

Editorial

What Counts as Regeneration? Aligning Claims With Evidence in Regenerative Medicine

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Improvement following treatment does not, in itself, establish what has recovered. Pain relief, new matrix formation, and the restoration of tissue function represent distinct outcomes. In regenerative medicine, these distinctions inform the design of subsequent experiments, the interpretation of clinical trials, and patients' expectations. Yet the term "regenerative" can obscure these differences when a therapeutic ambition is presented as an observed outcome.

As the Journal of Translational Regenerative Medicine (JTRM) enters 2027, I propose a simple editorial principle: the strength and scope of any claim of regeneration should be commensurate with the evidence supporting it. Authors should distinguish what an intervention contains, what it changes, and what those changes demonstrate. The guidelines of the International Society for Stem Cell Research (ISSCR) provide a foundation for responsible translation through rigorous evaluation and proportionate oversight [1]. In individual papers, these principles should also guide the wording of conclusions.

Regenerative medicine encompasses the stimulation of endogenous repair, cell delivery, and the use of engineered materials to guide tissue formation [2]. These approaches may yield varying degrees of recovery. When

interpreting claims, it is useful to distinguish the restoration of tissue continuity, which may involve scar formation, from the reconstitution of specific tissue components or architecture. Regeneration may be partial and demonstrated at the cellular or tissue level without establishing recovery of the whole organ. Claims of functional restoration require corresponding functional evidence. Authors should specify the level, extent, and duration of the recovery assessed; complete restoration of an organ to its uninjured state is not a universal requirement for demonstrating regeneration.

In orthopaedics, pain and physical function are essential outcomes, but symptom relief alone does not establish cartilage regeneration. In the RESTORE trial, 288 adults with mild to moderate radiographic knee osteoarthritis received platelet-rich plasma (PRP) or saline injections. At 12 months, the tested PRP regimen showed no statistically significant advantage over saline in pain reduction or change in medial tibial cartilage volume [3]. This trial illustrates the importance of assessing clinical and structural outcomes separately. It neither provides a comprehensive assessment of PRP nor establishes that all PRP preparations have equivalent effects.

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For biomaterials, outcome assessments must distinguish newly formed tissue from the implant itself. Mineral staining requires controls to assess deposition in the absence of cells, while radiopaque scaffolds require methods that distinguish residual scaffold material from newly formed bone. In orthopaedic and maxillofacial reconstruction, evidence of defect filling should be interpreted in conjunction with tissue identity, integration, and the functional demands of the reconstructed site. A load-bearing mandibular reconstruction raises different functional questions from an exploratory study of a calvarial defect. The choice of assessment should therefore be guided by the specific claim and experimental model, rather than by a fixed set of assays.

Product identity is therefore part of the evidence. Reproducibility is difficult to assess when a treatment label implies greater specificity than its characterisation supports. The minimum information for studies evaluating biologics in orthopaedics (MIBO) recommendations address the reporting of PRP and mesenchymal stromal or stem cell interventions in orthopaedics [4]. The minimal information for studies of extracellular vesicles (MISEV2023) guidance provides detailed recommendations on extracellular vesicle nomenclature, separation, characterisation, and functional investigation [5]. Such guidance helps readers determine what was studied and on what basis an observed effect was attributed to it. Adherence to reporting recommendations does not, in itself, establish therapeutic efficacy. A well-characterised preparation may be ineffective, whereas an apparently positive finding obtained with an inadequately described preparation may remain difficult to reproduce.

I suggest that authors explicitly link their principal claim to the measurements supporting it before interpreting their results. Table 1 provides a practical aid by separating questions often subsumed under the adjective “regenerative”. These categories do not constitute a validated scoring system, a consensus standard, or a mandatory sequence through which every study must progress. Mechanistic experiments and clinical trials serve different purposes. Each should address its research question convincingly while identifying the questions that remain unanswered.

The most demanding task is often evaluating the inference drawn from an observation. A change in gene expression may indicate a biological response without establishing the formation of functional tissue. A favourable imaging finding may support structural repair while leaving mechanical competence unresolved. Improved organ function may reflect compensation rather than res-

toration of the injured tissue. When a proposed mechanism is central to the claim, the study design should address plausible competing explanations. When a study is designed to estimate clinical benefit, uncertainty about the mechanism does not necessarily invalidate a reliable estimate of the treatment effect. Confidence in the findings depends on controls that address spontaneous repair, measurement bias, and alternative explanations, together with effect estimates and measures of their uncertainty. Multiple correlated assays do not necessarily provide independent confirmation.

Evidentiary requirements should also be appropriate to the research setting. Animal studies should transparently report randomisation, blinding of outcome assessment, the experimental unit, and the justification for sample size. The animal research: Reporting of in vivo experiments (ARRIVE) 2.0 guidelines provide a foundation for such reporting [6]. The choice of species, injury model, and follow-up duration should be justified in relation to the research question. In human studies, tissue sampling solely to substantiate a mechanistic claim may not be ethically justified. Appropriate imaging and functional assessments can provide valuable evidence, but their limitations should be explicitly acknowledged. Uncertainty should limit the scope of the conclusion rather than prompt an ethically unnecessary procedure.

The duration of follow-up determines what can reasonably be claimed. An early biological response does not establish whether an effect persists after treatment cessation, following scaffold degradation, or under sustained mechanical loading. Follow-up duration should therefore reflect the proposed mode of action and clinically relevant modes of failure. The same principle applies to safety: the absence of observed adverse events in a small, short-term study provides limited evidence about uncommon or delayed harms. Transparent reporting in accordance with the consolidated standards of reporting trials (CONSORT) 2025 guidelines helps readers assess trial methods and findings, but no reporting checklist can compensate for a study design that cannot address the research question [7].

A claim of readiness for clinical use raises further questions about manufacturing reproducibility, delivery, and comparison with existing care. An intervention that is effective under tightly controlled experimental conditions still requires evidence that its essential properties can be maintained as production processes and conditions of use change. For implants, the surgical procedure and rehabilitation may contribute substantially to the observed outcomes and should be accounted for when selecting

Table 1. Matching claims to evidence

Claim	Evidence to Examine	Inference Still Requiring Support
Biological activity	Defined preparation; relevant assay; suitable controls; reproducible response.	Formation of functional tissue or benefit in patients.
Structural repair or partial regeneration	Tissue identity, quantity and organization; integration; distinction from residual material.	Restoration of tissue-specific function and durability.
Regeneration with functional restoration	Convergent structural and functional evidence; relevant loading or physiological demand; persistence.	Clinical benefit in a different population or setting.
Clinical benefit	Credible comparison; patient-relevant outcomes; effect estimates and uncertainty; harms and follow-up.	A regenerative mechanism unless independently examined.
Readiness for clinical use	Reproducible manufacture and delivery; appropriate clinical evidence; applicable regulatory requirements.	Transferability across products, indications or production changes.

comparators and interpreting treatment effects. The call to standardise clinical studies of synthetic matrices for rotator cuff tears highlights how differences in control groups and follow-up can limit interpretation even within a specific application [8]. Translation requires continuity between the intervention evaluated and the intervention intended for clinical use.

Developmental biology introduces a further distinction: tissue identity and developmental maturity are separate considerations. Kidney organoid research has identified maturation and vascularisation as important translational challenges [9]. Cardiac organoid studies likewise assess maturation using molecular, metabolic, and contractile measures [10]. A nephron-like structure or a contracting construct may serve as an informative experimental model without demonstrating the capacity to replace adult kidney or heart function. Skin provides another example: wound closure and the restoration of skin appendages represent distinct aspects of recovery [11]. These distinctions inform tissue-specific questions for reviewers, including questions about barrier function in skin and physiological integration in cardiac or renal constructs. The assessments required should reflect the claim; an individual study need not establish every property of an intact organ.

Editorial practice can help maintain these distinctions. For JTRM, I propose that manuscript assessment begin by identifying the principal claim in the title and abstract, then examining whether the study design and measured outcomes support it. Reviewers should identify specific inferences that exceed the evidence and, where possible, recommend more narrowly framed conclusions. A carefully conducted feasibility study may merit publication on its own terms. A study with negative findings may be particularly valuable when it provides a convincing answer to a well-founded research question. Neither should require exaggerated claims of clinical applicability to attract attention.

This approach also shapes how findings are communicated beyond the paper. A carefully qualified discussion offers limited protection against misinterpretation if the title, graphical abstract, or plain language summary implies that tissue restoration has been demonstrated. The distinctions among biological activity, structural change, and patient benefit should be preserved at every stage of communication. Maintaining these distinctions is a scientific responsibility shared by authors and journals, particularly when the language used to describe an intervention may shape treatment expectations.

For JTRM in 2027, the practical aim should be to publish a body of work in which readers can identify what has been restored, how strong the supporting evidence is, and which questions remain unanswered. This approach accommodates exploratory biology, rigorous studies with negative findings, and therapies whose clinical benefits are better established than their mechanisms of action. It also provides subsequent investigators with a sound basis for deciding what to test next. The journal's contribution will depend on how consistently and accurately these distinctions are maintained across the papers it publishes.

This author-proposed interpretive aid is neither a validated scoring system nor a consensus standard. Measurements should be tailored to the tissue, intervention, experimental model, and study objectives. Relevant methodological guidance is provided in references [1, 2, 4–11].

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