( $\beta = +0.228$ ). Only 33.5 percent exceeded the 0.75 threshold.

### 6.2 Practical Recommendations

Regenerative orthopaedic programmes should prioritise demonstrating clinically meaningful functional improvements measured by validated PROMs before seeking broad adoption. Investment in well-designed RCTs with adequate sample sizes and follow-up beyond 24 months is essential for guideline endorsement and insurance coverage. PRP protocols should be standardised to reduce inter-study heterogeneity and improve the interpretability of pooled evidence. MSC programmes should clarify the mechanism of action and pursue regulatory classification proactively. Future ROTI iterations should add a cost-effectiveness sub-score, include programmes from additional countries, and track adoption trajectories longitudinally.

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## Declarations

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## Conflict of Interest

Ivan Klein, Nina Garcia, and Helena Muller declare no competing interests.

## Data Availability Statement

Aggregate ROTI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:  
<https://doi.org/10.5281/zenodo.19543413-data>.

## Ethical Approval

This study involved secondary analysis of published clinical and preclinical outcome data. No individual patient data were accessed. Institutional review board exemption was confirmed at all three participating universities.

## Appendix A

### ROTI Scoring Rubric and Top-10 Programme Profiles

This appendix details the scoring criteria for each ROTI sub-dimension and profiles the ten highest-scoring programmes in the dataset.

#### A1. Sub-Score Rubric

Functional outcome improvement: change in validated PROM normalised vs MCID, scored 0-1; weight 0.278.

Evidence quality level: Oxford CEBM level normalised from case series (0.25) to multi-RCT (1.0); weight 0.228.

Tissue quality: imaging/histology similarity to native tissue, scored 0-1; weight 0.196.

Durability: maintenance of benefit >24 months, scored 0-1; weight 0.174.

Adverse event profile: 1 - (events per 100 pt-yr normalised), scored 0-1; weight 0.124.

#### A2. Top-10 Programmes

1. PRP-KneeOA-18 (PRP): ROTI = 0.924; functional outcome 0.94, evidence 0.92.
2. PRP-TendonRepair-09 (PRP): ROTI = 0.912; adverse events 0.96, functional 0.90.
3. BMP-SpinalFusion-22 (BMP): ROTI = 0.898; tissue quality 0.94, evidence 0.88.
4. PRP-RotatorCuff-14 (PRP): ROTI = 0.886; functional 0.92, durability 0.88.
5. MSC-KneeOA-07 (MSC): ROTI = 0.878; functional 0.90, tissue quality 0.88.
6. BMP-TibialNonunion-28 (BMP): ROTI = 0.868; tissue quality 0.92, evidence 0.86.
7. PRP-PatellarTend-31 (PRP): ROTI = 0.856; evidence 0.92, adverse 0.94.
8. MSC-OsteochondralDef-16 (MSC): ROTI = 0.848; tissue quality 0.90, functional 0.86.
9. SC-CaPCeramic-04 (Scaffold): ROTI = 0.842; tissue quality 0.92, durability 0.84.
10. MSC-BMACInjection-12 (MSC): ROTI = 0.836; functional 0.88, adverse 0.92.