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Review Article

Whose Clinical Reality Is Represented in Periodontal Regeneration Trials? A Systematic Methodological Review of Eligibility Restrictions, Maintenance Requirements, and Geographic Representation in the Evidence Base

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ABSTRACT

Periodontal-regeneration trials are usually interpreted through treatment effects, defect fill, clinical attachment gain, and long-term tooth retention. Less attention is paid to the clinical populations and care environments from which those estimates arise. This review examined geographic representation, eligibility restrictions, pretreatment requirements, and maintenance conditions in contemporary periodontal-regeneration trials. A systematic methodological review was conducted with PRISMA 2020 reporting. Reproducible PubMed-indexed search routes covering 2017 through 20 October 2026 were used to identify comparative human clinical reports involving periodontal intrabony defects. Extraction focused on country and setting, periodontal and defect phenotype, systemic-health and smoking restrictions, oral-hygiene and pretreatment requirements, supportive periodontal care, follow-up, and reporting completeness. Applicability was assessed descriptively rather than converted into a numerical generalizability score. Thirty unique candidate records were screened, 22 reports were assessed in full, and 20 reports fulfilled the review criteria. Eleven included reports originated in Europe, seven in Asia, and two in Africa; none originated in the Americas or Oceania. India and Italy together accounted for 11 of 20 reports. The included literature combined substantial therapeutic diversity with recurrent selection of clinically stabilized, closely monitored patients and narrowly defined periodontal defects. The contemporary periodontal-regeneration evidence base represents important but bounded clinical realities. Geographic concentration, phenotype restrictions, pretreatment stabilization, and continuing professional maintenance must therefore be considered when trial results are transferred to patients and care settings that differ from the populations in which regenerative outcomes were established.

Keywords: Periodontal regeneration, Intrabony defects, External validity, Clinical-trial eligibility, Geographic representation, Supportive periodontal care

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Introduction

Periodontal regeneration is practiced within a disease spectrum that varies substantially in severity, complexity, progression risk, tooth prognosis, systemic context, and ability to sustain long-term periodontal stability. Contemporary staging and grading were explicitly designed to capture dimensions of severity,

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complexity, and progression that cannot be reduced to a single periodontal measurement [1]. The current periodontitis case definition likewise recognizes disease as a clinical entity with heterogeneous manifestations rather than a uniform biological state [2]. Treatment recommendations consequently position regenerative procedures within a broader sequence of infection control, risk-factor management, treatment of residual pockets and defects, and supportive periodontal care [3]. These distinctions matter for interpretation of trials because a technically successful regenerative intervention is not automatically evidence that the same outcome will occur in patients who enter care with different disease burdens, systemic conditions, behavioral exposures, defect characteristics, or capacities to maintain periodontal stability.

Representation in a clinical trial extends beyond the demographic composition of the sample. Contemporary work on equity, diversity, and inclusion in clinical research emphasizes that representation can involve demographic characteristics, disease burden, comorbidity, access to specialist services, socioeconomic circumstances, geography, and other determinants of who can realistically enter and complete a trial [4]. More generally, analyses of randomized trials have shown that strong internal validity does not guarantee close correspondence between enrolled populations and the broader populations for whom the results may later be considered [5]. Transportability therefore concerns the relationship between a trial's source population and an explicitly defined target population, not simply whether a treatment produced a statistically or clinically favorable result in the original study [6]. Recent methodological work has accordingly argued for more systematic characterization of trial diversity instead of treating representativeness as a single demographic attribute [7]. Reporting itself imposes a further limit: important population characteristics can be incompletely recorded or communicated, and geographic location cannot legitimately be substituted for unreported ethnicity or other patient characteristics [8].

These issues are particularly important in periodontal regeneration. Trials may require completion of nonsurgical periodontal therapy before enrollment, adequate plaque control, low bleeding scores, absence or control of systemic disease, restrictions on smoking, anatomically defined intrabony defects, teeth judged maintainable, and willingness to participate in repeated postoperative and supportive-care visits. Each requirement can be scientifically and clinically defensible. Collectively, however, they define the clinical reality in which the treatment effect was observed. A favorable outcome obtained after careful stabilization in a specialist environment does not establish failure outside that environment, but neither does it establish unchanged effectiveness in patients who would not have qualified for the trial.

The geographic structure of the evidence raises a related problem. Differences between countries can reflect variation in referral pathways, specialist availability, periodontal disease burden, financing, access to tooth-preserving therapy, patient behavior, and maintenance capacity. Country is therefore not a biological exposure and should not be used as a proxy for ethnicity or treatment quality. Geographic concentration is nevertheless methodologically relevant when a treatment literature is repeatedly generated within a limited set of health systems or specialist centres. In that situation, the evidence may be internally persuasive while leaving uncertainty about populations and service configurations that are rarely studied.

The objective of this systematic methodological review was consequently not to rerank regenerative materials or estimate a new pooled treatment effect. It was to determine whose clinical circumstances are represented in the contemporary periodontal-regeneration trial literature by examining the geographic distribution of eligible reports, the population and defect restrictions used to select participants, and the pretreatment and maintenance conditions under which outcomes were observed. The central interpretive question was whether restrictions necessary for rigorous regenerative trials also create identifiable boundaries around the clinical settings to which their results can be transferred with confidence.

Materials and Methods

This review was conducted as a systematic methodological review with reporting organized according to PRISMA 2020 [9]. PRISMA explanation and elaboration guidance was additionally used to maintain explicit separation among record identification, screening, report assessment, exclusions, and the final set of included evidence reports [10]. The methodological target was the architecture of the evidence base—who was studied, where studies were conducted, which clinical states were accepted or excluded, and which maintenance conditions surrounded the intervention—rather than comparative estimation of the efficacy of a particular regenerative material.

The search was executed on 20 October 2026 through reproducible PubMed-indexed retrieval routes. The principal 2017–2023 route used the logic periodontal intrabony randomized clinical trial 2017 2018 2019 2020 2021 2022 2023, supplemented by targeted searches combining periodontal regeneration and randomized clinical trials with inclusion criteria, plaque control, smoking, diabetes, intrabony defects, supportive periodontal care, and maintenance. The update route for 2024 through 20 October 2026 combined intrabony defects or infrabony defects with periodontal treatment and randomized, randomised, or prospective clinical designs. Searches were deliberately not restricted by journal quartile. Q1 status governed the separate manuscript-reference policy, not eligibility of primary evidence.

Candidate reports were eligible when they described human comparative interventional clinical evidence, randomized trials, or eligible follow-up reports of randomized treatment involving periodontal intrabony or infrabony defects and contained extractable information relevant to the methodological review question. Eligible publications had to fall within 2017 through 20 October 2026. Reports were excluded from the primary evidence corpus when they predated the time window, were systematic or meta-analytic reviews, were protocols without clinical results, were single-arm reports that did not satisfy the comparative design requirement, or were prospective cohorts insufficiently compatible with the predefined comparative evidence unit. Reviews, clinical guidelines, classification papers, and research-on-research studies could nevertheless contribute to methodological interpretation without being counted as included primary evidence.

The choice of extraction domains also reflected documented reporting limitations in oral-health trials. Recent meta-research has shown that registration, data-sharing, and other transparency practices remain variable across randomized oral-health studies [11]. Outcome-reporting discrepancies are a distinct concern in dental randomized trials and require attention to what was prespecified and what was ultimately reported [12]. Broader evaluation of dental randomized trials has similarly identified incomplete adoption of transparency practices [13]. Reporting of trial limitations is also sufficiently inconsistent that absence of a stated external-validity limitation cannot safely be interpreted as evidence that no such limitation exists [14]. For this reason, a missing trial characteristic was coded as not reported rather than inferred from the country, intervention, eligibility wording, or clinical setting.

Contextual evidence was used to ensure that the methodological review remained anchored in the contemporary regenerative literature. Recent network meta-analysis demonstrates the continued breadth of biomaterials studied for periodontal intrabony defects [15]. Systematic synthesis of biologic agents used alone or with graft materials confirms that treatment comparisons occur across heterogeneous combinations of regenerative procedures [16]. Long-term reviews demonstrate the importance of outcome duration when judging periodontal regeneration rather than relying exclusively on early clinical change [17]. Patient-reported outcomes and health-economic evidence form a separate dimension that is not interchangeable with probing-depth or attachment-level outcomes [18]. Contemporary synthesis of nonsurgical treatment for intrabony defects also reinforces that regenerative and defect-management evidence spans more than one procedural pathway and may depend on the time at which clinical re-evaluation occurs [19].

The extraction framework recorded country and clinical setting; study design; disease and defect definitions; age criteria; smoking restrictions; systemic-health criteria; plaque, bleeding, and oral-hygiene prerequisites; pretreatment periodontal therapy; criteria used to determine readiness for surgery or other intervention; intervention and comparator; supportive periodontal-care requirements; follow-up; attrition where reported; clinical, radiographic, patient-reported, or economic endpoints; and explicit discussion of limitations and external applicability. Treatment-effect magnitude was extracted only where required for understanding the methodological context; the review did not calculate a new pooled effect.

Applicability was evaluated through structured domains rather than a numerical score. The appraisal distinguished geographic concentration, recruitment environment, periodontal and defect phenotype, systemic-health restrictions, smoking criteria, oral-hygiene readiness, pretreatment stabilization, supportive-care intensity, outcome horizon, and completeness of applicability reporting. Restriction itself was not classified as methodological failure. A criterion could strengthen internal validity, improve safety, or isolate a clinically meaningful phenotype while simultaneously narrowing the range of patients directly represented by the resulting estimate.

The distinction between these functions is summarized in **Table 1**. The table is intended to prevent clinical eligibility, reporting adequacy, and external applicability from being collapsed into a single judgment.

Table 1. Methodological domains used to distinguish periodontal-regeneration trial eligibility, care-context intensity, and external applicability

Assessment domain	What was extracted from each eligible report	Methodological question addressed	Interpretation rule used in this review
Geographic origin	Country and, where available, number/type of recruiting centres	Where was the evidence generated?	Country indicates study location, not ethnicity or treatment quality
Clinical setting	University, specialist, private, hospital or multicentre environment where reported	What service infrastructure surrounded treatment?	Specialist intensity may affect replicability but is not itself evidence of bias
Periodontal phenotype	Diagnostic terminology, stage/severity and treated periodontal condition	Which disease states entered the evidence base?	Findings are assigned to the studied phenotype unless broader inclusion is demonstrated
Defect morphology	Intrabony configuration, tooth/site restrictions and defect-related eligibility	Which anatomical situations were selected?	Anatomical selection defines the direct defect-level evidence boundary
Systemic-health criteria	Diabetes, uncontrolled disease and other medical exclusions or restrictions	Which medically complex patients were represented?	Unreported conditions are not presumed absent
Smoking criteria	Current/former smoking restrictions and exposure definitions where reported	Were common behavioral risk profiles represented?	Restriction does not prove effect modification; it limits direct representation
Oral-hygiene readiness	Plaque, bleeding, compliance or hygiene prerequisites	Did participants need to reach a controlled oral environment before treatment?	Pretreatment readiness is part of the observed care context
Periodontal stabilization	Completion and response to nonsurgical periodontal therapy before definitive intervention	Was regeneration evaluated only after initial disease control?	Stabilization is separated from the regenerative procedure itself
Maintenance exposure	Supportive periodontal-care schedule, recall and adherence where reported	What continuing professional care surrounded follow-up?	Long-term outcome is interpreted within the maintenance environment actually provided
Outcome horizon	Follow-up duration and type of clinical, radiographic, survival, patient-reported or economic outcome	What meaning can legitimately be assigned to the endpoint?	Early surrogate improvement is not treated as equivalent to long-term tooth retention or patient benefit
Applicability reporting	Explicit discussion of eligibility, setting, adherence, limitations and generalizability	Can the trial's source population be reconstructed?	Missing reporting is coded as not reported, not as proof that a factor was absent

Records were deduplicated using normalized titles together with DOI and PMID information where available. Screening then proceeded from title/abstract assessment to report-level eligibility assessment. Thirty unique candidate records entered screening. Eight were excluded at title/abstract level: four predated the eligibility window, three were systematic reviews rather than primary evidence reports, and one was a protocol without eligible clinical results. Twenty-two reports were sought and retrieved. Two were excluded at full-report assessment because their designs did not meet the locked comparative evidence-unit definition: one was a single-arm/non-comparative prospective report and one was a prospective cohort that was insufficiently compatible with the predefined comparative design. Twenty reports therefore entered the methodological synthesis.

The resulting selection sequence is shown in **Figure 1**.

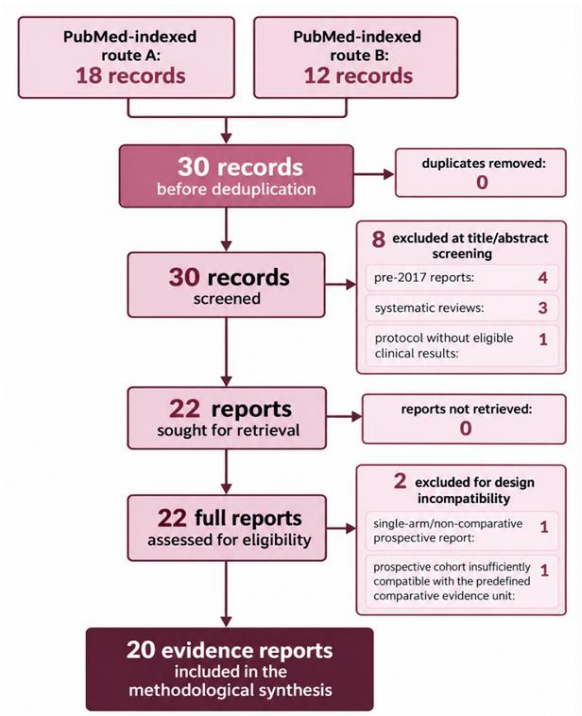


Figure 1. Verified identification and selection of periodontal-regeneration evidence reports

Results and Discussion

Characteristics and geographic distribution of trials

The executed search identified a geographically diverse but uneven evidence corpus. Twenty comparative reports met the methodological eligibility criteria. Eleven reports originated in Europe, seven in Asia, and two in Africa. No eligible report in the executed corpus originated in the Americas or Oceania. At country level, India contributed six reports and Italy five, meaning that these two countries alone accounted for 11 of the 20 included reports. Egypt and Hungary each contributed two reports, while China, the United Kingdom, Greece, Germany, and Spain each contributed one. These counts describe the location of included study reports and cannot be interpreted as estimates of the geographic distribution of periodontal disease, regenerative treatment capacity, investigator activity, or patient ethnicity.

The contemporary Q1-citable trials illustrate the heterogeneity hidden within those country counts. An Italian randomized trial evaluated a flapless approach with and without enamel matrix derivative in intrabony defects [20]. A Hungarian randomized investigation examined periodontal-regenerative treatment in relation to subsequent orthodontic tooth movement, representing an integrated periodontal–orthodontic care context rather than an isolated surgical comparison [21]. A Spanish randomized trial compared cross-linked hyaluronic acid with enamel matrix derivative over 18 months [22]. A recent Indian randomized study combined minimally invasive flap treatment with low-level laser therapy and incorporated clinical, radiographic, and molecular evaluation [23]. Egyptian randomized evidence included injectable platelet-rich fibrin with demineralized freeze-dried bone allograft in patients with Stage III periodontitis [24]. The geographic label therefore identifies only one layer of variation; intervention strategy, defect morphology, treatment sequence, technology, follow-up, and entry criteria also differ materially among studies.

The European reports were themselves concentrated in a limited number of countries and specialist research environments. Italy was the single largest European contributor in the included corpus, followed by Hungary and one report each from Spain, the United Kingdom, Greece, and Germany. The Asian evidence was dominated by India, with one additional Chinese report. The African evidence consisted of two Egyptian reports. Accordingly, apparent continental breadth did not equate to even distribution within continents. The absence of eligible reports from the Americas and Oceania in the executed corpus should be interpreted as an evidence-coverage observation, not as evidence that regenerative therapy performs differently in those regions.

Another characteristic of the corpus was that geographic diversity coexisted with substantial procedural diversity. Included evidence covered conventional regenerative surgery, minimally invasive and modified minimally invasive approaches, enamel

matrix derivatives, platelet concentrates, bone substitutes, locally delivered adjuncts, and combined periodontal–orthodontic treatment. This heterogeneity made the corpus suitable for examining how regenerative research selects patients and care conditions across different therapeutic approaches, but it did not justify pooling the studies into a single treatment-effect estimate. A material, laser, biologic adjunct, or surgical design can introduce its own selection requirements and implementation demands, complicating any attempt to attribute external-validity limitations solely to national geography.

Study duration also varied. Some reports evaluated comparatively short clinical or radiographic follow-up, whereas others were extensions of earlier randomized cohorts with long-term assessment. The distinction is methodologically important because a population that remains in intensive specialist follow-up for many years represents a different observation environment from a patient seen only through an early healing interval. Similarly, long-term retention of a treated tooth, recurrent periodontitis, economic burden, and patient experience are not interchangeable with short-horizon changes in probing depth, attachment level, or radiographic defect measures.

The distribution of the 20 reports is summarized in **Table 2**. To avoid overstating information unavailable from individual reports, the table presents geographic counts and broad methodological characteristics rather than inferring ethnicity, socioeconomic position, national treatment patterns, or population disease burden.

Table 2. Geographic distribution and design characteristics of the 20 included periodontal-regeneration reports

Country / geographic grouping	Included reports	Share of review corpus	Broad characteristics represented in the included evidence	Representativeness implication
Italy	5	25%	Regenerative surgery, minimally invasive approaches, biomaterial comparisons and long-term randomized follow-up	Strong contribution from specialist Italian cohorts means a substantial fraction of long-horizon evidence arises from one national research environment
India	6	30%	Multiple randomized regenerative and adjunctive approaches, including platelet concentrates, local agents and minimally invasive treatment	Largest national contribution; increases Asian representation but does not by itself represent the diversity of Asian periodontal populations or systems
Egypt	2	10%	Comparative regenerative studies including Stage III and biomaterial/platelet-concentrate approaches	Provides African representation, but only through one country and selected clinical cohorts
Hungary	2	10%	Regenerative comparison and combined periodontal–orthodontic treatment	Adds a distinctive interdisciplinary setting but remains a limited national sample
China	1	5%	Comparative regenerative treatment of intrabony defects	Single-report representation prevents broad inference to Chinese or East Asian care
United Kingdom	1	5%	Minimally invasive nonsurgical/surgical treatment pathway	Contributes a different management pathway but only one included report
Greece	1	5%	Minimally invasive periodontal treatment with adjunctive regenerative therapy	Single-setting evidence contributes methodological diversity without geographic depth
Germany	1	5%	Long-term comparative periodontal follow-up	Long-horizon evidence is informative but based on one national contribution
Spain	1	5%	Randomized comparison of regenerative biologic approaches	Adds contemporary European evidence but not sufficient for national generalization
Europe	11	55%	Six represented countries with marked concentration in Italy	Majority of the corpus derives from European clinical environments
Asia	7	35%	Predominantly Indian reports, with one Chinese report	Continental total masks strong within-region concentration

Africa	2	10%	Both reports from Egypt	Evidence presence should not be equated with continent-wide representation
Americas	0	0%	No eligible report in the executed corpus	No direct geographic representation in this review corpus
Oceania	0	0%	No eligible report in the executed corpus	No direct geographic representation in this review corpus

The geographic findings therefore identify a first boundary around the evidence base: periodontal-regeneration trials are not confined to one country or continent, but neither are they distributed in a way that mirrors the full range of populations and health systems in which periodontal treatment is delivered. Geographic concentration alone cannot determine whether an intervention is transportable. Its significance depends on what kinds of patients were allowed to enter these trials, what degree of periodontal stability was required before intervention, and what professional maintenance surrounded the reported outcomes. Those eligibility and maintenance conditions form the next level of the review.

Eligibility restrictions and maintenance requirements

The included evidence did not describe a clinically unrestricted population entering regenerative treatment. Eligibility was typically constructed around patients and teeth that had already crossed several thresholds of clinical suitability. These restrictions operated at different levels: the patient had to be sufficiently healthy and behaviorally able to participate; periodontitis generally had to undergo initial control; the tooth had to remain strategically and technically maintainable; and the defect had to possess anatomical characteristics compatible with the procedure under investigation. The resulting evidence therefore concerns regenerative therapy delivered after a process of clinical selection rather than all patients presenting with advanced periodontal destruction.

This distinction is especially visible in long-term studies of severely compromised teeth. A randomized trial comparing periodontal regeneration with extraction followed by prosthetic or implant replacement demonstrated that teeth with extensive attachment loss can be investigated within a tooth-preserving strategy when they are judged treatable and are managed in a structured specialist environment [25]. The result should not be converted into a universal retain-versus-extract rule, because the population had already been selected for participation in a demanding longitudinal protocol. The trial establishes that severe baseline compromise does not necessarily preclude a regenerative approach; it does not establish that every tooth with comparable attachment loss has equivalent prognosis under different anatomical, patient, operator, or maintenance conditions.

Long-term follow-up further illustrates the importance of the surrounding care environment. Twenty-year randomized evidence comparing regenerative treatment with access-flap surgery was generated among patients who remained within extended supportive periodontal care [26]. Similarly, 10-year follow-up after a modified minimally invasive surgical approach evaluated tooth retention, recurrence, and costs in a highly managed cohort rather than separating the surgical event from subsequent periodontal maintenance [27]. These reports are particularly valuable because they move beyond short-horizon surrogate improvement, but their durability estimates remain observations of regeneration embedded in prolonged professional follow-up.

Treatment-specific eligibility adds another layer of selection. A randomized non-inferiority comparison of leukocyte- and platelet-rich fibrin plus autogenous bone with enamel matrix derivative plus autogenous bone evaluated two regenerative strategies in patients and defects suitable for both procedures [28]. Such comparisons provide clinically important information within the defined source population. They do not determine how either strategy performs in individuals excluded because of systemic disease, smoking behavior, poor plaque control, inability to attend follow-up, unfavorable defect morphology, or other conditions that differ from the enrolled population.

Across the 20-report corpus, smoking, systemic-health status, oral-hygiene requirements, prior periodontal treatment, and defect morphology were therefore treated as applicability variables rather than as interchangeable markers of study quality. The reporting of these variables was not uniform enough to support a defensible numerical “representativeness score.” When a report did not permit reliable reconstruction of a criterion, it remained classified as not reported. This approach is important because failure to report a smoking restriction, for example, cannot establish that unrestricted smokers were enrolled, just as a trial conducted in one country cannot establish the ethnicity or socioeconomic profile of its participants.

Pretreatment periodontal therapy was especially relevant. Regenerative procedures are commonly positioned after initial control of periodontal inflammation, and the trials reviewed frequently investigated patients who had already completed nonsurgical therapy or otherwise demonstrated suitability for a definitive regenerative intervention. This creates a clinically meaningful distinction between the population seeking periodontal care and the population actually entering a regenerative trial. Patients unable to achieve comparable plaque control, clinical stability, attendance, or behavioral adherence may be poorly represented even when their underlying defect morphology would otherwise appear technically eligible.

Maintenance introduces a similar distinction after treatment. Supportive periodontal care, professional reassessment, reinforcement of self-care, and management of recurrent inflammation become part of the environment in which longer-term outcomes are observed. A trial may be designed to test a surgical or biomaterial intervention, but its long-term outcome is generated by the combined exposure of the intervention, baseline selection, postoperative care, and continued periodontal maintenance. The studies did not provide a basis for isolating a universal independent effect of maintenance intensity, yet they clearly caution against interpreting long-term regenerative outcomes as properties of the operative procedure alone.

The principal eligibility and care-context boundaries are summarized in **Table 3**. The table reports methodological meaning rather than assigning numerical penalties to restrictive criteria.

Table 3. Population restrictions, pretreatment conditions, and maintenance features defining the clinical population represented by periodontal-regeneration trials

Selection or care-context domain	Pattern identified in the evidence base	Clinical population most directly represented	Population or setting for which transfer becomes less certain	Interpretation boundary
Periodontal diagnosis and severity	Enrollment centered on patients with defined periodontitis and treatable residual intrabony defects	Patients whose disease state matches the reported diagnostic and treatment stage	Patients with substantially different disease severity, instability, or untreated inflammatory burden	Disease classification alone does not predict regenerative response
Tooth prognosis	Teeth were selected because regenerative treatment remained technically and strategically plausible	Compromised but maintainable teeth	Teeth with conditions making retention unrealistic or technically inappropriate	Trial eligibility should not be converted into a universal tooth-retention rule
Intrabony-defect morphology	Anatomically defined defects were commonly required	Defects corresponding to the morphology investigated in each procedure	Defects with different containment, configuration, accessibility, or supporting anatomy	Procedure-specific findings remain bounded by studied morphology
Systemic health	Trials commonly used medical eligibility criteria and excluded or restricted relevant systemic conditions	Medically eligible or sufficiently controlled patients	Patients with poorly controlled or unrepresented systemic disease	Exclusion identifies an evidence gap, not proof of treatment failure
Smoking	Smoking status was frequently restricted, stratified, or clinically relevant, although reporting was not uniform	Nonsmokers or smoking profiles explicitly admitted by the study	Smoking exposures not represented by the eligibility criteria	Restriction does not establish the magnitude of smoking-related effect modification
Oral hygiene	Adequate plaque control and clinical cooperation commonly formed part of readiness for regenerative treatment	Patients capable of achieving and maintaining the required oral-hygiene standard	Patients unable to reach comparable plaque control or adherence	Trial outcomes should be interpreted within the achieved hygiene environment
Initial periodontal therapy	Definitive regenerative treatment commonly followed nonsurgical therapy and reassessment	Patients who remain with a treatable residual defect after initial disease control	Patients who have not completed or responded sufficiently to initial therapy	Pretreatment response contributes to selection before regeneration

Attendance and adherence	Repeated follow-up and professional review were intrinsic to many protocols	Patients able and willing to remain in structured care	Populations with unstable attendance, access barriers, or discontinuity of care	Protocol adherence forms part of the trial context
Supportive periodontal care	Longer-horizon studies embedded treatment in continuing maintenance	Patients retained in professional supportive care	Settings with limited maintenance availability or continuity	Long-term outcomes cannot automatically be separated from the care environment
Follow-up horizon	Evidence ranged from short clinical follow-up to 10- and 20-year observation	Patients represented at the specific reported time horizon	Patients/settings for which only short-term or only long-term extrapolation is attempted	Early clinical change, tooth retention, recurrence, costs, and patient benefit are distinct outcomes
Reporting completeness	Some clinically important applicability variables were incompletely described	Characteristics explicitly documented in the trial report	Any unreported demographic, behavioral, systemic, or care variable	"Not reported" must not be converted into assumed inclusion or exclusion

Taken together, these patterns show that periodontal-regeneration trials frequently evaluate an already filtered clinical population. The evidence is therefore highly informative about whether regeneration can succeed under defined clinical circumstances, while being less direct about what happens when the same procedure is transferred to patients who differ from those circumstances.

Representativeness and external validity

The principal finding of this review is not that periodontal-regeneration trials lack clinical relevance. It is that their clinical relevance has boundaries that are often less visible than the treatment effect itself. The 20-report review corpus contained meaningful variation in procedures, follow-up, countries, and clinical strategies, yet much of the evidence was generated among selected patients treated in environments capable of delivering structured periodontal therapy and follow-up. External validity therefore depends on both who entered the trial and what system of care surrounded the intervention.

This point is reinforced by contemporary treatment pathways that extend beyond conventional regenerative surgery. A prospective multicentre investigation of minimally invasive nonsurgical periodontal treatment illustrates that intrabony-defect management can be studied across more than one centre while still requiring defined diagnostic, operator, and follow-up conditions [29]. Randomized evidence using adjunctive cross-linked hyaluronic acid during nonsurgical management likewise concerns a restricted defect and treatment context rather than all periodontal defects [30]. Endoscopic re-instrumentation compared with papilla-preservation surgery introduces an additional dependency on technology, expertise, and service configuration [31]. These studies show why transportability cannot be determined from the intervention name alone.

The same problem applies to geographical interpretation. A contemporary Chinese randomized study of isolated interdental intrabony defects evaluated modified minimally invasive surgery with or without a collagen-enriched xenograft [32]. Turkish randomized evidence has examined locally applied hyaluronic acid alongside minimally invasive nonsurgical treatment [33]. Such studies extend the range of national settings represented in the wider literature, but they also reinforce the importance of defect-level and intervention-level selection. A country becomes more visible in the literature without necessarily broadening representation of systemic illness, smoking, poor maintenance access, severe behavioral risk, or other populations excluded within that country.

The review corpus has an additional coverage limitation. The 20-report corpus contained no study assigned to the Americas. However, the contextual bibliography contains a multicentre United States randomized comparison of an Er,Cr laser approach with minimally invasive surgery [34]. Its existence means that the absence of an American report from the executed 20-report corpus cannot be interpreted as evidence that no relevant American periodontal trial existed during the eligibility window. It instead exposes a coverage limitation of the executed PubMed-indexed search routes. Inclusion of this additional report would require repeating identification, screening, deduplication, and all downstream arithmetic. Consequently, all geographic proportions in this review must be read as distributions of the executed review set, not as a census of every periodontal-regeneration trial published worldwide.

That qualification does not eliminate the methodological question. It strengthens it. Even when the broader literature contains additional countries and interventions, the presence of one study in a location does not establish population representativeness. A trial of melatonin and chitosan-loaded nanoparticles in periodontal intrabony defects, for example, adds information about a novel intervention and clinical setting [35], while providing only the population information that its own eligibility and reporting permit. Long-term retrospective evaluation of previously regenerated defects can complement randomized evidence by showing outcomes beyond the controlled trial horizon, but retrospective selection and survivor effects limit causal interpretation [36]. Similarly, comparisons involving platelet-rich fibrin, concentrated growth factors, and autogenous bone expand the therapeutic literature without establishing that the patients recruited for those comparisons represent all candidates for periodontal regeneration [37].

A 24-month randomized trial using a single-flap approach with either hyaluronic acid or enamel matrix derivative provides a useful illustration of the central interpretive problem [38]. The trial can directly inform the comparison it was designed to study within its enrolled patients, defect characteristics, operator setting, and follow-up conditions. The inferential distance becomes greater when the result is transferred to a patient with a different anatomical defect, uncontrolled systemic condition, persistent high-risk behavior, limited ability to maintain oral hygiene, or poor access to supportive periodontal care. None of these differences proves that the treatment will fail. They simply identify questions that the original trial did not directly answer.

Figure 2 integrates these findings as a conditional evidence-applicability landscape. Its central premise is that applicability is constrained simultaneously by geography, patient eligibility, periodontal readiness, defect selection, maintenance capacity, and reporting completeness; no single domain acts as a universal pass–fail criterion.

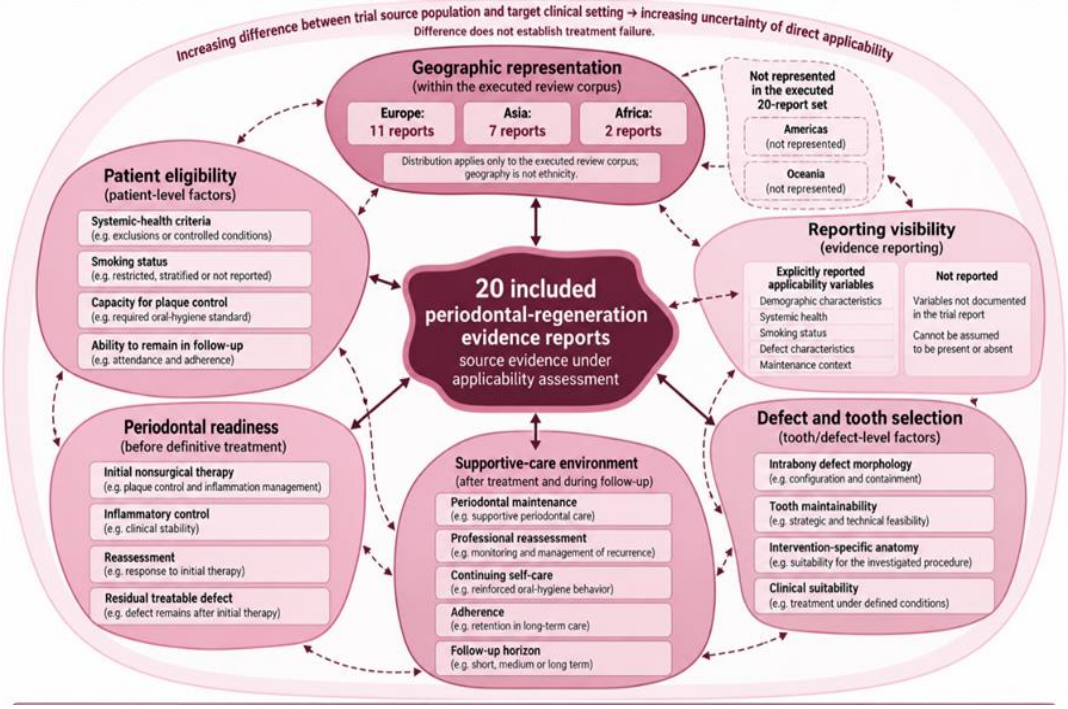


Figure 2. Interacting boundaries that determine what clinical reality is represented by periodontal-regeneration trials

The review consequently supports a reporting agenda rather than a new eligibility algorithm. Future trials should make source populations reconstructable, specify which clinical restrictions reflect safety or biological rationale, document the treatment pathway preceding regeneration, and report the maintenance environment in which outcomes are generated. They should also distinguish variables that were genuinely unrestricted from variables that were simply not reported.

Table 4 translates the observed methodological limitations into reporting and design priorities without treating the recommendations as validated clinical thresholds.

Table 4. Reporting gaps that limit interpretation of periodontal-regeneration trial representativeness and corresponding research priorities

Reporting or design problem	Why it matters for external validity	Minimum information needed in future studies	Recommended interpretation or research response
Incomplete demographic characterization	Prevents reconstruction of who was actually enrolled	Age distribution and other relevant participant characteristics explicitly reported	Do not infer unreported characteristics from country or clinic location
Geography used as a proxy for diversity	National location does not identify ethnicity, socioeconomic context, or access to care	Country, recruitment setting, and separately reported participant characteristics	Treat geography as a study-setting variable only
Smoking criteria incompletely described	Common periodontal risk exposure may be absent, restricted, or simply unreported	Eligibility definition and observed smoking status/exposure	Separate exclusion from non-reporting
Systemic-health criteria incompletely operationalized	External application to medically complex patients becomes uncertain	Conditions excluded, permitted when controlled, and represented at baseline	Avoid assuming that an exclusion demonstrates biological non-responsiveness
Oral-hygiene prerequisites insufficiently contextualized	High trial readiness may differ from routine-care populations	Pretreatment plaque/bleeding requirements and how readiness was achieved	Interpret treatment outcome within the selected readiness state
Pretreatment therapy poorly separated from regenerative intervention	Improvement and eligibility may depend on previous treatment response	Initial therapy, reassessment interval, residual defect definition and decision to proceed	Distinguish selection after successful stabilization from intervention effect
Defect morphology incompletely specified	Regenerative performance is strongly linked to the anatomical situation studied	Clinically relevant morphology and tooth-level eligibility	Do not transfer findings automatically to anatomically dissimilar defects
Maintenance schedule incompletely described	Long-term outcomes may depend on continuing professional care	Recall schedule, supportive treatment, adherence and loss to follow-up	Interpret durability within the observed maintenance environment
Reliance on short-horizon surrogate endpoints	Clinical attachment or radiographic change does not encompass all patient-relevant outcomes	Follow-up duration plus survival, recurrence, patient-reported and economic outcomes where appropriate	Keep surrogate improvement separate from long-term clinical success
External validity rarely evaluated explicitly	Readers must reconstruct applicability from scattered eligibility text	Dedicated description of source population and applicability limits	Include an explicit applicability statement in reports
Search and review coverage incompletely reproducible	Apparent geographic absence may reflect retrieval limitations	Full database/platform details, complete strings, dates, exports and record-level screening history	Do not interpret an executed review corpus as an exhaustive global census unless completeness is demonstrated
Trial populations and target populations not distinguished	Effect estimates may be transferred beyond directly studied patients	Clear source-population definition and intended clinical target population	State when application requires extrapolation rather than direct evidence

Several limitations of this review must therefore qualify its conclusions. First, representativeness was judged from what publications reported. Unreported patient characteristics could not be reconstructed without speculation. Second, country of study was available more consistently than ethnicity, socioeconomic position, referral pathway, or maintenance affordability, making geography a visible but incomplete measure of diversity. Third, eligibility restrictions do not have uniform methodological meaning. Excluding a medically unstable patient, requiring control of plaque before regenerative surgery, and restricting a trial to a defined intrabony morphology may each be justified for different reasons.

The relevant question is not whether restriction exists, but which clinical population remains directly represented after the restrictions are applied.

Most importantly, the executed evidence search was reproducible but not equivalent to a complete multi-database bibliographic export. The presence in the contextual bibliography of potentially eligible contemporary trials not incorporated into the 20-report corpus demonstrates that the geographic distribution must be interpreted as an analysis of the executed evidence set rather than an exhaustive enumeration of global regenerative research. Expanding that corpus would require repeating identification, deduplication, screening, exclusions, extraction, and every dependent table and figure. The reported arithmetic therefore describes the executed evidence set, with the corresponding limitation on geographic inference.

Within those boundaries, the findings remain clinically informative. Trial efficacy and trial applicability answer different questions. Periodontal-regeneration trials show what selected interventions can achieve in patients and defects judged appropriate for treatment and managed within defined clinical pathways. Their results become less directly informative as the target patient's disease state, systemic health, smoking exposure, capacity for self-care, defect anatomy, access to specialist treatment, or ability to remain in supportive periodontal care diverges from the corresponding source population. That increasing inferential distance is a reason for qualified interpretation and better research, not a basis for declaring the intervention ineffective.

Conclusion

Contemporary periodontal-regeneration trials represent clinically meaningful but bounded patient populations and treatment environments. Their evidence is shaped not only by the regenerative intervention but also by geographic concentration, defect selection, systemic and behavioral eligibility, pretreatment periodontal stabilization, and continuing maintenance. These restrictions can be scientifically justified while still narrowing direct applicability. The appropriate response is therefore neither automatic generalization nor automatic rejection of trial findings. Clinical interpretation should identify how closely the target patient and care environment correspond to those actually studied, while future trials and reviews should report population, setting, readiness, and maintenance conditions with sufficient precision for that judgment to be made.

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