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RESEARCH

The ISSLS VERTEBRA initiative: establishing reporting standards for regenerative medicine trials in disc degeneration and low back pain

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Abstract

Purpose Regenerative medicine (RM) trials for intervertebral disc degeneration (IDD) are gaining increasing visibility and clinical relevance, yet reporting quality remains inconsistent and often incomplete. Critical details on trial methodology, biologic product specifications, imaging criteria, and outcome assessment are frequently insufficiently reported, limiting reproducibility and hindering the interpretation of available evidence. The aim of this study was to develop a spine-specific reporting guideline to support authors, reviewers, and readers in producing transparent and interpretable RM clinical trial reports.

Methods A three-stage process was undertaken to establish a consensus-based reporting guideline. First, a systematic review of published RM trials employing intradiscal biologic treatments was conducted to identify recurring reporting deficiencies. Second, an expert focus group and subsequent international survey hosted by the International Society for the Study of the Lumbar Spine (ISSLS) generated and prioritized candidate reporting items. Third, the finalized VERTEBRA checklist was applied to an updated cohort of clinical trials to evaluate reporting completeness across predefined domains.

Results Across 36 eligible clinical trials, the mean VERTEBRA completeness score was 53.8%, with substantial variability among studies. Recurrent deficiencies were consistently observed in product characterization, methodological transparency, imaging acquisition and analysis, baseline reporting, and management of missing data. Only a minority of studies referenced established reporting guidelines. Reporting quality showed an association with journal impact factor, but not geographic region or funding disclosures. Expert polling demonstrated strong agreement on the need for a spine-specific reporting tool, resulting in the development of a 50-item checklist organized across five domains.

Conclusion The VERTEBRA reporting guideline provides a structured, field-specific framework to elevate transparency, reproducibility, and interpretability in RM trials for IDD. Its adoption may enhance manuscript quality, strengthen peer review, and improve the reliability of evidence guiding the development and clinical translation of future regenerative therapies for IDD.

Keywords Intervertebral disc degeneration · Low back pain · Regenerative medicine · Biologic therapy · Clinical trials · Systematic review

Introduction

Clinical trials investigating regenerative therapies for intervertebral disc degeneration (IDD) and related low back pain (LBP) are increasing in number and clinical relevance [1]. These studies require substantial financial, logistical, and patient investment, making the evidence they generate particularly valuable. However, the scientific value of many regenerative medicine (RM) trials is undermined by incomplete and inconsistent reporting [1, 2]. Critical

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details, including trial design, statistical analyses, intervention characterization, and outcome reporting, are frequently inadequately described or omitted altogether, hindering the interpretation, reproducibility, and comparability of findings.

Generic reporting guidelines such as CONSORT [3, 4], SPIRIT [5], and STROBE [6] have substantially improved the design and reporting of clinical trials across many medical fields. However, these frameworks do not fully address several features unique to regenerative spine interventions, including biologic product characterization, procedure-specific technical details, imaging assessments, and spine-specific outcome measures [7–9]. Consequently, important information is often reported inconsistently or neglected entirely, seriously threatening data reliability and their translational potential. Beyond scientific implications, incomplete reporting also raises ethical concerns, as participants who undertake the risks associated with experimental therapies deserve that the knowledge generated from their involvement is reported with maximum rigor and transparency [10, 11]. Strengthening reporting standards is therefore essential to maximize the value of research investments, protect patients, and advance RM within the spine field [11].

To address persistent reporting deficiencies in regenerative spine research, we undertook a multi-stage initiative to develop a consensus-based reporting framework. First, a systematic review of published RM trials for IDD was conducted to identify common reporting gaps. Second, an international expert workshop convened under the auspices of the International Society for the Study of the Lumbar Spine (ISSLS) identified and prioritized reporting elements considered essential for RM spine trials. These efforts culminated in the development of the VERTEBRA (Vision for Excellence in Reporting on Trial-based Evidence for Biologic and Regenerative Approaches) reporting guideline. Finally, the VERTEBRA checklist was applied to an updated body of clinical evidence to assess contemporary reporting quality and evaluate its utility as a standardized reporting tool.

This study presents the outcomes of this three-stage initiative to establish consensus on minimal reporting standards for RM clinical trials in the spine field. Through the VERTEBRA reporting guideline, we aim to provide a practical framework that supports more transparent, reproducible, and interpretable reporting, ultimately strengthening the quality of evidence guiding regenerative therapies for spinal disorders.

Methods

Systematic review of clinical trial quality

To characterize the reporting quality of RM clinical trials in the spine field, we first conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] and our prospectively registered PROSPERO protocol (CRD420251037074) [13]. The review question was structured using the PICO framework. Briefly, eligible studies included patients aged ≥ 18 years affected by LBP and/or leg pain associated with IDD (P) who received single or multilevel intradiscal treatment strategies involving a (speculated) regenerative component (I) with (i.e., sham, placebo, standard of care) or without a comparator (C). The primary outcomes (O) were reporting completeness across key domains, including trial design, product characterization, patient characteristics, and outcome reporting.

A comprehensive search of PubMed/MEDLINE, Scopus, EMBASE, CENTRAL, CINAHL, and ClinicalTrials.gov was conducted from database inception to April 2025 using terms related to IDD, LBP, RM, and clinical trials (Supplementary Material 1). Records were screened independently by two reviewers (JS and LA) using Rayyan (Rayyan Systems Inc., Qatar) with disagreements resolved by consensus or third-party adjudication. Studies were excluded if they were non-peer-reviewed, non-English, retracted, outside the scope of degenerative lumbar spine disorders, included fewer than 10 participants receiving regenerative therapies, lacked efficacy or safety outcomes, or had less than 6 months follow-up. Data on study characteristics, interventions, outcomes, and reporting practices were extracted into a standardized database. To provide an overall subjective assessment of reporting quality, each trial was independently scored for methodological rigor, data transparency, and manuscript clarity using a specifically designed Likert scale (1 to 10 points per domain), and the mean score was used as a subjective quality grade.

Consensus workshop and expert polling

Findings from the systematic review informed an open focus group held during the 2025 ISSLS Annual Meeting (Atlanta, USA), where participants identified candidate reporting criteria for RM-spine trials across four preliminary domains: patient characteristics, product characterization, outcomes, and other reporting considerations. Suggestions were collected in real time using Wooclap (Wooclap SA, Belgium), consolidated by the VERTEBRA Working Group, and refined into a draft checklist. Draft items were subsequently circulated to selected ISSLS members and

external experts through an online survey (Google Forms, Google LLC, USA), in which respondents rated each item as "essential", "important", "desirable", "not important", or "no opinion/don't know". Items rated as essential or important by ≥80% of respondents were retained. The 80% threshold was selected a priori as a conservative criterion representing strong agreement for inclusion in a minimum reporting framework. Items falling below this threshold were not automatically excluded but were reconsidered during the final consensus discussion to allow incorporation of contextual and field-specific considerations. The VERTEBRA process was designed as a structured, iterative expert-consultation process rather than a formal Delphi study. This approach combined evidence-informed item generation, multidisciplinary discussion during the open ISSLS workshop, broad polling of the ISSLS membership and external experts, and final consensus discussion.

VERTEBRA reporting guideline performance assessment

Following consensus, the finalized VERTEBRA checklist was developed and applied to an updated cohort of clinical trial reports identified through an updated systematic review, which extended the original search through October 24, 2025. Three reviewers (JS, LA, and CRF) independently assessed all eligible studies using the VERTEBRA reporting guideline. Each item was scored according to the extent to which it was reported in the article as "Yes" (2 points), "Partly" (1 point), "No" (0 points), or "Not applicable" (NA). Overall reporting completeness was calculated by dividing the total score by the maximum attainable score for all applicable items (i.e., "total score/((50 – "NA" items) × 2 points)) and expressed as a percentage.

Data handling, presentation, and statistical analysis

Extracted data were compiled in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) for cleaning, organization, and descriptive analysis. VERTEBRA checklist scores were expressed as percentages of applicable items reported per study. Continuous variables were summarized as means ± standard deviation (SD) or medians with 95% confidence intervals (CI), as appropriate, while categorical variables were presented as frequencies and percentages. Each study was independently assessed by three reviewers. For quantitative analyses, reviewer scores were averaged. Individual item ratings of "Yes", "Partly", and "No" were assigned 2, 1, and 0 points, respectively. Mean item scores were subsequently categorized as "Yes" (1.50–2.00), "Partly" (0.50–< 1.50), or "No" (<0.50). Statistical analyses were performed using GraphPad Prism (GraphPad Software LLC, San Diego, CA, USA; Version 11). Associations between VERTEBRA completeness scores and subjective quality grades were assessed using Spearman's rank correlation coefficient. Comparisons involving more than two groups were performed using one-way ANOVA with Tukey's multiple-comparison correction, while two-group comparisons were performed using the Mann–Whitney U test. Interrater reliability was assessed using intraclass correlation coefficients (ICC) for overall VERTEBRA completeness scores, calculated using JASP (JASP Team, Netherlands; Version 0.19.3). Statistical significance was defined as a two-sided p-value < 0.05.

Results

Systematic review of clinical trial quality

The initial search identified 14,024 records, of which 9,765 remained after duplicate removal. Following screening and eligibility assessment, 31 published clinical trial reports [14–44] met the inclusion criteria for the systematic review (Fig. 1, Table 1).

Across trials published between 2011 and 2024, reporting quality was consistently limited. Over one third of the studies were controlled (12/31), although only 29.0% incorporated a placebo or sham comparator (Fig. 2A). Cell-based therapies were the most frequently investigated intervention, representing 35.5% of all products and 71.0% when combined approaches were included (Fig. 2B), followed by biomaterials and platelet-rich plasma. No eligible trials evaluated gene therapy, extracellular vesicles, or growth factor-based therapies. Follow-up ranged from 6 months to 9 years, highlighting substantial heterogeneity in study design. In total, the included studies reported outcomes for 1,731 participants receiving RM-related interventions (including biomaterial-carrier control arms), while 315 participants were allocated to sham, placebo, or standard-care control groups.

Adherence to established reporting standards was limited, with only two of the 31 studies referencing guidelines such as CONSORT [3] and SPIRIT [5]. Just seven studies reported prospective power calculations and only fifteen were prospectively registered (Table 1). Among the ten randomized controlled trials (RCTs), three failed to describe their randomization procedures, while only two of the eight blinded studies reported allocation concealment (Fig. 2F). These findings highlight substantial methodological deficiencies even among the highest levels of clinical evidence in the field. Reporting gaps were observed across all major domains (Fig. 2C-I). Eligibility criteria were often incompletely defined, with inconsistent reporting of clinical thresholds, prior treatment failure, and demographic

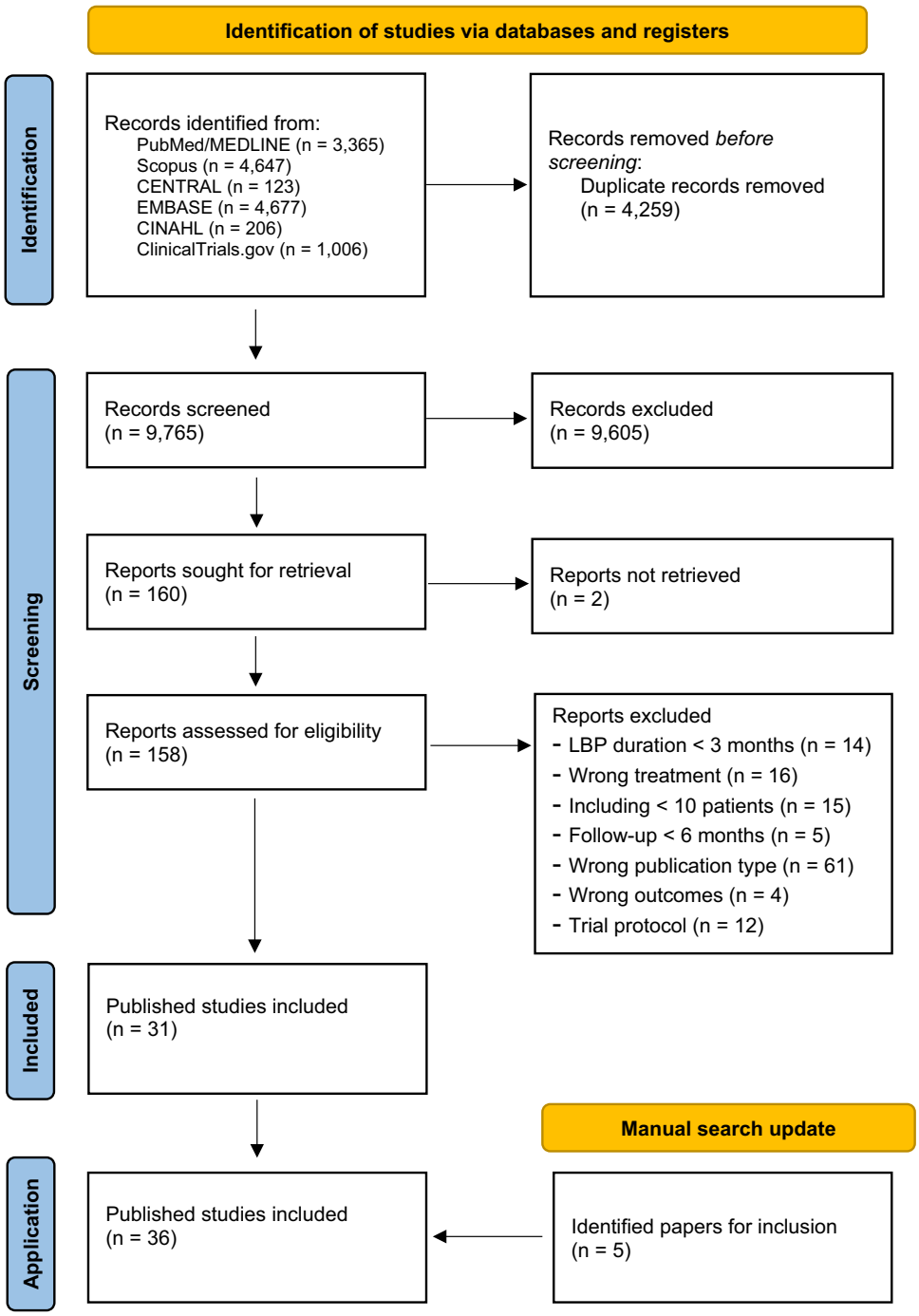


Fig. 1 PRISMA flowchart. Flow diagram summarizing the identification, screening, eligibility assessment, and inclusion of clinical trials on regenerative medicine interventions for lumbar spine disorders. The process followed PRISMA 2020 guidelines [12], illustrating the number of records retrieved from each database, duplicates removed, studies screened, and those meeting inclusion criteria for the systematic review and subsequent VERTEBRA checklist development

restrictions. Key participant characteristics, including body mass index (BMI), smoking status, and psychiatric history, were frequently omitted. Trial methodology was similarly underreported, particularly with respect to prospective powering, randomization procedures, blinding, allocation concealment, data monitoring, and disclosures of funding or conflicts of interest. Intervention reporting commonly lacked details on injected volume, concentration, treated levels, delivery equipment, and post-procedural recommendations. Outcome reporting was also inconsistent, with limited use of minimal clinically important difference (MCID) thresholds, sparse documentation of imaging endpoints and adverse events, and inadequate handling of missing data or statistical reporting. Collectively, these findings demonstrate widespread deficiencies in methodological and results transparency across RM spine trials.

Table 1 Overview of included clinical studies on intradiscal regenerative and biologic therapies. This table summarizes all included clinical studies that investigated intradiscal regenerative or biologic treatments for discogenic low back pain

Study	References	Country	Registration ID	Study design	Max FU (months)	Patients (n)	Product	Product description	Control group
Gornet 2024	[14]	USA	NCT03347708	Multicenter phase I/II double-blind placebo-controlled RCT	24	60	Rebonuputemcel (DiscGenics)	Allogeneic NP-derived cells + HA	Vehicle (HA) control Placebo (saline) control
Navani 2024	[15]	USA	NCT04102761	Prospective multicenter open-label RCT with crossover	12	28	-	LP-PRP BMC	Placebo (saline) control
Lewandrowski 2023	[16]	USA	-	Multicenter retrospective single-arm observational cohort study	24	32	-	UC-MSCs + HA	-
Haines 2022	[17]	USA	-	Single-center prospective cohort study	12	32	-	BMAC	-
Zhang 2022	[18]	China	ChiCTR1900024268	Prospective single-arm clinical trial	12	31	-	PRP	-
Xuan 2022	[19]	China	-	Single-center prospective open-label nonrandomized controlled trial	72	18	-	IVD-derived and cultured cells	Discectomy-only
Akeda 2022	[20]	Japan	-	Prospective single-center survey follow-up of prior clinical trial	72	11	-	PRPr	-
Papadimitriou 2022	[21]	Sweden	-	Single-center prospective open-label feasibility pilot study	24	10	-	Iron-sucrose-labeled BM-MSCs	-
Schepers 2022	[22]	The Netherlands	-	Single-center prospective single-blind RCT	12	44	-	PRP	Placebo (saline) control
Beall 2021	[23]	USA	NCT03709901	Prospective multicenter single-blind RCT with crossover	12	140	VIA Disc Allograft (VIVEX Biologics, Inc.)	NP allograft seeded with unspecified cells	Placebo (saline) control Conservative care
Xu 2021	[24]	China	NCT03002207	Prospective two-arm RCT	24	15	-	BM-MSCs in gelatin sponge	Microdiscectomy Microdiscectomy + AF suture
El-Kadiry 2021	[25]	Canada	-	Single-center retrospective nonrandomized comparative case series	12	13	-	BMAC	Facet joint injection
Beall 2020	[26]	USA	NCT03709901	Prospective multicenter parallel-arm RCT	12	16	VIA Disc Allograft (VIVEX Biologics, Inc.)	NP allograft seeded with unspecified cells	Placebo (saline) Conservative care
Mazza 2020	[27]	Italy	-	Prospective multicenter open-label pre-market clinical study	6	22	HYADD4-G (Fidia Farmaceutici S.p.A.)	Amidic derivative of HA hydrogel	-
Ceylan 2019	[28]	Turkey	NCT02763956	Single-center retrospective cohort study	12	29	GelStix (Replication Medical)	Modified filamentous polyacrylonitrile hydrogel	-
Cheng 2019	[29]	USA	-	Prospective single-arm long-term follow-up study	108	29	-	LR-PRP	-

Table 1 (continued)

Study	References	Country	Registration ID	Study design	Max FU (months)	Patients (n)	Product	Product description	Control group
Kumar 2017	[30]	South Korea	NCT02338271	Single-center prospective open-label phase I trial	12	10	Cells + Tissuefill® (CHA Meditech Co., Ltd)	AT-MSCs + HA	-
Pettine 2017	[31]	USA	-	Single-center prospective open-label phase I trial	36	26	-	BMC	-
Akeda 2017	[32]	Japan	-	Single-center prospective single-arm clinical study	12	14	-	PRPr	-
Comella 2017	[33]	USA	NCT02097862	Single-center prospective open-label phase I trial	6	15	-	SVF + PRP	-
Noriega 2017	[34]	Spain	ECT2012-004444-30 NCT01860417	Single-center prospective double-blind placebo-controlled RCT	12	24	-	BM-MSCs	Placebo (saline) control
Tuakli-Wosornu 2016	[35]	USA	-	Prospective double-blind RCT with crossover	12	29	-	PRP	Placebo (contrast agent) control
Pettine 2016	[36]	USA	-	Single-center prospective open-label phase I trial	36	26	-	BMC	-
Pettine 2015	[37]	USA	-	Single-center prospective open-label phase I trial	12	13	-	BMC	-
Coric 2013	[38]	USA	BB-IND 13985	Two-center prospective feasibility trial	12	15	NuQu (ISTO Technologies)	Juvenile chondrocytes + Fibrin	-
Orozco 2011	[39]	Spain	ECT2008-001191-68	Single-center prospective phase I pilot study	12	10	-	BM-MSCs	-
Beall 2024	[40]	USA	NCT05201287	Prospective multicenter single-arm pilot study	6	29	VIA Disc NP® (VIVEX Biologics, Inc.)	Lyophilized NP allograft	-
Pauza 2024	[41]	USA	-	Single-center retrospective registry study	36	826	-	Fibrin	-
Pers 2024	[42]	France	ECT2017-002092-25 NCT03737461	Prospective multicenter double-blind placebo-controlled phase IIb RCT	24	58	-	BM-MSCs	Sham injection control
Amirdelfan 2021	[43]	USA	NCT01290367	Prospective multicenter double-blind placebo-controlled phase Ib/IIa RCT	36	60	Rexlemestrocel-L (Mesoblast) + HA	MPC precursors + HA	Vehicle (HA) control Placebo (saline) control
Navani 2018	[44]	USA	-	Single-center prospective single-arm cohort study	18	20*	-	PRP (Pfirrmann 1–2) BMC (Pfirrmann 3–4)	-
Beall 2025	[45]	USA		Prospective multicenter double-blind placebo-controlled phase Ib/IIa trial	36	272	Rexlemestrocel-L (Mesoblast) + HA	MPC precursors + HA	Placebo (Saline) control Conservative care
Azeem 2025	[46]	USA		Prospective multicenter single-arm cohort study	6	21	VIA Disc NP® (VIVEX Biologics, Inc.)	Lyophilized NP Allograft	-

Table 1 (continued)

Study	References	Country	Registration ID	Study design	Max FU (months)	Patients (n)	Product	Product description	Control group
Yamada 2025	[47]	Japan		Prospective open-label nonrandomized phase I/II trial	24	40	-	Ultra-purified alginate gel with discectomy	Discectomy only
Beall 2025	[48]	USA		Prospective single-arm clinical feasibility study	12	28	VIA Disc NP® (VIVEX Biologics, Inc.)	Lyophilized NP allograft	-
Vadala 2025	[49]	Italy		Single-center prospective double-blind sham-controlled phase IIb RCT	6	21	-	BM-MSC	Sham injection control

*Distribution between treatments not specified. AF: annulus fibrosus; AT-MSCs: adipose tissue derived mesenchymal stromal cells; BM-MSCs: bone marrow mesenchymal stromal cells; BMAC: bone marrow aspirate concentrate; BMC: bone marrow concentrate; FU: follow-up; HA: hyaluronate or hyaluronic acid; IVD: intervertebral disc; LP-PRP: leukocyte-poor platelet-rich plasma; LR-PRP: leucocyte-rich platelet-rich plasma; MPCs: mesenchymal precursor cells; NP: nucleus pulposus; PRP: platelet-rich plasma; PRPr: platelet-rich plasma releasate; RCT: randomized controlled trial; SVF: stromal vascular fraction; UC-MSCs: umbilical cord-derived mesenchymal stromal cells.

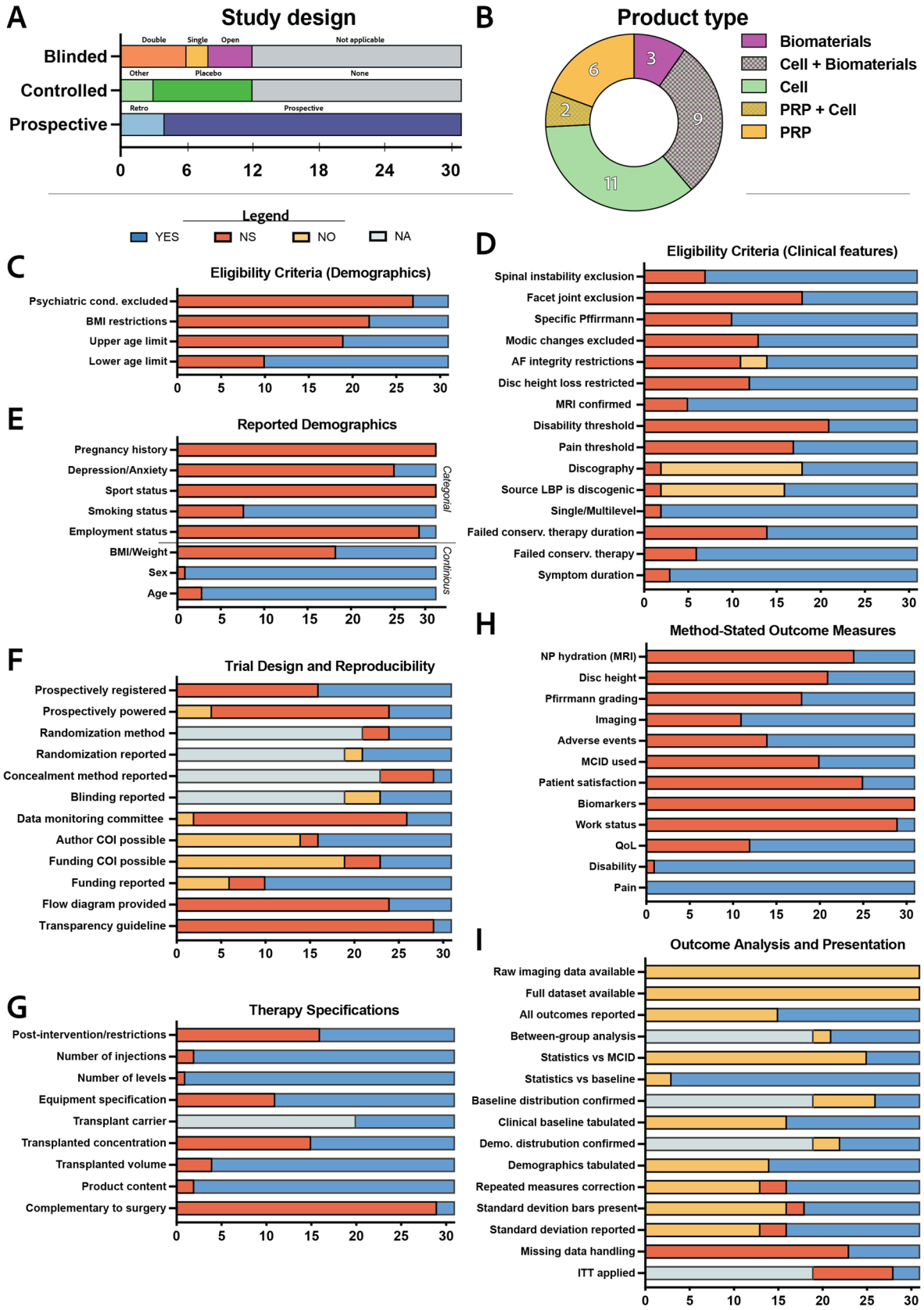
Expert polling and consensus formation

A preliminary VERTEBRA checklist developed during the 2025 ISSLS Annual Meeting was subsequently evaluated by ISSLS members and external experts through an online survey. Twenty-five experts responded to the survey distributed to ISSLS members and external experts. Of these, 56% were clinicians and 40% researchers or scientists (Fig. 3A). Respondents showed a relatively balanced geographic distribution across Europe (36%), Asia (28%), and North America (28%), with no respondents affiliated with institutions in Africa or South America (Fig. 3B). Most respondents (64%) had more than 10 years of spine-related experience (Fig. 3C), while 72% reported prior experience with RM clinical trials (Fig. 3D). Regarding conflicts of interest, 84% reported none, 8% declared a conflict, and 8% preferred not to disclose.

Prior to rating the checklist items, respondents were asked to assess the overall reporting quality of RM spine trials. Most rated current reporting as poor (64%) or acceptable (28%), while none considered it good (Fig. 3E). As shown in Fig. 3F-J, all but three proposed items achieved ≥80% agreement as either essential or important. Following a final consensus meeting, reporting of BMI or weight criteria (76%) was retained despite falling below the predefined threshold, whereas items related to provocative discography (52%) and identification of treating surgeons (76%) were excluded. Participants additionally recommended the inclusion of anonymized imaging datasets in publicly accessible repositories when feasible. The finalized VERTEBRA checklist comprised 50 items organized into five domains: Patient, Methodology, Product, Baseline, and Outcomes (Table 2).

Updated systematic review and VERTEBRA-based assessment

The updated systematic search identified five additional eligible clinical trial reports [45–49], resulting in 36 studies available for VERTEBRA-based evaluation (Figs. 1, 4A-B, Table 1). Several items demonstrated high reporting completeness, particularly specification of the treatment site (34/36 studies), symptom duration (30/36), and avoidance of regenerative claims without supporting imaging evidence (28/36) (Fig. 4C, Supplementary Material 2). In contrast, reporting of manufacturer information, endplate integrity criteria, product half-life, mental health eligibility criteria, and deposition of anonymized imaging datasets was rare. Most deficiencies in demographic reporting were attributable to omission of smoking status. Baseline imaging assessments, imaging acquisition parameters, and product personalization were also inconsistently reported.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Randomization reported
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Blinding reported
Data monitoring committee
Author COI possible
Funding COI possible
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MCID used
Patient satisfaction
Biomarkers
Work status
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Pain
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Outcome Analysis and Presentation
Raw imaging data available
Full dataset available
All outcomes reported
Between-group analysis
Statistics vs MCID
Statistics vs baseline
Baseline distribution confirmed
Clinical baseline tabulated
Demo. distrubution confirmed
Demographics tabulated
Repeated measures correction
Standard devition bars present
Standard deviation reported
Missing data handling
ITT applied

Fig. 2 Summary of key characteristics in contemporary regenerative medicine clinical trial reports. (**A**, **B**) Overview of 31 included clinical trial reports showing their study design features and the type of regenerative medicine products assessed. (**C**-**I**) Evaluation of whether each study specified predefined elements related to eligibility criteria, demographics, clinical features, trial design, therapy specifications, outcome measures, and outcome analysis. AF: annulus fibrosus; BMI: body mass index; COI: conflict of interest; ITT: intention to treat; MCID: minimal clinically important difference; MRI: magnetic resonance imaging; NA: not applicable; NP: nucleus pulposus; NS: not specified; PRP: platelet-rich plasma; QoL: quality of life

Only three studies explicitly referenced established reporting guidelines such as CONSORT [3]. Across checklist domains, reporting completeness was broadly similar, with all domains demonstrating substantial room for improvement (Fig. 4D-E).

Application of the VERTEBRA reporting guideline yielded a mean reporting completeness score of 53.8 ± 10.9% across all studies (Fig. 4F), with substantial variability between reports. Only two studies (5.6%) achieved a completeness score of at least 75%, while eight (22.2%) scored between 60 and 75%. In contrast, over one third of all reports (14/36, 38.9%) scored 50% or lower, highlighting the widespread nature of reporting deficiencies within the field. Reporting completeness was broadly similar between studies with and without declared funding conflicts of interest, whereas studies lacking funding disclosures generally achieved lower scores (Fig. 4G). No clear regional differences were observed, although European studies showed a slight trend toward higher scores (Fig. 4H). Journal impact factor demonstrated a modest association with reporting completeness, where high impact factor (>5.0) journal significantly outperformed low (<2.5) impact factor journals (Fig. 4I). Studies referencing established reporting guidelines tended to achieve higher scores though only a limited number of studies included such guidelines (n=3; Fig. 4J). VERTEBRA completeness scores correlated significantly with subjective quality grades assigned during initial screening ($r = 0.6101$, $p < 0.0001$), supporting the ability of the checklist to capture perceived reporting quality (Fig. 4K). Collectively, these findings demonstrate persistent deficiencies and substantial variability in the reporting of regenerative spine trials, highlighting the need for field-specific reporting standards. Interrater reliability of the VERTEBRA completeness score was excellent. Agreement between individual reviewers was high (ICC(3,1) = 0.969, 95% CI 0.948–0.983), while reliability of the averaged three-reviewer score was similarly high (ICC(3,3) = 0.990, 95% CI 0.982–0.994). These findings indicate that the reporting guideline can be applied consistently across independent assessors.

Discussion

In this study, we report the development of the first spine-specific reporting guideline for RM clinical trials. Built through expert consensus within the ISSLS community, VERTEBRA complements established guidelines such as CONSORT [3], SPIRIT [5], and STROBE [6] by addressing reporting considerations unique to regenerative spine research. The proposed framework comprises five domains covering methodology, patient selection, product and technique characterization, baseline assessment, and outcomes. Application of the VERTEBRA checklist revealed a mean reporting completeness of only 53.8%, indicating substantial deficiencies across the current literature. Given the biological and technical complexity of RM therapies, such shortcomings limit reproducibility, evidence synthesis, and the ability to accurately determine whether observed outcomes are attributable to the intervention itself or to study-specific factors.

A major focus of VERTEBRA is the transparent reporting of patient selection and disease characterization. Regenerative therapies are inherently dependent on the biological environment into which they are delivered, and treatment responsiveness may vary according to patient characteristics, disease severity, and the underlying pathology being targeted [50–52]. This consideration is particularly important in LBP, which represents a heterogeneous clinical syndrome [53], and in IDD, which encompasses a broad spectrum of structural and biological phenotypes [54]. Without adequate reporting of eligibility criteria and baseline disease characteristics, it becomes difficult to determine whether differences in outcomes reflect the intervention itself or differences in the populations being treated. The VERTEBRA framework therefore emphasizes transparent documentation of patient selection, disease characterization, and the rationale underlying these decisions. Importantly, the reporting guideline does not advocate for any specific diagnostic/therapeutic strategy or definition of discogenic LBP. Rather, it seeks to ensure that readers can understand how participants were selected and interpret findings within the appropriate clinical context.

Transparent reporting of the investigational product and delivery procedure represents another central objective of VERTEBRA. RM-interventions often involve complex biologic products, specialized manufacturing processes, and procedure-dependent variables that may substantially influence clinical outcomes. At the same time, reporting requirements must remain compatible with the protection of intellectual property and proprietary manufacturing methods [55–57]. Accordingly, VERTEBRA focuses on the minimum information necessary to understand, evaluate, and reproduce an intervention, including its biological rationale,

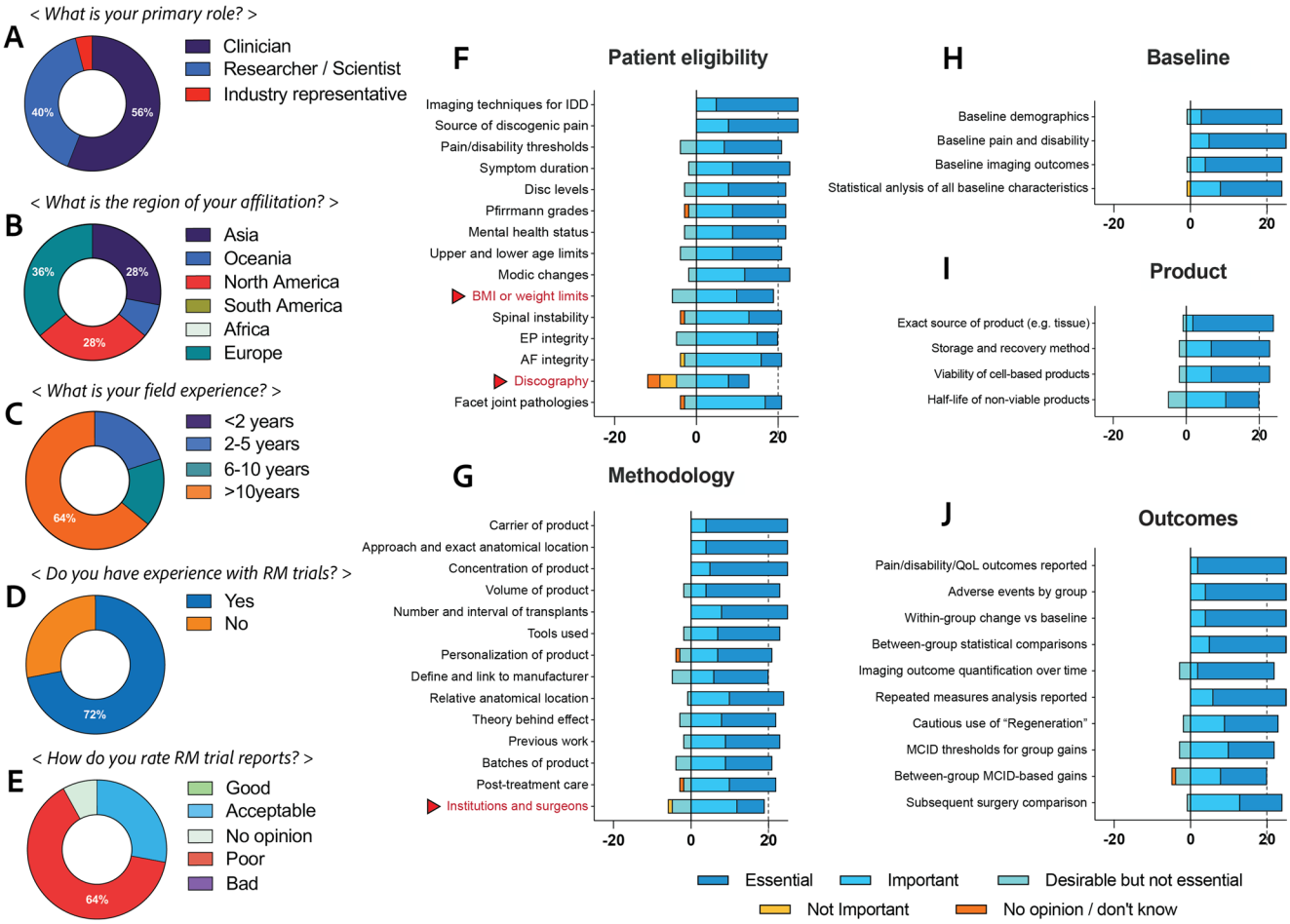

Fig. 3 Preliminary VERTEBRA checklist rating. Responses from participants (n = 25) to the preliminary VERTEBRA checklist survey. (**A**) Primary professional role distribution among respondents. (**B**) Geographic distribution of respondents according to the country of their primary affiliation. (**C**) Field experience in spine-associated medicine and research. (**D**) Proportion of respondents with prior experience in RM trials. (**E**) Overall rating of RM trial reports. (**F-J**) Rating of item importance for inclusion in the VERTEBRA checklist, scored by respondents as "Essential", "Important", "Desirable but not essential", "Not important", or "No opinion/don't know". Items marked in red scored below 80% of "Essential + Important" response rates. AF: annulus fibrosus; BMI: body mass index; EP: endplate; MCID: minimal clinically important difference; RM: regenerative medicine

product characteristics, and delivery approach. This is particularly relevant in RM, where seemingly small differences in product composition, administration technique, or procedural factors may influence both safety and efficacy. By promoting consistent reporting of these elements, VERTEBRA aims to improve reproducibility, facilitate comparisons across studies, and strengthen confidence in the interpretation of regenerative medicine trial outcomes.

Similarly, comprehensive reporting of baseline characteristics is essential for interpreting and comparing regenerative medicine trials. Authors should report key demographic and clinical variables, including age, sex, BMI, smoking status, symptom duration, baseline pain and disability scores, and the number of affected spinal levels. These characteristics should be compared between groups, particularly in non-randomized studies where baseline differences may act as confounders and influence outcomes. Baseline imaging characteristics should likewise be reported using the measures employed to define or classify IDD, such as Pfirrmann grade [58], T2-signal intensity, or other relevant imaging biomarkers. Clinical and imaging data should be presented transparently using appropriate measures of central tendency and variability, ideally within baseline characteristics tables. Such reporting enables readers to assess cohort comparability, understand the disease phenotype under investigation, and evaluate the generalizability of study findings.

Finally, outcome reporting remains a critical area for improvement. Although composite and responder-based endpoints may be clinically intuitive and can increase statistical power, they may also amplify the apparent magnitude of treatment effects despite relatively modest absolute differences between treatment groups [53, 59]. Given their frequent use in the reviewed literature, it is important that these measures supplement, rather than replace, transparent

Table 2 VERTEBRA Checklist for Standardized Reporting in Regenerative Medicine Trials for Disc Degeneration. This table outlines the core reporting items recommended by the VERTEBRA framework to enhance transparency, reproducibility, and interpretability of regenerative medicine clinical trials targeting lumbar disc degeneration. For practical use, a worksheet version of the VERTEBRA checklist is provided in Supplementary File 3

Domain	No	Item	Item description
Methods	1	Guideline	Follow established reporting guidelines for clinical trials (e.g., STROBE for observational studies and CONSORT for RCTs) and explicitly state this in the Methods section with an appropriate reference
	2	VERTEBRA	Specify and reference the VERTEBRA reporting guideline in the Methods as a tool to enhance transparency in reporting on regenerative medicine clinical trials for IDD
	3	Preclinical	Include references to any preclinical studies or prior clinical trials used to assess efficacy and safety of the product in the Methods section. Note any updates or revisions to the referenced materials
	4	Rationale	Specify the rationale or theory of how the product being tested is expected to resolve LBP or IDD
	5	Post-transplant	Specify the post-operative/transplant care (e.g., analgesic consumption, physical therapy, additional healthcare utilization) or patient behavior recommendations. If no recommendation or requirements are set, explicitly state this
	6	Transplant site	Specify the specific tissue(s) receiving the transplantations/interventions
	7	Tissue region	Specify the relative location within the tissue (e.g., centrally in the disc based on intraoperative imaging)
	8	Equipment	Specify tools used for transplantation, including needle gauge or dimensions of other specific instruments
Patient	9	Age limits	Specify the lower and upper age limits used for patient inclusion or exclusion
	10	BMI limits	Specify any BMI or weight criteria used for participant inclusion or exclusion. If none were applied, explicitly state this
	11	Mental health	Specify whether participants with mental health conditions (particularly depression and anxiety) were eligible or excluded, and clearly describe how these conditions were defined and assessed
	12	Disc levels	Specify the spinal disc level(s) eligible for inclusion
	13	LBP definition	Specify how the discogenic source of LBP was determined and defined. If not assessed, explicitly state "not assessed"
	14	Imaging	Specify the imaging modalities and the imaging observations or features used to identify and define the target degenerative disc(s)
	15	Disc health quantification	Specify and reference the standardized grading, scoring, or quantitative imaging method (e.g., Pfirrmann grading, T2 intensity) used to assess disc health/degeneration severity at baseline and follow-up. If none was used, explicitly state this
	16	Symptom duration	Specify the required symptom duration (for example, chronic LBP >6 months) for inclusion
	17	Prior treatments	Specify whether conservative treatment or previous intradiscal injections were allowed, including the types of modalities and the required duration of treatment before inclusion
	18	Thresholds	Specify whether minimum pain and/or disability thresholds were used for inclusion, and list the instruments and cutoff values applied (for example, VAS ≥4, ODI ≥30%). If not applied, explicitly state this
	19	AF integrity	Specify whether assessment of AF integrity was required and if specific features were considered for eligibility. State the methods used to determine this
	20	EP integrity	Specify whether assessment of EP integrity was required and if specific features were considered for eligibility. State the methods used to determine this
	21	Instability	Specify whether spinal instability was included, excluded, or explicitly report if not assessed in the inclusion criteria
	22	Modic change	Specify whether the presence of Modic changes was allowed, excluded, or not assessed as an inclusion criterion
	23	Facet joints	Specify whether facet joint degeneration was allowed, excluded, or not assessed as an inclusion criterion

Table 2 (continued)

Domain	No	Item	Item description
Product	24	Volume	Specify the exact volume or size of the transplanted product per disc (for example, mL, cc)
	25	Dosage	Specify the concentration of the transplanted product (for example, cells/mL, ng/mL)
	26	Carrier	Specify the solution or carrier medium used for transplantations. If none, specify "transplanted as is"
	27	Batches	For non-autologous products, specify the source and number of different batches transplanted within the trial
	28	Transplants	Specify the number of transplantations performed and, if more than one, the time interval between them
	29	Manufacturer	For commercially available products, specify the commercial entity and country
	30	Personalizations	Specify any personalized modifications or tailoring of the product allowed or performed in this trial (e.g., adjusting the volume of injected product based on disc size)
	31	Viability	Report the average or estimated cell viability (%) of the product dose administered in the trial
	32	Product source	Specify the source of the product (autologous, allogeneic, or xenogeneic)
	33	Cell type	Specify the exact source of the viable product, including the specific tissue source for "discal" tissue, specify whether it contains NP, inner AF, outer AF, and/or EP
	34	Production	Specify or reference the production process and any modifications applied to create the final transplantation product
	35	Storage	Specify the storage method and recovery process at transplantation
	36	Half-life	Specify the half-life of the product. If unknown, state this and mention it as a limitation
Baseline	37	Demographics	Specify baseline demographic characteristics, including at minimum: age, sex, BMI, and smoking status
	38	Clinical baseline	Specify baseline clinical characteristics, including at minimum: pain intensity, disability level, duration of LBP, treated disc level(s), and distribution of multi- or single-level LBP
	39	Imaging baseline	Specify baseline imaging measurements from all imaging modalities applied, including at minimum: Pfirrmann grading and T2-weighted signal intensity values
	40	Comparison	Specify all variables in tabular form, including mean (± SD) or median (IQR). If more than one group is included, add appropriate statistical comparisons (including p-values) between groups
Outcomes	41	Clinical outcomes	Specify all clinical outcomes of pain, disability, and quality of life as mean (± SD) values at each time point, either in a (supplementary) table or in graphical form
	42	Imaging outcomes	Quantify and specify all described imaging outcomes, including changes over time, either in a (supplementary) table or in graphical form
	43	Imaging upload	Upload anonymized raw imaging DICOM files (or equivalent) of full cohorts to a public repository
	44	Within-group	For each group, compare outcomes to baseline values (including p-values) to assess within-group improvement over time
	45	Between-group	Specify between-group comparisons to determine statistically significant differences related to the interventions at each time point
	46	Repeated measures	Specify whether statistical analysis accounted for repeated measures over time (for example, through repeated-measures ANOVA)
	47	MCID	Evaluate whether within-group improvements meet predefined or validated MCID thresholds, and explicitly state the clinical significance of reported effects
	48	Adverse events	Specify and compare the rate and nature of adverse events across groups
	49	Surgery	Specify and compare the proportion of patients undergoing subsequent surgical interventions between groups
	50	Regeneration	Avoid using the term "regeneration" unless supported by clear evidence from imaging-based or structural outcome measures showing improvement in disc structure compared to baseline

AF: annulus fibrosus; ANOVA = analysis of variance; BMC: bone marrow concentrate; BMI: body mass index; DICOM: digital imaging and communications in medicine; EP: endplate; IDD, intervertebral disc degeneration; IQR: interquartile range; LBP: low back pain; MCID: minimal clinically important difference; NP: nucleus pulposus; ODI: Oswestry Disability Index; RCT = randomized controlled trial; SD: standard deviation; SF: Short Form Health Survey; VAS: Visual Analogue Scale

reporting of direct clinical outcomes. Authors should report pain, disability, and other key outcome measures at all follow-up time points using appropriate measures of central tendency and variability. Particular attention should also be given to imaging outcomes, which were among the most poorly reported domains identified in this study.

As RM therapies are frequently proposed to slow, halt, or reverse IDD, imaging outcomes require particular attention. Regeneration is fundamentally a structural claim; therefore, evidence of regenerative activity or alleviation of deterioration should not rely on clinical improvement alone, but should be supported by objective and clearly quantified imaging findings. Standardized imaging acquisition,

analysis, and reporting are essential to determine whether structural changes accompany symptomatic improvement and to enable comparison across studies [9, 53]. Notably, our systematic screening identified imaging acquisition, quantification, and outcome reporting as among the most frequently underreported aspects of contemporary regenerative spine trials, highlighting a critical area for improvement. To further enhance transparency and facilitate independent verification and future evidence synthesis, investigators should be encouraged to share anonymized imaging datasets through appropriate repositories whenever feasible. Comprehensive reporting of adverse events is equally important. Authors should describe the nature, frequency, and severity of adverse events and compare these outcomes between study groups. Particular attention should be given to treatment failures requiring surgical intervention, whether due to inadequate symptom relief or complications, as these outcomes provide important insight into both the safety and effectiveness of regenerative therapies. Finally, outcome reporting should include both within-group changes from baseline and between-group differences using statistical approaches that account for repeated measurements over time. Particularly concerning was the frequent presentation of graphical outcomes without error bars, measures of dispersion, or statistical comparisons between groups, all fundamental elements of scientific reporting. Such omissions limit interpretation and weaken confidence in reported findings. Whenever possible, outcomes should also be contextualized using predefined thresholds for clinical significance to clarify the clinical relevance of observed treatment effects [60].

This study has several strengths, including the development of the first spine-specific reporting framework for RM clinical trials through an international expert consensus process and its application across a contemporary body of published evidence. Studies were identified using predefined eligibility criteria, including minimum follow-up duration and cohort size. Consequently, reports with weaker methodology, limited follow-up, or poorer reporting may have been excluded, suggesting that the observed VERTEBRA completeness scores likely represent a best-case estimate of current reporting practices. Despite this, mean reporting completeness was only 53.8%, with relatively few studies exceeding 60%, highlighting persistent deficiencies across the field. Importantly, similar to CONSORT, VERTEBRA was developed as a reporting framework rather than a tool for evaluating methodological quality. A study may achieve high reporting completeness while remaining methodologically limited, just as a well-designed study may incompletely report important details. The primary purpose of VERTEBRA is therefore to improve transparency, reproducibility, and interpretability of RM trial reports, rather than to provide a measure of scientific quality. For optimal implementation, VERTEBRA (Supplemental Material 3) should be completed by study authors at the time of manuscript submission and submitted alongside the manuscript as supplementary material. For each checklist item, authors should indicate the corresponding manuscript page and line numbers or clearly state, with justification where appropriate, why the item is not applicable. (Table 2) Similar to CONSORT [3] and related reporting frameworks, this process is intended to support authors in providing complete and transparent reporting, facilitate peer review, and ensure that key elements can be readily identified and evaluated within the manuscript. Future initiatives may build upon this work by developing consensus recommendations for the design, conduct, and analysis of RM trials in the spine field. Such objectives, however, fall outside the intended scope of VERTEBRA.

Several limitations should be acknowledged. RM, IDD phenotyping, imaging biomarkers, and clinical trial methodology continue to evolve rapidly. Accordingly, VERTEBRA should be regarded as a living framework that will require periodic refinement as new therapies, technologies, and methodological standards emerge. Although developed through an international expert consensus process informed by systematic evidence synthesis, the methodology did not employ a formal Delphi process and future iterations may benefit from broader stakeholder engagement, including patient representatives and regulatory bodies [61]. The overlap between literature informing VERTEBRA development and its initial application may introduce confirmation bias, warranting future independent external evaluation. Future efforts should focus on prospective implementation of VERTEBRA within trial protocols, registries, manuscript submissions, and peer-review processes, together with evaluation of its impact on reporting quality over time.

Ultimately, regenerative spine medicine cannot mature as a clinical discipline without transparent, reproducible, and interpretable evidence. VERTEBRA was developed not as a static checklist, but as a living framework designed to evolve alongside the field, strengthen methodological rigor, improve comparability across studies, and maximize the scientific and ethical value of data generated from RM trials, thereby supporting greater confidence in the evidence guiding patient care.

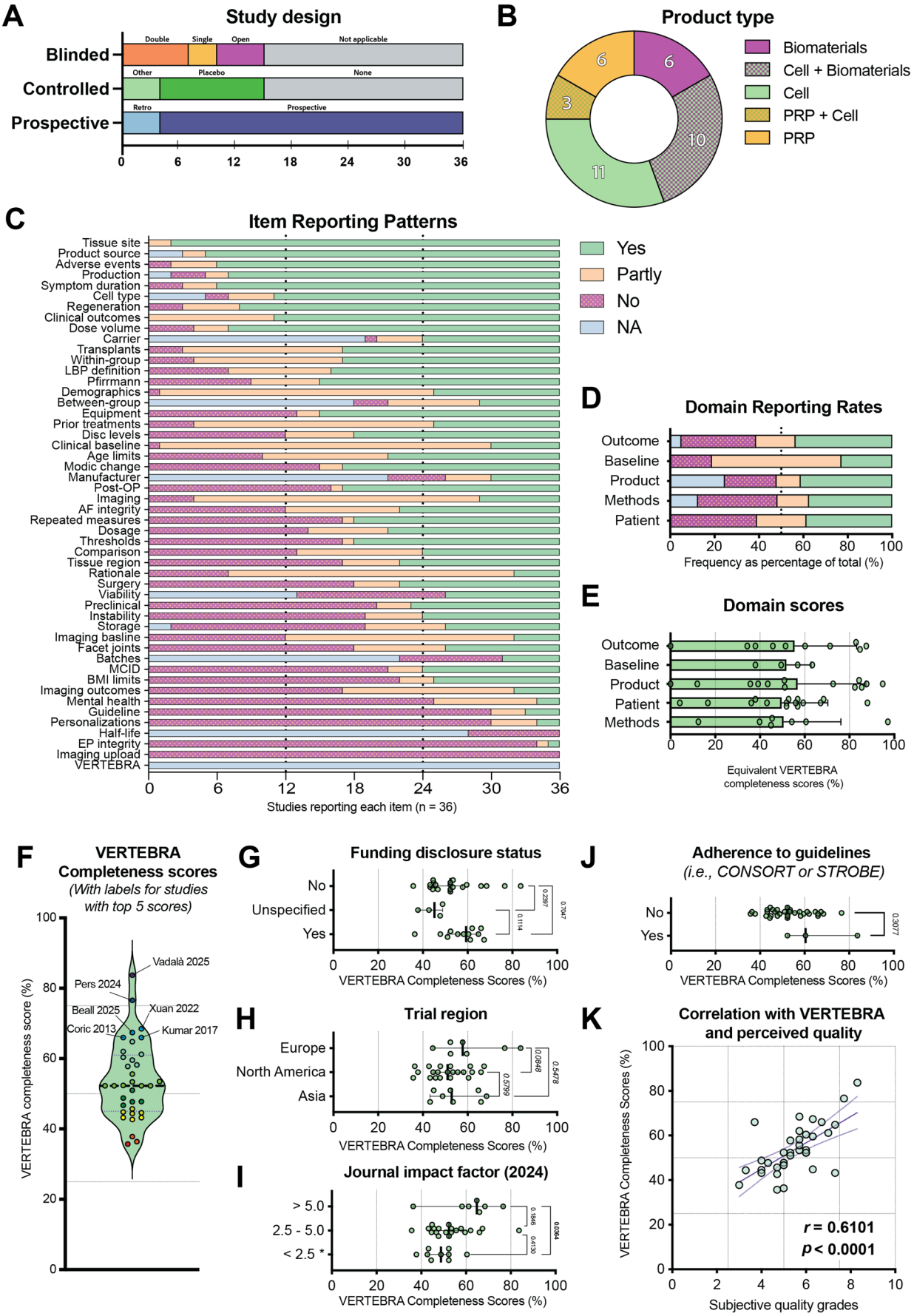
A
Study design
Blinded
Controlled
Prospective
Double
Single
Open
Not applicable
Other
Placebo
None
Retro
Prospective
0
6
12
18
24
30
36
B
Product type
6
6
3
10
11
Biomaterials
Cell + Biomaterials
Cell
PRP + Cell
PRP
C
Item Reporting Patterns
Tissue site
Product source
Adverse events
Production
Symptom duration
Cell type
Regeneration
Clinical outcomes
Dose volume
Carrier
Transplants
Within-group
LBP definition
Pfirrmann
Demographics
Between-group
Equipment
Prior treatments
Disc levels
Clinical baseline
Age limits
Modic change
Manufacturer
Post-OP
Imaging
AF integrity
Repeated measures
Dosage
Thresholds
Comparison
Tissue region
Rationale
Surgery
Viability
Preclinical
Instability
Storage
Imaging basline
Facet joints
Batches
MCID
BMI limits
Imaging outcomes
Mental health
Guideline
Personalizations
Half-life
EP integrity
Imaging upload
VERTEBRA
0
6
12
18
24
30
36
Studies reporting each item (n = 36)
Yes
Partly
No
NA
D
Domain Reporting Rates
Outcome
Baseline
Product
Methods
Patient
0
20
40
60
80
100
Frequency as percentage of total (%)
E
Domain scores
Outcome
Baseline
Product
Patient
Methods
0
20
40
60
80
100
Equivalent VERTEBRA
completeness scores (%)
F
VERTEBRA
Completeness scores
(With labels for studies
with top 5 scores)
VERTEBRA completeness score (%)
100
80
60
40
20
0
Vadalà 2025
Pers 2024
Beall 2025
Xuan 2022
Coric 2013
Kumar 2017
G
Funding disclosure status
No
Unspecified
Yes
0.2287
0.7047
0.1114
0
20
40
60
80
100
VERTEBRA Completeness Scores (%)
H
Trial region
Europe
North America
Asia
0.0848
0.5478
0.5799
0
20
40
60
80
100
VERTEBRA Completeness Scores (%)
I
Journal impact factor (2024)
> 5.0
2.5 - 5.0
< 2.5 *
0.1946
0.0094
0.4130
0
20
40
60
80
100
VERTEBRA Completeness Scores (%)
J
Adherence to guidelines
(i.e., CONSORT or STROBE)
No
Yes
0.3077
0
20
40
60
80
100
VERTEBRA Completeness Scores (%)
K
Correlation with VERTEBRA
and perceived quality
VERTEBRA Completeness Scores (%)
100
80
60
40
20
0
r = 0.6101
p < 0.0001
0
2
4
6
8
10
Subjective quality grades

Fig. 4 Scoring results of the updated systematic review using the VERTEBRA reporting guidelines. (**A**, **B**) Characteristics of the 36 included clinical trial reports, showing study design features and types of RM products evaluated. (**C**) Reporting frequencies for each VERTEBRA checklist item across all studies, ordered by the number of reports receiving a "Yes" + "Partly" scores. Bars indicate the number of studies scored as "Yes", "Partly", "No", or "NA" for each item. (**D**) Distribution of "Yes", "Partly", "No", and "NA" scores across the five VERTEBRA domains. (**E**) Distribution of domain-specific completeness scores across all studies. (**F**) Overall VERTEBRA completeness scores for individual studies, highlighting the five highest-scoring reports. (**G-J**) Associations between VERTEBRA completeness scores and study characteristics, including funding disclosure status (**G**), geographic region of the corresponding or first author (H), journal impact factor in 2024 (I), and adherence to established reporting guidelines such as CONSORT or STROBE (**J**). (**K**) Correlation between VERTEBRA completeness scores and subjective quality grades assigned during the initial systematic review assessment. Spearman correlation coefficient (r) and corresponding p-value are shown. *Journal with an impact factor < 2.5 or no reported impact factor in the 2025 Journal Citation Reports. AF: annulus fibrosus; BMI: body mass index; EP: endplate; LBP: low back pain; MCID: minimal clinically important difference; NA: not applicable; RM: regenerative medicine

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Author contributions Jordy Schol: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing, Original Draft Preparation, Project Administration. Luca Ambrosio: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing, Original Draft Preparation, Project Administration. Clara Ruiz-Fernandez: Investigation, Data Curation, Review and Editing. Daisuke Sakai: Conceptualization, Supervision, Writing, Review and Editing. Gianluca Vadalà: Conceptualization, Supervision, Methodology, Writing, Review and Editing. VERTEBRA Working Group: Contributed to the development, discussion, refinement, prioritization, and consensus evaluation of the VERTEBRA reporting guideline through participation in surveys, workshops, and consensus activities. All authors reviewed and approved the final manuscript.

Data availability The data generated and analysed during the current study are provided within the article and its Supplementary Information. Additional data are available from the corresponding authors upon reasonable request.

Declarations

Competing interests Daisuke Sakai has received consulting fees from TUNZ Pharma Inc. He is also an inventor on multiple patents and patent applications assigned to Tokai University and/or Nippon Zoki Pharmaceutical Co., Ltd., related to nucleus pulposus cell evaluation, intervertebral disc regeneration, and the culture of Tie2-positive stem/progenitor cell-containing populations. Relevant granted patents include JP5863639B2, JP6712740B1, JP6779492B2, JP6905234B2, JP7421182B2, JP7554436B2, and JP7626993B2, as well as earlier foundational patents, including JP4036881B2 (expired). In addition, Jordy Schol and Daisuke Sakai are co-inventors on patents assigned to Tokai University and/or Kyoto University related to transcription factor-based generation of nucleus pulposus and progenitor cells (JP7298858B2 and JP7388755B2). A full list of conflict of interest is listed in Supplemental data for members of the VERTEBRA Working Group (Supplemental Data 4).

Ethics approval and consent to participate Ethics approval was not sought because the focus-group discussions and online survey were conducted as professional consultation activities for the development of a reporting guideline. The focus groups were held as voluntary workshops during the ISSLS Annual Meetings. CONSENT TO PARTICIPATE: Participation in the focus-group workshops and online survey was voluntary. Participants provided professional opinions on proposed checklist items, and findings were reported only in aggregate. CONSENT TO PUBLISH: All contributors were contacted by email and provided consent to be identified by name as members of the VERTEBRA Working Group in the manuscript.

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