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RESEARCH ARTICLE

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Why clinical trials in disc regeneration strive to achieve completion: Insights from publication status and funding sources

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Abstract

Background: Chronic discogenic low back pain (LBP) poses a significant global burden, yet effective therapeutic interventions directly targeting the underlying degenerative process remain elusive. After demonstrating promising results in preclinical studies, intradiscal injection of cell-based treatments has been increasingly investigated in the clinical setting. However, most clinical trials failed to reach publication, with the few available reports showing only minor improvements. The aim of this study was to analyze the prospective clinical trials registered on ClinicalTrials.gov investigating cell therapies for LBP, with a specific emphasis on identifying critical obstacles hindering study completion, including trial design and funding sources.

Methods: A systematic search of prospective clinical trials investigating cell-based treatments for chronic LBP due to intervertebral disc degeneration was performed on ClinicalTrials.gov. Extracted data encompassed study design, recruitment, experimental treatment modalities, investigated outcomes, current status, completion date, publication status, and funding sources. Fisher's exact test assessed associations between categorical variables, while a multiple logistic regression model aimed to identify factors potentially linked to the publication status of the studies.

Results: Our search identified 26 clinical trials. Among these, only 7 (26.9%) were published, and none of the other studies marked as completed reported any results on ClinicalTrials.gov. Fifty percent of included trials were funded by universities, whereas the rest was sponsored by industry (38.5%) or private institutions (11.5%). Experimental treatments primarily involved cell-based or cell-derived products of varying sources and concentrations. Products containing carriers, such as hyaluronic acid or fibrin, were more frequently funded by industry and private organizations ($p = 0.0112$). No significant differences emerged when comparing published and

nonpublished studies based on funding, as well as between publication status and other variables.

Conclusion: Most clinical trials exploring cell-based disc regenerative therapies for chronic LBP have never reached completion, with only a small fraction reporting preliminary data in publications.

KEYWORDS
clinical trial, intervertebral disc degeneration, intervertebral disc regeneration, low back pain, regenerative medicine, stem cells

1 | INTRODUCTION

Low back pain (LBP) stands as the predominant global cause of years lived with disability, afflicting over 500 million individuals worldwide and imposing a substantial socioeconomic burden.[1] Despite its multifactorial pathophysiology, the main cause of LBP is intervertebral disc degeneration (IDD): a chronic, progressive process characterized by the alteration of disc integrity and function ultimately leading to biomechanical overloading and structural derangement. At the tissue level, IDD is hallmarked by the gradual loss of resident cells, which fail to maintain the highly specialized disc matrix composition. Furthermore, increased oxidative stress, tissue inflammation, and decreased nutrient supply perpetuate this degenerative cascade.[2,3]

In the last decade, the possibility to directly tackle the pathophysiology of IDD by replenishing the disc cell content via transplantation of de novo cells has gained significant momentum in the field.[4] Several preclinical studies have demonstrated the capacity of transplanted cells, especially mesenchymal stromal cells (MSCs), to limit, halt, or even reverse IDD both in vitro and in vivo, variably reporting significant enhancements of cell metabolism, matrix composition, and inflammation inhibition, eventually leading to structural restoration of degenerative discs.[5–7] Therefore, the increasing body of preclinical evidence has promoted the translation of cell therapy for IDD to the clinical setting, with multiple prospective clinical trials emerging over the last few decades.[8] Several cell types, sources, and related products have been investigated, including autologous and allogeneic MSCs isolated from diverse tissues (e.g., bone marrow, adipose tissue, umbilical cord), variable cell concentrations, different formulations (e.g., suspended in saline or blended with specific carriers), and single versus multiple injections (i.e., single-level vs. multilevel).

However, despite the preclinical evidence, most published studies have failed to confirm substantial clinical benefit over placebo or sham controls, cost-effectiveness compared with already available treatments, and measurable regenerative outcomes (e.g., imaging improvement).[9,10] This discrepancy may be attributed to interventional variability and substantial heterogeneity in study design, eligibility criteria, and outcome measures, potentially introducing bias and limiting the generalizability of individual trial results.[11] In addition, the results of some trials have been published, while others have not. The underlying reasons are multifactorial, although a previous study has linked funding sources to publication failure, with results from trials funded by the industry less likely to be published than those from nonindustry-funded studies.[12]

The aim of this study was to analyze the prospective clinical trials registered on ClinicalTrials.gov investigating cell-based regenerative therapies for LBP. Our objective was to identify critical issues that may have hindered study publication, with a specific focus on trial design and funding sources.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A systematic search was performed on ClinicalTrials.gov, the largest global database of privately and publicly funded clinical trials, with more than 470 000 registered studies.[13] As part of section 402(j) of the Public Health Service Act, every clinical trial investigating a Food and Drug Administration (FDA)-regulated drug or medical device must be registered in this database.[14] The terms "spine," "spinal," "lumbar," "disc," "cells," "regeneration," "mesenchymal," and "stem" were used in combination with Boolean operators to search for interventional prospective studies evaluating intradiscal cell-based regenerative treatments for LBP due to IDD in adult patients from inception to November 12, 2023. The full search strategy was composed as follows: "Interventional Studies | (spine OR spinal OR lumbar OR disc) AND (cells OR regeneration OR mesenchymal OR stem) NOT cord NOT infection | Adult, Older Adult." The initial search of the studies was conducted by two reviewers (LA and GP). In case of disagreements, a third reviewer (CC) was involved to solve inconsistencies.

2.2 | Data extraction

The study variables extracted included national clinical trial (NCT) identification number, country, trial status, funding source, trial start date, trial completion date (if any), estimated enrollment, actual enrollment (if any), type of intervention, number of treated disc levels, follow-up, primary outcome(s), secondary outcome(s), blinding (if any), number of study arms, randomization (if any), study model, study

phase, publication status, and number of citations according to Scopus (if published). Publication status was assessed via a PubMed search of trial titles, NCT numbers, and/or investigator names.

2.3 | Statistical analysis

Categorical variables were shown as absolute (*n*) and relative (%) frequencies. The Fisher's exact test was utilized to test the association of categorical variables between groups. A multiple logistic regression model was built to evaluate the association between the publication status of each trial (dependent variable: yes/no) and funding source, number of primary outcomes, number of secondary outcomes, follow-up (months), estimated enrolment, number of study arms, blinding (yes/no), randomization (yes/no), missed completion date (yes/no). Odds ratio and 95% confidence intervals were estimated for each reference category. Statistical significance was set at $p < 0.05$. Formal analysis was conducted using Prism 10 (v. 10.1, GraphPad Software).

3 | RESULTS

3.1 | Search output

Our search identified a total of 625 studies. Among these, 20 studies met eligibility criteria, and 6 additional studies were manually identified, resulting in a total of 26 trials included for analysis (Table 1). These studies were conducted in Italy,[15–17] South Korea,[18–21] Greece,[22] USA,[23–34] Indonesia,[35] China,[36] Spain,[17,37,38] Australia,[29,31] Japan,[39] Germany,[17,40] Austria,[40] France,[17] and Ireland[17] starting from 2008.[37] The status of most included studies was flagged as "unknown" (eight studies, 30.8%), while the others were categorized as "not yet recruiting" (one study, 3.8%), "suspended" (one study, 3.8%), "completed" (eight studies, 30.8%), "withdrawn" (three studies, 11.5%), "terminated" (two studies, 7.6%), or "active, not recruiting" (three studies, 11.5%). The primary sources of funding were universities (13 studies, 50%), followed by industry (10 studies, 38.5%) and private institutions (3 studies, 11.5%).

3.2 | Study design

Among the included trials, 12 (45.6%) were open-label, unblinded, single-arm, nonrandomized, phase I or IIA studies (Table 1).[18,20–22,26–28,33,35–37,40] The remaining trials were characterized by a parallel design (13 studies, 50%)[15–17,19,23,24,29–32,34,38,39] and included one cross-over study (3.8%).[25] Among multiple-arm studies, experimental cell-based products were compared with either a sham procedure,[15–17,25,29–32,34,38,39] intradiscal administration of hyaluronic acid (HA),[19,31,32] corticosteroids and local anesthetic,[23] sequestrectomy,[40] or no treatment.[24,26] All parallel studies were blinded, consisting of single (outcome assessors[23,24]), double (participants and outcome assessors[31,32,34,39]), triple (participants, care providers, and outcome assessors)[15–17,19,38] or quadruple (participants, care providers, outcome assessors, investigators[29,30]) masking. The only trial with a cross-over design was a single-blind study in which participants randomized to receive either the interventional experimental therapy or placebo were unaware of treatment allocation. However, patients assigned to conservative care were unblinded but had the possibility to cross-over at 3 months into the experimental group.[25]

3.3 | Study interventions

The experimental treatments investigated in the included trials consisted of the intradiscal administration of cells, platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), or tissue allografts (Table 2). Carrier-free bone marrow-derived mesenchymal stromal cells (BM-MSCs), either autologous[15,16,23,26,37] or allogeneic,[17,38] constituted the most common cell-based intervention (7 studies, 26.9%). Autologous adipose-derived stromal cells were injected in 5 studies (19.2%), alone[18,21,27,28] or mixed with HA derivatives.[20] Allogeneic umbilical cord-derived mesenchymal stromal cells were utilized in three studies (11.5%), alone[35,36] or resuspended in HA.[19] Two studies (7.6%)[32,39] assessed the effect of injectable discogenic cell therapy, a blend of sodium hyaluronate and allogeneic discogenic cells, on a cell population derived from human nucleus pulposus (NP) cells following in vitro expansion in a specific culture environment.[41] Two clinical trials (7.6%) investigated the intradiscal administration of Rexlemestrocel-L, a combination of human BM-MSC precursor cells and HA patented by the company Mesoblast Ltd (Melbourne, Australia).[29,31]

One trial (3.8%) aimed at investigating the effectiveness of intradiscal NuQu®, a blend of culture-expanded allogeneic juvenile chondrocytes delivered in a fibrin carrier.[30] One (3.8%) study evaluated the administration of Novocart® Disk Plus, a carrier designed for autologous disc-derived chondrocyte transplantation.[40] More specifically, patients enrolled in this trial underwent surgical sequestrectomy for single-level lumbar disc herniation. Subsequently, disc cells were isolated from the herniated material, culture-expanded, and re-injected after 90 days in combination with additional components in the form of a hydrogel with anti-inflammatory, anti-angiogenic, and anti-osteogenic properties.[42] This strategy was compared with the same hydrogel without active cells and with sequestrectomy alone. The concentration of investigated cell-based treatments ranged between 0.7×10^6 and 40×10^6 cells per disc level.[19–21]

Platelet-rich plasma was injected in both facet joints and affected discs in one study (3.8%).[22] Intradiscal BMAC administration was investigated in three studies (11.5%)[24,33,34]; among these, one trial assessed the injection of BMAC into the discs, facet joints, epidural space, and sacroiliac joints.[24] One trial investigated the intradiscal injection of an NP-viable allograft produced by VIVEX Biologics, Int. (Marietta, GA, USA), composed of a suspension of cryopreserved cells reconstituted in saline before administration.[25] Allogeneic treatments were formulated as a commercial product in seven trials (26.9%).[25,29–32,39,40] Interestingly, there was a significant association between

TABLE 1 Basic information and design of included clinical trials.

NCT ID	Country	Status	Funding source	Study design				
				Blinding	Study arms (*n*)	Randomization	Model	Study phase
NCT05066334[16]	Italy	Unknown	University	Triple (participant, care provider, and outcome assessor)	2	Yes	Parallel	IIB
NCT05011474[18]	South Korea	Unknown[a]	University	No	1	No	Open label	I/IIA
NCT04816747[22]	Greece	Not yet recruiting	University	No	1	No	Open label	I
NCT04759105[15]	Italy	Active, not recruiting	University	Triple (participant, care provider, and outcome assessor)	2	Yes	Parallel	IIB
NCT04735185[23]	United States	Suspended	University	Single (outcome assessor)	2	Yes	Parallel	NS
NCT04559295[24]	United States	Unknown	Private	Single (outcome assessor)	2	No	Parallel	NS
NCT04530071[19]	South Korea	Completed	Industry	Triple (participant, care provider, and outcome assessor)	3	Yes	Parallel	I/IIA
NCT04499105[35]	Indonesia	Unknown	University	No	1	No	Open label	I
NCT04414592[36]	China	Unknown	University	No	1	No	Open label	I
NCT03709901[25]	United States	Unknown[a]	Industry	Single (participant)	3	Yes	Cross-over	NS
NCT03692221[26]	United States	Withdrawn[b]	University	No	3	Yes	Open label	I
NCT03461458[27]	United States	Terminated	University	No	2	No	Open label	I
NCT02440074[37]	Spain	Withdrawn[a]	University	No	1	No	Open label	I
NCT02412735[29]	United States, Australia	Completed	Industry	Quadruple (participant, care provider, outcome assessor, and investigator)	3	Yes	Parallel	III
NCT02338271[20]	South Korea	Unknown[a]	University	No	1	No	Open label	I
NCT02097862[28]	United States	Completed	Industry	No	1	No	Open label	I
NCT01860417[38]	Spain	Completed	University	Triple (participant, care provider, and outcome assessor)	2	Yes	Parallel	I/II
NCT01771471[30]	United States	Terminated	Industry	Quadruple (participant, care provider, outcome assessor, and investigator)	2	Yes	Parallel	II
NCT01643681[21]	South Korea	Withdrawn	Industry	No	1	No	Open label	I
NCT01290367[31]	United States, Australia	Completed	Industry	Double (participant and outcome assessor)	4	Yes	Parallel	I/II
NCT03955315[39]	Japan	Completed	Industry	Double (participant and outcome assessor)	3	Yes	Parallel	I/II
NCT03347708[32]	United States	Completed	Industry	Double (participant and outcome assessor)	4	Yes	Parallel	I/II

TABLE 1 (Continued)

NCT ID	Country	Status	Funding source	Study design				
				Blinding	Study arms (*n*)	Randomization	Model	Study phase
NCT01640457[40]	Germany, Austria	Completed	Industry	No	3	Yes	Open label	I/II
NCT03912454[33]	United States	Active, not recruiting	Private	No	1	No	Open label	NS
NCT03340818[34]	United States	Unknown	Private	Double (participant and outcome assessor)	2	Yes	Parallel	NS
NCT03737461[17]	France, Italy, Spain, Ireland, and Germany	Active, not recruiting	University	Triple (participant, care provider, and outcome assessor)	2	Yes	Parallel	II/III

Abbreviations: COVID, coronavirus disease; NCT, national clinical trial; NS, not specified.
[a]Trial status not corresponding to the actual status of the study. See text for explanations.
[b]Stalled due to COVID.

funding sources and composition of experimental treatments, with investigational products containing carriers (e.g., HA, fibrin, etc.) being more likely funded by industry and private organizations compared with other funding sources ($p = 0.0112$, Figure 1).

Investigational treatments were injected into either a single-disc level in the majority of trials (14 studies, 53.8%[17,19–21,26,27,29–32,36,37,39,40]), whereas remaining studies treated 1–2,[18,22,23,25,33,38] 1–3,[16,28] or 1–4 disc levels.[15] The number of treated discs was not specified in three trials.[24,34,35]

3.4 | Study outcomes

The primary outcomes of included trials primarily focused on LBP intensity measured via a visual analogue scale (11 studies, 42.3%),[15–17,22,25,28,33–35,37,39] followed by LBP-related disability assessed by the Oswestry Disability Index (9 studies, 34.6%).[15–17,24,25,30,33,34,40] Safety endpoints, in terms of adverse events, alterations of vital signs, laboratory values, and complications, constituted the primary outcome of other nine studies (34.6%).[18–20,26,27,31,32,38,39] In the remaining trials, the primary outcomes included LBP severity rated with the numeric rating scale (NRS)[23] and related quality of life (Short Form-36[22]), work capacity (Work Ability Index [WAI][15]), overall treatment success,[29] and structural disc improvements at magnetic resonance imaging (MRI).[21,35,36]

Secondary outcomes included, in addition to the aforementioned scores, other quality of life measurements (Short Form-12 [SF-12], European Quality of Life-5 dimensions, Global Health Scale [GHS], Euro Quality of Life [EuroQoL], patient global impression of change [PGIC], Patient-reported Outcome Measure Information System Global-10, North American Spine Society [NASS] score), assessment of psychosocial aspects (Hospital Anxiety and Depression Scale [HADS], Athens Insomnia Scale [AIS]), X-ray and MRI changes, disability (Japanese Orthopedic Association Back Pain Evaluation Questionnaire [JOABPEQ]), painkiller and narcotic consumption, work status, cost analyses, complications, magnetic resonance spectroscopy of injected discs, and biochemical analyses of injected treatments (Table 2). Follow-up ranged from 6[18,21,28,35] to 48 months,[32,40] with 12 months being the most common time point among included trials (11 studies, 42.3%[15,19,20,23,26,33,34,36–39]).

3.5 | Study enrolment and publication status

The estimated enrolment among included studies ranged from 4[18] to 330 participants,[29] with an average of 64.8 patients per trial. Out of 26 studies, 14 (53.9%) exceeded their estimated completion date, with an average delay of 17.9 months. Among all trials, 11 (42.3%) were completed, but only 7 were published (26.7%; Table 2).[43–49] Of these, one is a short report of treatment safety at 6 weeks of follow-up,[42] although the results of the whole trial,[40] if ever concluded, are lacking.

Although being successfully concluded and reported,[44] one study status was flagged as "withdrawn"[37] due to nonfulfillment of administrative formalities, where as another three studies were categorized as "unknown"[18,20,25] because of missing updates for more than 2 years, even if concluded.[47–49] One study was stalled due to coronavirus disease 2019 (COVID-19)[26] (Table 1). Study results were uploaded on ClinicalTrials.gov only in one case.[29]

There was no statistically significant difference when comparing published and nonpublished studies based on funding sources (Table 3). Similarly, no significant association was found between publication status and other variables, namely funding source, number of primary outcomes and secondary outcomes, follow-up duration, estimated enrolment, number of study arms, blinding, randomization, and missed completion date (Table S1).

TABLE 2 Therapeutical interventions, outcomes, and actual status of included trials.

NCT ID	Intervention	Comparison	Disc levels (*n*)	Primary outcome(s)	Secondary outcome(s)	Follow-up (months)	Estimated enrolment	Actual enrolment	Start date	Missed estimated study completion date?	Completion date	Published?	Citations
NCT05066334[16]	Intradiscal injection of autologous BM-MSCs (15×10^6 cells/disc)	Sham	1–3	VAS, ODI	SF-36, quality of life evolution, painkiller consumption, work status, MRI changes, cost analysis, and safety	24	52	39	March 2021	Yes		No	
NCT05011474[18]	Intradiscal injection of matrilin-3-pretreated autologous ADSCs	-	1–2	Safety	VAS, ODI, and MRI changes	6	4	8	April 2021	Yes	December 2022	Yes[49]	0
NCT04816747[22]	Intradiscal and intra-articular facet injection of autologous PRP	-	1–2	VAS, SF-36	Complications	24	50		April 2022	No		No	
NCT04759105[15]	Intradiscal injection of autologous BM-MSCs (15×10^6 cells/disc)	Sham	1–4	VAS, ODI, WAI	SF-36, quality of life evolution, painkiller consumption, work status, MRI changes, cost analysis, safety, and MRS	12	52	52	November 2020	No		No	
NCT04735185[23]	Intradiscal injection of autologous BM-MSCs	Intradiscal CCS and local anesthetic	1–2	NRS	HADS, AIS, PGIC, ODI, and MRI change	12	106		September 2025	No		No	
NCT04559295[24]	Delivery of BMAC into discs, facet, epidural space, and sacroiliac joints	No treatment	NS	ODI	NRS, VAS, PROMIS Global-10, NASS, and EuroQoL	24	80		November 2018	Yes		No	
NCT04530071[19]	Intradiscal injection of allogeneic UC-MSCs suspended in saline and HA (0.7×10^6 or 21×10^6 cells/disc)	HA + saline + placebo	1	Safety	NS	12	36	36	September 2020	Yes	April 2023	No	
NCT04499105[35]	Intradiscal injection of allogeneic UC-MSCs	-	NS	VAS, MRI changes	NS	6	10		July 2017	Yes		No	
NCT04414592[36]	Intradiscal injection of allogeneic UC-MSCs (20×10^6 cells/disc)	-	1	MRI changes	VAS, ODI, SF-36, DHI, disc herniation size, and AEs	12	20		June 2020	Yes		No	
NCT03709901[25]	Intradiscal injection of NP viable allograft	Sham	1–2	ODI, VAS	MRI changes, X-ray changes, AEs, and Resource Utilization Questionnaire	36	218	218	August 2017	No	March 2020	Yes[47]	9
NCT03692221[26]	Intradiscal injection of autologous BM-MSCs (2×10^6 or 4×10^6 cells/disc)	No treatment	1	Safety	VAS, ODI, SF-36, and MRI changes	12	24	0	June 2019	Yes		No	
NCT03461458[27]	Intradiscal injection of autologous ADSCs (5×10^6 or 20×10^6 cells/disc)	-	1	Safety	VAS, GHS, ODI, SF-36, Narcotic Use Questionnaire, MRI changes, and X-ray	24	16	1	October 2018	No		No	
NCT02440074[37]	Intradiscal injection of autologous BM-MSCs	-	1	VAS	NS	12	10	10	December 2008	No	June 2011	Yes[44]	387
NCT02412735[29]	Intradiscal injection of Rexlemestrocel-L cells (6×10^6 cells/disc) versus Rexlemestrocel-L + HA (6×10^6 cells/disc)	Sham	1	Overall treatment success	VAS, ODI, and time to first intervention	24	330	404	March 2015	Yes	June 2021	No	
NCT02338271[20]	Intradiscal injection of autologous ADSCs (20×10^6 or 40×10^6 cells/disc) + HA derivatives	-	1	Safety	MRI changes, DHI, VAS, ODI, and SF-36	12	10	10	January 2015	No	September 2017	Yes[48]	127

TABLE 2 (Continued)

NCT ID	Intervention	Comparison	Disc levels (*n*)	Primary outcome(s)	Secondary outcome(s)	Follow-up (months)	Estimated enrolment	Actual enrolment	Start date	Missed estimated study completion date?	Completion date	Published?	Citations
NCT02097862[28]	Intradiscal injection of autologous ADSCs + PRP	-	1–3	VAS	ODI	6	100	15	March 2014	No	January 2017	Yes[45]	61
NCT01860417[38]	Intradiscal injection of allogeneic BM-MSC (25×10^6 cells/disc)	Sham	1–2	Safety	VAS, MRI changes, and SF-12	12	24	24	April 2013	No	March 2016	Yes[43]	160
NCT01771471[30]	Intradiscal injection of allogeneic juvenile chondrocytes in fibrin carrier	Sham	1	ODI	Satisfaction, MRI changes, and VAS	24	44		November 2012	Yes		No	
NCT01643681[21]	Intradiscal injection of autologous ADSCs (40×10^6 cells/disc)	-	1	MRI changes	VAS, neurological examination, and safety	6	8	0	July 2012	Yes		No	
NCT01290367[31]	Intradiscal injection of MPCs with HA (6×10^6 or 18×10^6 cells/disc)	Sham control, intradiscal HA control	1	Safety	MRI changes and VAS	36	80	100	August 2011	Yes	July 2015	Yes[46]	35
NCT03955315[39]	Intradiscal injection of IDCT (3×10^6 or 9×10^6 cells/disc)	Sham	1	Safety, VAS	ODI, JOABPEQ, MRI changes, and X-ray changes	12	38	38	May 2019	No	February 2022	No	
NCT03347708[32]	Intradiscal injection of IDCT (3×10^6 or 9×10^6 cells/disc)	Sham control, intradiscal HA control	1	Safety	ODI, MRI changes, and X-ray changes	48	60	60	February 2018	Yes	November 2022	No	
NCT01640457[40]	Intradiscal injection of ND plus (autologous disc chondrocyte transplantation system) versus ND basic (media with no active cell component)	Sequestrectomy	1	ODI	MRI changes, VAS, SF-36, EQ-5D, neurological status, functional status, return to work, painkiller consumption, periprocedural outcomes, histology, and biomarkers	48	120	120	August 2012	No	June 2021	No	
NCT03912454[33]	Intradiscal injection of autologous BMAC	-	1–2	VAS, ODI	Satisfaction, MRI changes, and CFU-F analysis	12	20		April 2020	Yes		No	
NCT03340818[34]	Intradiscal injection of autologous BMAC	Sham	NS	VAS, ODI (6 months)	VAS, ODI, medication usage, and adjunct therapy	12	60		August 2018	Yes		No	
NCT03737461[17]	Intradiscal injection of allogeneic BM-MSCs (20×10^6 cells/disc)	Sham	1	VAS, ODI	SF-36, painkiller consumption, work status, MRI changes, cost analysis, MSC immune profile, and safety	24	112	113	February 2019	No		No	

Abbreviations: ADSCs, adipose-derived stromal cells; AE, adverse event; AIS, Athens Insomnia Scale; BMAC, bone marrow aspirate concentrate; BM-MSCs, bone marrow-derived mesenchymal stromal cells; CCS, corticosteroids; CFU-F, colony-forming units fibroblastic; DHI, disc height index; EuroQoL, Euro Quality of Life; EQ-5D, European Quality of Life-5 Dimensions; GHS, Global Health Scale; HA, hyaluronic acid; HADS, Hospital Anxiety and Depression Scale; IDCT, injectable discogenic cell therapy; JOABPEQ, Japanese Orthopedic Association Back Pain Evaluation Questionnaire; MPCs, mesenchymal precursor cells; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NASS, North American Spine Society; ND, Novocart® Disk; NP, nucleus pulposus; NRS, numeric rating scale; ODI, Oswestry Disability Index; PGIC, patient global impression of change; PROMIS, Patient-reported Outcome Measure Information System; PRP, platelet-rich plasma; SF, Short Form; UC-MSCs, umbilical cord-derived stem cells; VAS, visual analogue scale; WAI, work ability index.

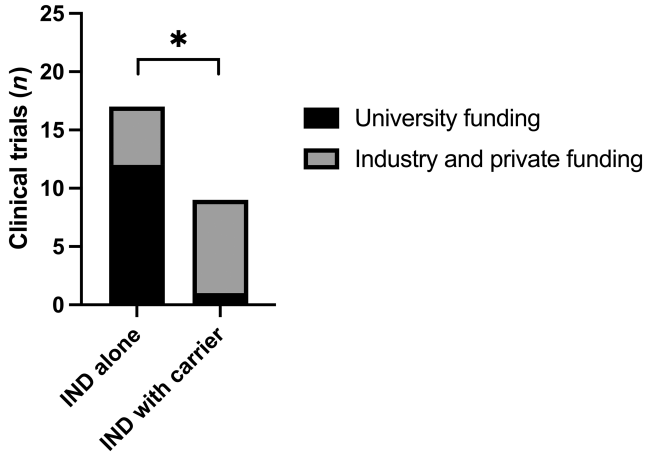

FIGURE 1 The proportion of clinical trials investigating investigational new drugs (INDs) alone or combined with a carrier or scaffold between university and industry or privately funded studies. *$p = 0.0112$.

TABLE 3 Funding source and publication status of included studies.

	Published	Nonpublished	Total
Industry or private funding	3	10	13
University funding	4	9	13
Total	7	19	26

4 | DISCUSSION

Our study revealed that most clinical trials investigating cell-based regenerative treatments for chronic discogenic LBP and registered in ClinicalTrials.gov, the largest clinical study database in the world, were never completed nor published. Indeed, <30% of prospective trials made it from conception to publication. Among these studies, 71% included fewer than 25 patients,[43–45,48,49] 57% were characterized by a single-arm, open-label, and unblinded design,[44,45,48,49] with one study[45] having enrolled only 15% of the initially estimated population, therefore collectively providing a considerably low level of evidence. Previous investigations have shown that private- and industry-funded trials in spine research were less likely to be published.[12,50] In our study, we did not find any statistical difference in terms of publication status among trials sponsored by universities and private companies. However, trials exploring regenerative therapies involving acellular scaffolds or matrices (e.g., HA, fibrin, etc.) were more likely to be sponsored by private companies, which were—not unexpectedly—proprietary of such technology.

Our data also displayed that the rate of registered trials not achieving publication was alarmingly high (73%), even when compared with publication rates of clinical trials related to orthopedic trauma (43%),[51] biologics for cartilage repair and osteoarthritis (44%),[52] and adult spine surgery (21%).[50] Nonetheless, it is noteworthy that 19.2% of the trials included in the analysis were flagged as completed but lacked any reported results, potentially indicating a concern for publication bias. Indeed, it is widely known that studies with positive outcomes have a higher chance of being published compared with negative studies.[53] This selective dissemination of positive results can skew the perceived efficacy of treatments and distort the interpretation of clinical evidence, with possibly disastrous consequences.[54]

The premature termination or failure to finalize clinical trials in the disc regeneration field appears to be a complex issue, common to several early-stage studies in translational research.[55] Various factors may contribute to this phenomenon, including inadequate study design, low statistical power, inappropriate eligibility criteria, patient dropout, and financial constraints.[11]

A significant portion of the studies included in the analysis recruited patients with chronic LBP associated with imaging findings of mild-to-moderate IDD. However, an inherent selection bias may be related to the fact that LBP is a symptom, while IDD is not always a disease. Indeed, chronic LBP may be caused by multiple conditions other than IDD[56] and has global prevalence rates between 1.4 and 15.6%.[57] However, IDD changes are present in high proportions of asymptomatic individuals, ranging from 52% in 30-year-old patients to 88% in sexagenarians.[58] Therefore, the likelihood of including patients whose LBP is due to other causes, despite concomitant IDD, is remarkably high and may introduce confounding. Hence, the administration of biological intradiscal therapies in this subset of patients may significantly bias the evaluation of treatment outcomes.

Similarly, a high rate of patient dropout can notably affect the conduction of a clinical trial and even prevent its conclusion. Indeed, uncontrolled loss to follow-up results in a decrease of statistical power and may seriously impact study results. Previous research suggests that dropout rates exceeding 5% introduce bias, whereas rates surpassing 20% pose serious threats to study validity, even in the presence of specific strategies to address missing data.[59] Among published trials from our search, loss to follow-up rates ranged from 9%[42] to 27%,[46] therefore posing a substantial risk of bias. According to the authors of one study,[47] patient dropout was mainly attributed to discontinuation because of perceived improvement or seeking other medical options in case of treatment failure. Both phenomena may be associated with placebo and nocebo effects, which can be defined as the consequences of patients' positive and negative expectations on their outcomes, respectively.[60] This type of cognitive bias is more common in patients with a history of psychological distress and anxiety, which is also more common in individuals with chronic LBP.[56] Because most trials in disc regeneration include subjective scores among their primary outcomes, exaggeration or minimization of reported symptoms can significantly alter the nature and direction of collected data, irrespective of the treatment (if any).

The high costs associated with the biological treatments investigated in these trials represent another significant obstacle. For instance, the production of autologous MSCs often requires a two-step procedure during which cells are first harvested, then isolated, culture-expanded, and later injected into the patients. Expenses are further amplified by the need for specialized facilities, time and consumables required for in vitro cell expansion, good manufacturing

practice-compliant handling of experimental products, and repeated hospital admissions, potentially reaching several thousand dollars per patient.[61,62] In this context, the combination of high costs, potential underfunding, and patient dropout may further reduce the opportunity to generate positive outcomes, thus possibly leading to a premature termination of the study.[11]

Altogether, the disc regeneration field is likely facing the hurdles of the translational gap between the bench and bedside, also known as the "Valley of Death."[55] As discussed above, such issues are multifactorial and need to be carefully examined to prevent premature study failure. One main reason could be related to the discrepancies between preclinical models of IDD and their human counterpart, which may not be fully replicated in terms of structure, complexity, and clinical features. In this regard, preferring the use of animal models which can better resemble the human pathology (e.g., chondrodystrophic dogs) may enhance their translational potential.[63] However, because chronic LBP may be triggered by several causes other than IDD, novel tools for LBP phenotyping may be of help during patient recruitment to avoid selection bias.[64] This may, in turn, increase the internal validity and reliability of study outcomes, possibly reducing patient dropout due to stricter selection criteria. In this context, a thorough, collaborative, and extensive education of included patients is essential to adjust their expectations and avoid unwanted loss to follow-up. Another major point is the necessity to enhance the transparency of conducted studies and encourage the publication of negative results. This would not only avoid the design of additional futile trials but also enhance the credibility of researchers in front of funding agencies. Furthermore, considering the socioeconomic resonance of chronic LBP, the involvement of patient associations would further raise awareness and attract potential funders, which may support the successful completion of these trials.

This study has some limitations. Although extensive, ClinicalTrials.gov does not comprehensively encompass all historical and ongoing clinical trials within a specific research field. Although the FDA specifically demands all clinical studies run in the USA to be registered on ClinicalTrials.gov, this requirement may not extend to trials conducted outside the USA. Varied regional, local, and institutional policies contribute to the potential absence of numerous clinical trials that have received approval from alternative regulatory bodies, such as the European Union Drug Regulating Authorities Clinical Trials Database, national boards, or local institutional review boards. Indeed, recent systematic reviews investigating the available clinical evidence on disc regeneration have included a significantly higher number of published studies in addition to the trials found in our search.[4,65] Therefore, although representative, the conclusions of this study may be partial and not completely faultless. In addition, data extracted from ClinicalTrials.gov may not be always accurate, because the reliability of data entry depends on the principal investigator and the reported status of a trial may not consistently align with its actual progress. For example, a trial status is automatically flagged as "unknown" if the investigators do not update it for more than 2 years, independent of its progression (Table 1). Therefore, the potential discrepancies in data reliability from this source necessitate a cautious interpretation of our findings. Furthermore, careful considerations should be made regarding the interpretation of publication rates described in this study, which were calculated as the percentage of registered trials eventually published in a peer-reviewed journal. Although simplistic, this did not distinguish unpublished studies among those which were withdrawn, terminated due to safety and/or efficacy issues, or completed but still in the process of being submitted or published.

5 | CONCLUSION

The majority of prospective clinical trials investigating innovative cell-based regenerative treatments for chronic LBP due to IDD never reached completion, with only a small percentage (26.9%) being published. No significant effect of funding sources or other variables seemed to impact this process. Failure to conclude these studies is likely multifactorial and can be imputed to a combination of high costs, uncontrolled dropout rate, heterogeneous patient selection, and difficulty in translating preclinical disease models and therapies to a real-world clinical scenario. Future large-scale, randomized, placebo-controlled studies specifically recruiting patients with discogenic chronic LBP will likely shape the role of regenerative treatments for IDD in the next years.

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CONFLICT OF INTEREST STATEMENT

Gianluca Vadalà is an Editorial Board member of JOR Spine and co-author of this article. He was excluded from editorial decision-making related to the acceptance of this article for publication in the journal.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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