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SYSTEMATIC REVIEW

A systematic review of intervertebral disc degeneration clinical trial protocols

[version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Introduction

Intervertebral disc degeneration (IDD) is a significant contributor to chronic back pain and disability. Despite its global prevalence, the knowledge about treatment options that can be appraised is limited, and some current interventions often fail to provide enduring relief. This review explores IDD management strategies.

Methods

A systematic search of ClinicalTrials.gov was conducted in September 2024 for interventional trials targeting intervertebral disc degeneration IDD. Data including interventions, study design, sample size, phase, outcomes, sponsor, and status were extracted following PRISMA guidelines. Data was synthesized, focusing on trial protocols and methodologies.

Results

Eighteen trials met the inclusion criteria, that enrolled approximately 1,272 participants. Interventions included surgical implants (44%, e.g., novel cages, artificial discs), biologic therapies (28%, e.g., stem cell injections, allografts), pharmacologic adjuncts (22%, e.g., tranexamic acid, analgesics), and conservative care (6%, bracing). Primary outcomes were diverse, including patient-reported outcomes (PROs, 33%), imaging-based measures (fusion/alignment, 39%), composite endpoints (17%), and safety/perioperative metrics (11%). Most studies (72%) were device or procedural trials without a phase designation; one Phase 3 trial investigated mesenchymal stem cells. Sponsorship

Open Peer Review

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was mixed between academic/institutional (50%) and industry (50%). Notably, 6 out of 18 trials (33%) were terminated early.

Discussion

IDD clinical trials have significant emphasis on optimizing spinal fusion and exploring regenerative medicine. Patient-centered outcomes have been increasingly prioritized alongside structural endpoints. The high rate of early trial termination highlights that research challenges remain. This review maps current innovations, providing a foundation for understanding emerging evidence that may shape future IDD treatment paradigms.

Plan language summary

Intervertebral disc degeneration (IVD) is a common cause of long-lasting back pain and disability affecting many people worldwide. Although this condition is widespread, there are still limited effective treatment options available, and many current methods do not provide lasting relief. This study looks into different approaches to managing IVD by reviewing clinical trials that have been conducted to identify trends and areas where more research is needed.

This study analyzed 18 clinical trial protocols registered between 2013 and 2024 and found that surgical implants were the most common treatment methods (44% of trials), followed by biological therapies (28%), and pharmacological adjuncts (17%). Other types of treatments, such as conservative care approaches, were less frequently used (6%).

Our findings show a shift in pharmacological treatments toward managing pain with fewer opioids and using specialized drug formulations as alternatives. Medical devices generally aim to improve spine fusion outcomes (75%), some including personalized device geometries (38%), and few spine motion preserving devices (25%) were reported. Biological interventions increasingly focus on regenerative medicine. The study also found significant differences in the design and quality of these clinical trials, with a notable 33% of early termination rate, suggesting remaining challenges in intervertebral disc disease and treatment research, as well as a need for standardized guidelines to improve the consistency and reliability of clinical trial outcomes.

Keywords
Intervertebral disc degeneration (IDD), chronic back pain, clinical trial protocols, interventions, standardization



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Introduction

Intervertebral disc degeneration (IDD) is a prevalent condition that results in chronic back pain and disability. The degenerative process is marked by intricate biological and structural alterations in the intervertebral disc, potentially leading to disc herniation, spinal stenosis, and other spinal disorders[1]. It's global prevalence has been reported to be as high as 58 – 84% in individuals aged 40–59, making it a leading cause for disability worldwide[2]. Despite its widespread occurrence and significant impact on quality of life, the available treatment options for IDD are limited and often fail to provide enduring relief[3].

The initial step in managing IDD is an accurate diagnosis, typically involving a comprehensive medical history, physical examination, and imaging studies such as MRI or CT scans. The diagnosis of IDD is often based on characteristic symptoms, such as back or neck pain and evidence of disc degeneration in imaging studies[4].

Conservative treatment is commonly the first line of therapy for IDD, encompassing a variety of approaches such as physical therapy, pain management with medications, and lifestyle modifications. Physical therapy can aid in strengthening the muscles that support the spine, improving flexibility, and promoting good posture. Pain management can involve using non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and, in some cases, opioid medications[5].

If conservative treatments prove ineffective, non-surgical treatments may be considered. Examples of these include epidural steroid injections, which can help to reduce inflammation and relieve pain and nerve blocking and radiofrequency ablation, which can help to disrupt the pain signals from the affected disc[6].

When conservative and non-surgical treatments fail to provide relief or when the patient has severe or progressive neurological symptoms, surgical treatment is considered. Surgical options can include discectomy, where part or all of the degenerated disc is removed, and spinal fusion, where two or more vertebrae are fused to stabilize the spine[7].

Regenerative medicine also offers a promising direction for treatment, aiming to restore disc integrity through cell therapy and tissue engineering. Preclinical studies suggest that mesenchymal stem cells (MSCs) can differentiate into disc cells and produce vital matrix proteins, while advances in biomaterials provide scaffolds for cell delivery and disc repair[8]. These approaches could shift IDD treatment from symptom relief to addressing root causes.

In addition to those, alternative approaches such as acupuncture, chiropractic care, and massage therapy may be considered. While these treatments may not be as widely accepted or as well-studied as conventional treatments, some patients may find them helpful for managing their symptoms[9]. Regardless of the treatment approach chosen, follow-up care and rehabilitation are crucial components of the treatment plan. This can include ongoing physical therapy, pain management, and lifestyle modifications to help prevent further disc degeneration and promote overall spinal health[10].

The adoption of these treatments relies on clinical trials confirming their safety and efficacy. To understand what researchers have devised to intervene in IDD, clinical trial platforms are a rich source of data that facilitate a standardized evaluation of existing clinical trials[10]. To key stakeholders, clinical trial protocols emerge as the foundational documents for capturing the comprehensive aspects of trials, such as design, methodology, and ethical considerations[11].

Related studies

Several studies, summarized by Table 1 below, analyze clinical trial protocols across different diseases and therapeutic areas, providing valuable insights into protocol quality, design

Table 1. Related Studies.

Study	Disease Area	Protocols Analyzed	Key Findings
Langrand-Escure *et al.*	Oncology	557 protocols	Only 26.2% achieved highest quality; 66% missing sample size calculations
Bush *et al.* (2017)	Infectious Disease	145 protocols	26,986 patients; sufficient consistency for data pooling
Linardon *et al.* (2024)	Mental Health	171 protocols	Only 32% reported adverse events; significant reporting heterogeneity
Ha *et al.* (2023)	Precision Oncology	29 protocols	Most used NGS/IHC; central vs. local lab differences
Ciaranello *et al.* (2009)	Pediatric HIV	31 protocols	Plans for trial participation payment and injury care payment were mentioned more often than posttrial services.

characteristics, and methodological trends. These analyses reveal significant variations in protocol development and reporting standards across medical specialties.

Oncology protocol analysis

Langrand-Escure *et al*. (2017)[12] conducted a systematic review of 557 phase II oncology trial protocols, finding that only 26.2% achieved the highest methodological quality score, with sample size calculation missing in 66% of protocols. Their analysis identified three variables independently associated with higher reporting quality: presence of statistical design, multicenter design, and per-protocol analysis.

Ha *et al*. (2023)[13] performed a systematic review of precision oncology clinical trials with phase II, biomarker-driven, adaptive design, analyzing 29 eligible trials from 2015–2023. Their study revealed that most trials used next-generation sequencing and/or immunohistochemistry for biomarker screening, with investigator-initiated trials primarily using central laboratories while sponsor-initiated trials used both central and local facilities.

Mental health protocol analysis

Linardon *et al*. (2024)[14] systematically reviewed 171 clinical trials of mental health apps, finding that only 55 trials reported adverse events, with significant heterogeneity in assessment methods and event recording. Their meta-analysis showed a deterioration rate of 6.7% across 13 app conditions, with no significant difference between app and control groups.

Petrie *et al*. (2019)[15] conducted a systematic review of interventions to reduce mental health symptoms in physicians, including eight studies with 1,023 physicians. They found that physician-directed interventions were associated with small reductions in symptoms of depression and anxiety.

Pediatric HIV protocol analysis

Ciaranello *et al*. (2009)[16] reviewed protocols and informed consent forms from Phase 3 and 4 antiretroviral trials in adults, finding that post-trial medications and medical care were mentioned in fewer than half (45%) of all trials. Their analysis showed plans for trial participation payment (74%) and injury care payment (94%) were mentioned more often than posttrial services. A summary of all related studies can be found on Table 1.

Methods

Study design

This study is a systematic review of clinical trial protocols focusing on interventions for intervertebral disc degeneration. We designed the review according to PRISMA 2020 guidelines for transparent reporting of systematic reviews. No meta-analysis was performed because our analysis was limited to trial protocols without outcome data. Instead, we conducted a descriptive overview of protocol characteristics and did not calculate pooled effect estimates.

Information sources

The primary source was ClinicalTrials.gov targeting intervertebral disc degeneration protocols. All searches were initially conducted in September 2024 and updated through December 31, 2024. No restrictions on language or publication status were applied in the searches.

Search strategy

A comprehensive search strategy was developed using both controlled vocabulary and free-text keywords to capture the concept of intervertebral disc degeneration and related terms. The search combined Medical Subject Headings (MeSH) and keywords: “intervertebral disc” OR “intervertebral disk” AND “degeneration” OR “degenerative disc disease”. Boolean operators and truncation were applied as appropriate to broaden the search (e.g., using variations of the term “degeneration”).

Eligibility criteria

We pre-specified inclusion and exclusion criteria to determine which records would be included in this review:

Inclusion criteria

We included studies that

- were described as interventional clinical trials (e.g., randomized or non-randomized trials) investigating intervertebral disc degeneration in human participants;
- had a protocol available through a trial registry entry or a published protocol article; and
- were registered (or published) from January 2013 onward (to focus on trials developed after the introduction of the SPIRIT guidelines).

We imposed no restrictions on the type of intervention (e.g., surgical, pharmacological, biological, or device-based therapies were all eligible) or comparator (placebo, active control, or no-treatment control), as long as the study’s primary focus was intervertebral disc degeneration. Trials of any phase (Phase I to IV) and any size were eligible provided they met the above criteria.

Exclusion criteria

We excluded:

- observational studies and other non-interventional study designs (such as case series, case reports, or reviews) because our focus was on prospective interventional trial protocols;
- trials that did not primarily address intervertebral disc degeneration (for example, studies focused on acute disc herniation or unrelated spinal conditions without a degenerative component were excluded)
- duplicate entries or reports

If a trial’s protocol information was so incomplete that key data items could not be obtained from either the registry or

publication (despite being labeled as a trial in disc degeneration), that trial was also not included in the synthesis.

Selection process

All protocols retrieved from the searches were imported into a reference management system. We then followed a two-stage screening process. First, two reviewers independently screened titles and registry entries to identify eligible studies. Protocols were filtered using the predefined inclusion/exclusion criteria. Any disagreements regarding study inclusion were resolved through discussion and consensus between the two reviewers. A third reviewer was designated to arbitrate unresolved conflicts. The results of the study selection process are documented in a PRISMA flow diagram (Figure 1), which illustrates the number of records identified, screened, excluded (with reasons for major exclusions), and ultimately included in the review.

Data items

From each included trial protocol, we extracted a comprehensive set of data items to characterize the study and evaluate its protocol content. Key data items collected were:

- **General Study Information:** Trial registry identifier (e.g., NCT number if from ClinicalTrials.gov), trial title, year of registration (or publication year for published protocols), and country or region where the trial was conducted or registered.

- **Study Design Characteristics:** The design of the trial (randomized controlled trial, non-randomized trial, etc.), including allocation method (e.g., randomized vs. non-randomized, and if randomized, whether allocation concealment and blinding were planned). We also noted the presence of a control group and the nature of the control (placebo, active comparator, etc.), as well as the trial phase (for drug or device trials, if reported).

- **Population and Sample Size:** The target patient population (key inclusion criteria such as patients with lumbar or cervical disc degeneration, age range, etc.) and the planned sample size (number of participants). We recorded whether the trial was single-center or multi-center.

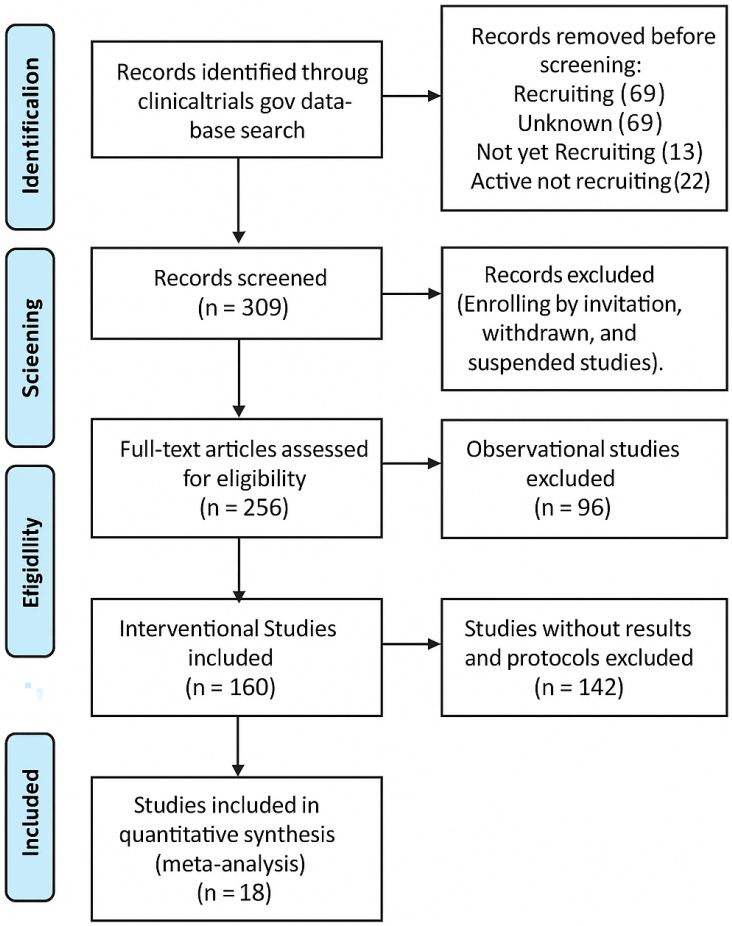

Figure 1. Selection of IDD Clinical Trial Protocols.

- **Interventions:** The type of intervention being tested (e.g., surgical procedure, pharmacological treatment, cell or biologic therapy, physiotherapy or exercise program, medical device, etc.). For multi-arm studies, we recorded all intervention arms and the comparator arm(s).

- **Outcomes:** The primary outcome(s) as stated in the protocol, and any key secondary outcomes whenever mentioned. We specifically noted outcomes relevant to intervertebral disc degeneration (such as pain, functional disability scores, imaging outcomes, or biomarkers), as well as the time points for primary outcome assessment.

- **Sponsor and Funding:** The sponsor type (industry-sponsored vs. investigator-initiated/academic) and any information on funding or funding source as reported in the protocol or registry entry.

- **Trial Status:** The recruitment status at the time of data extraction (e.g., recruiting, active not recruiting, completed, etc.) and whether results had been posted (if applicable). This was noted to contextualize the protocols (though we did not use results data in our analysis).

All data items were clearly defined prior to extraction to ensure uniformity. If any information was unclear or not explicitly stated in the protocol or registry entry, we recorded it as "not reported" for the purposes of our analysis.

Risk of bias and reporting bias assessment

We did not perform traditional risk of bias or reporting bias assessments because our review focused on trial protocols rather than reported outcomes. No risk of bias tool (e.g., Cochrane Risk of Bias 2 for RCTs) was applied, as typical domain-based evaluations (covering selection bias, performance bias, detection bias, etc.) are not applicable to protocol-only reviews. Similarly, reporting bias assessments like funnel plot analysis were not relevant since we performed no meta-analysis of outcome data. Our data sources were protocols accessed from registries regardless of whether trials eventually published results, making our selection process inherently less prone to publication bias than typical results-based reviews.

Synthesis methods

We synthesized the extracted data using descriptive and narrative methods. Given the qualitative nature of the data (trial characteristics and protocol content) and the absence of commensurate outcome metrics, no statistical meta-analysis was performed. Instead, we **tabulated** the data and summarized key findings in text. We calculated simple descriptive statistics to characterize the trial protocols: for example, we reported the number and percentage of trials by intervention type and by sponsor type. Categorical variables (like intervention category, presence of a control group, etc.) are presented as frequencies and percentages. Continuous variables (such as target sample size or planned trial duration) are summarized with medians and ranges. The results of the synthesis are presented narratively in the Results section. An earlier version of this work was published as a preprint[17].

Results

The search revealed 481 Intervertebral Disc Degeneration (IDD) clinical trials. After an initial screening, in which trials that were still looking for participants or not yet recruiting, ones that were actively not recruiting, enrolling by invitation, with unknown and suspended, withdrawn and unknown studies were excluded, 256 studies were selected for closer review, and were further narrowed down to 160 studies after excluding observational studies. A further criteria exluded 142 additional studies, as these were lacking results and protocols. This selection process resulted in 18 trials that spanned from 2013 to 2024.

Of the selected trials, the majority (13 trials) specifically targeted the lumbar spine, while 5 trials investigated degenerative disc interventions in the cervical spine (included here due to overlap in degenerative mechanisms). The inclusion of a few cervical IDD trials (e.g. a trial of an allograft in cervical fusion[18] and an artificial cervical disc trial[19]) reflects the breadth of our search; however, results will emphasize lumbar applications. Figure 1 summarizes the protocol selection process.

The selected trials represent a diverse mix of interventions and study designs. Altogether, these interventions and study designs planned to enroll approximately 1,272 participants (actual enrollment ranged from small pilot samples of <10 patients to a large Phase 3 trial with more than 400 participants). Trial statuses at the time of analysis included 11 completed studies, 6 terminated early (often due to low enrollment or futility), and 1 active but not recruiting (likely in follow-up phase). Notably, a substantial subset, 33%, of initiated trials ended prematurely ("Terminated" status), e.g., because of recruitment difficulty or interim results not meeting expectations. Geographically, most trials were conducted in the United States, often as multi-center studies across specialized spine centers. One trial was conducted in Europe (Spain)[20], reflecting an international interest in biologic therapies for IDD. The patient populations were generally adults with chronic low back pain due to lumbar IDD, often after failure of conservative management. Many trials focused on single-level disease, though some included multi-level degeneration or degenerative spondylolisthesis in inclusion criteria. Typical exclusion criteria (from descriptions) included prior lumbar fusion surgery, severe osteoporosis, or other spine pathologies that could confound outcomes (e.g. tumor, infection). Where cervical IDD trials were included, the populations were analogously adults with symptomatic cervical disc degeneration causing neck pain or radiculopathy. Table 2 summarizes the selected studies.

Combinations of device and biological interventions were present in 10.5% (2 trials), and similarly, biological-only and drug-only interventions were each found in 10.5% (2 trials) of the trials. Combinations involving biological and

Table 2. Characteristics of selected studies of IDD interventions.

NCT Number	Study Title	Status	Personalized Device/Drug?	Conditions	Interventions	Enrollment
NCT02667067	Investigation of the Simplify® Cervical Artificial Disc	Completed	No	Cervical Degenerative Disc Disease	DEVICE: Simplify® Disc, DEVICE: Anterior Cervical Discectomy & Fusion	150
NCT01860417	Treatment of Degenerative Disc Disease With Allogenic Mesenchymal Stem Cells (MSV)	Completed	No	Degenerative Disc Disease, Intervertebral Disc Disease, Low Back Pain	BIOLOGICAL: Allogenic Mesenchymal Stromal Cells, DRUG: Mepivacaine	24
NCT03817606	A Comparison of Stryker's Titanium (Tritanium® Technology) Posterior Lumbar Cage and PEEK Implant	Terminated	No	Degenerative Disc Disease, Degenerative Scoliosis	DEVICE: Titanium Posterior Lumbar Cage, DEVICE: AVS UniLIF® PEEK Posterior Lumbar Cage	4
NCT03018392	Clinical and Radiological Evaluation Following TLIF With 3D-Printed Titanium Cage	Completed	No	Intervertebral Disc Disease	DEVICE: Stryker Titanium Spinal System	20
NCT04272606	Tranexamic Acid in Spinal Fusion	Active, Not Recruiting	No	Degenerative Disc Disease	DRUG: Tranexamic Acid, DRUG: Saline Solution, DIAGNOSTIC: Visual Acuity Exam, 3D-CAM Interview	123
NCT02070484	NuCel® in Posterolateral Lumbar Fusions for DDD	Terminated	No	Lumbar DDD, Spinal Stenosis, Spondylolisthesis, Spondylosis, Disk Displacement, Disk Degeneration, Spinal & Bone Diseases	BIOLOGICAL: NuCel®, Demineralized Bone Matrix	6
NCT02412735	Rexlemestrocel-L ® With/Without Hyaluronic Acid in Chronic Low Back Pain	Completed	No	Degenerative Disc Disease	DRUG: Rexlemestrocel-L®, Rexlemestrocel-L® + HA, Placebo	404
NCT02347410	Spineology Clinical Outcomes Trial	Completed	No	Lumbar Degenerative Disc Disease	DEVICE: SIFS Graft Containment Device	102
NCT02704689	AccuLIF® Prospective Patient Outcomes Study	Terminated	No	Degenerative Disc Disease, Grade 1 Spondylolisthesis, Retrolisthesis	DEVICE: AccuLIF® Expandable TLIF Cage	9
NCT02182843	Cellentra® VCBM ACDF Outcomes Study (VCBM/MaxAn)	Completed	No	Cervical Disc Degenerative Disorder	BIOLOGICAL: Cellentra Viable Cell Bone Matrix	81
NCT03062657	Metal Concentration After PRESTIGE LP™ Cervical Disc Implantation	Terminated	No	Cervical DDD, Radiculopathy, Myelopathy	DEVICE: PRESTIGE LP™ Cervical Disc	25
NCT03484403	Lumbar Bracing for Chronic Low Back Pain	Completed	Yes	DDD, Lumbar Spondylosis, Low Back Pain	OTHER: Personalized Lumbar Brace, BEHAVIORAL: Back School Physical Therapy	61
NCT01829997	Assessment of nanOss® Bioactive 3D in the Posterolateral Spine	Completed	No	DDD, Spinal Stenosis, Spondylolisthesis	DEVICE: nanOss Bioactive 3D BVF	22

NCT Number	Study Title	Status	Personalized Device/Drug?	Conditions	Interventions	Enrollment
NCT03077204	BIO4® Case Study in Cervical Spine	Completed	No	DDD, Trauma (Fractures), Spondylolisthesis	BIOLOGICAL: BIO4 with Bio AVS Cervical Allograft, DEVICE: Aviator Cervical Plating System	20
NCT04007094	Use of ViviGen Bone Matrix in Lumbar Surgery	Terminated	No	DDD, Spinal Stenosis, Spondylosis, Spondylolisthesis	OTHER: ViviGen Cellular Bone Matrix	21
NCT02539394	Effect of Topical Corticosteroids on Dysphagia in ACDF	Completed	No	Cervical Herniation, Cervical DDD, Myelopathy, Dysphagia, Osteoarthritis	DRUG: Methylprednisolone Acetate, OTHER: Hemostatic Matrix Kit	128
NCT03514277	Bupivacaine and Exparel® for Postoperative Pain	Terminated	No	Low Back Pain, Radiculopathy, Disc Degeneration, Herniation, Stenosis, Spondylolisthesis, Spondylolysis, Deformity	DRUG: Exparel, Bupivacaine	19
NCT03647501	Lumbar Fusion with Nexxt® Spine 3D-Printed Titanium Cages	Completed	Yes	Lumbar DDD, Stenosis, Spondylolisthesis, Spinal Deformity, Spondylosis	DEVICE: Titanium Interbody Cage, PEEK Interbody Cage, with adjustable height	53

drug interventions, as well as drug and other interventions, each occurred in 10.5% (2 trials). Less common were combinations of device and drug, device and diagnostic test, and device and other interventions, each recorded in 5.3% (i.e., 1 trial each). Some trials featured only other types of interventions, representing 5.3% (1 trial) of the total.

Interventions

The interventions under investigation fell into several distinct categories: surgical implants, biologic therapies, pharmacologic adjuncts, and conservative treatments. Figure 2 illustrates the distribution of intervention types among the included trials.

Surgical implant-based approaches (e.g., novel interbody fusion cages or artificial discs) constituted the largest category (39% of trials). These included:

1. **AVS UniLIF©** PEEK Posterior Lumbar Cage: A posterior lumbar interbody fusion cage made of PEEK designed for PLIF or TLIF procedures with various configurations to accommodate patient anatomy and desired spinal alignment[21].

2. **Simplify® Cervical Artificial Disc**: A prosthetic disc for cervical disc replacement consisting of two PEEK endplates and a mobile ceramic core, with titanium coating to promote bone integration[19].

3. **Stryker Tritanium Spinal System**: A lumbar interbody fusion device manufactured using 3D-printing process, constructed from titanium alloy in a lattice structure to mimic trabecular bone[22].

4. **AccuLIF® expandable TLIF cage**: An expandable lumbar interbody cage for TLIF procedures that can be inserted at a reduced height and expanded in situ through a surgeon-controlled hydraulic mechanism[23].

5. **Spineology SIFS Graft Containment Device**: A novel approach using a collapsible PET mesh bag inserted into the disc space and filled with bone graft material[24].

6. **NEXXT® MATRIXX 3D-Printed Cages**: 3D-printed titanium fusion devices with porous geometry balancing strength and radiolucency[25].

7. **Prestige LP™ Cervical Disc**: A device for cervical disc replacement designed to maintain natural range of motion while potentially preventing adjacent segment degeneration[26].

Biologic or regenerative therapies (28%) were also prominent, including:

1. **Cellentra™ VCBM (Viable Cell Bone Matrix)**: An allogenic bone graft substitute incorporating living mesenchymal stem cells derived from adult adipose tissue[27].

2. **NuCel®**: A cryopreserved allograft product derived from human amniotic membrane and amniotic fluid components used as an adjunct to bone grafts in fusion procedures[18].

3. **Demineralized Bone Matrix (DBX®)**: A processed human donor bone with the inorganic mineral content removed, leaving organic collagen matrix and associated growth factors[18].

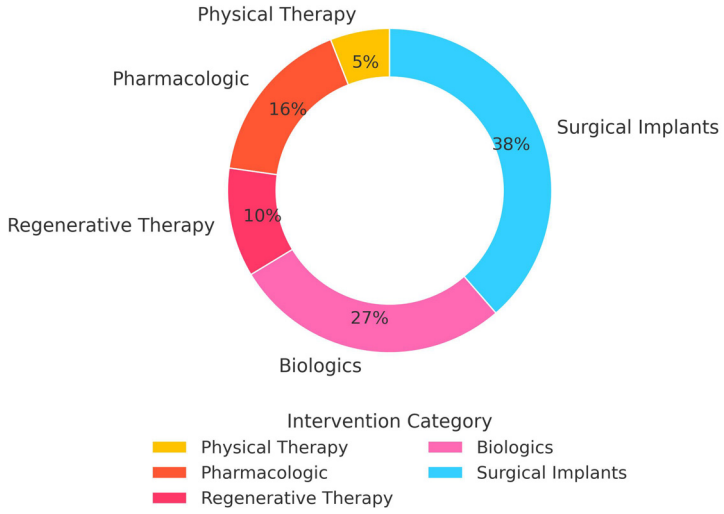

Figure 2. Types of interventions in IDD trials.

4. **BIO4® Bone Matrix(©)**: A viable bone matrix product containing osteoconductive scaffold, osteoinductive growth factors, osteogenic cells, and angiogenic components[28].

5. **Allogenic Mesenchymal Stromal Cells**: Stem cells derived from stroma with potential to differentiate into various cell types, used for regenerative treatment of disc degeneration[20].

Pharmacological interventions (17%) were evaluated in a few trials – these were not systemic drugs for disc disease per-se, but medications used as adjuncts to surgery:

1. **Bupivacaine**: A spinal anesthetic used in various forms for local anesthesia[29].

2. **Exparel®**: A liposome-encapsulated bupivacaine product designed for prolonged drug release[29].

3. **Methylprednisolone Acetate**: A corticosteroid particulate suspension injected into the spine to inhibit inflammation implicated in axial pain and radiculopathy[30].

4. **Rexlemestrocel-L©**: A product derived from human bone marrow, categorized as an allogeneic mesenchymal precursor cell therapy for inflammatory diseases[31].

5. **Mepivacaine**: An intermediate-acting local anesthetic with a shorter duration of action compared to bupivacaine[20].

6. **Tranexamic Acid**: A synthetic antifibrinolytic used to reduce perioperative blood loss and the need for blood transfusions in spine surgery[32].

Finally, **physical therapy-based strategies** (6%) were examined in one trial – the use of a lumbar back brace with physical therapy.

This spread of interventions highlights a multipronged research effort: from high-tech implants to regenerative medicine and rehabilitation techniques. Many trials targeted improved spinal fusion outcomes (either through better cages or bone graft substitutes), reflecting a continued emphasis on achieving solid arthrodesis in IDD patients. Meanwhile, a significant number pursued disc preservation or regeneration, such as the allogenic mesenchymal stem cell (MSC) therapy trial for chronic low back pain which delivered stem cells into degenerated discs[20]. Only one trial squarely addressed purely conservative care (evaluating whether adding a lumbar brace to therapy improves pain in chronic IDD[25], indicating that most registered studies are exploring surgical or minimally invasive interventions rather than non-invasive treatments.

Study designs

Among the 18 trials, 9 were randomized controlled trials (RCTs) and 9 were single-arm or non-randomized studies. Most implant and device trials were single-group feasibility studies or used a historical or performance goal as comparator rather than randomizing patients – for example, one trial of a 3D-printed titanium fusion cage enrolled patients to receive the device and compared outcomes to literature benchmarks[22]. In contrast, trials evaluating drugs or biologics were often randomized and placebo-controlled.

For instance, a Phase 3 Mesoblast-sponsored trial of an allogenic cell injection vs. placebo was a randomized, double-blind study in over 400 patients[31], and a smaller Phase 1/2 trial randomized 24 patients to stem cells vs. anesthetic for

IDD[29]. Surgical trials that did randomize typically compared two device techniques (e.g., a titanium cage vs. a PEEK cage in lumbar fusion) or compared an intervention vs. standard care.

Blinding was rarely possible in surgical device trials (surgeons and patients knew which procedure was done), though outcome assessors were sometimes blinded. In pharmacologic adjunct trials, blinding was feasible – for example, a trial comparing extended-release liposomal bupivacaine vs. standard bupivacaine for post-operative pain was double-blind[29].

Outcomes and endpoints

The primary outcomes varied based on the intervention type but broadly fell into a few categories: patient-reported pain/function measures, radiographic or biomechanical outcomes, composite endpoints, and safety metrics. About one-third of trials (6/18) set a **patient-reported outcome (PRO)** as the primary endpoint – typically improvement in pain or disability scores. For example, several trials used the Oswestry Disability Index (ODI) or Visual Analog Scale (VAS) pain score at 6 or 12 months as the primary measure of success. Another large subset (7/18, 39%) of trials primarily evaluated **imaging-based outcomes**, such as the proportion of patients achieving solid fusion on radiographs/CT or changes in disc height and alignment after treatment. These were common in fusion device trials and biologic fusion adjunct studies (e.g., fusion rate at 1 year as the primary endpoint in a bone graft product trial).

Composite endpoints were used in 3 trials (17%), especially in industry-sponsored device trials where an "overall success" composite was defined – for instance, a cervical disc replacement trial required concurrent improvement in Neck Disability Index (NDI) score, no neurological deterioration, and absence of serious adverse events to count as a success. Similarly, a lumbar fusion device trial defined success as a combination of pain reduction, ODI improvement, radiographic fusion, and no re-operations. Lastly, 2 trials (11%) had primary outcomes focused on **perioperative safety/efficacy metrics**: one examined blood loss and transfusion rates with vs. without tranexamic acid, and another monitored serum metal ion levels after implantation of a metal cervical disc implant as a safety outcome. Figure 3 below shows the primary outcome categories.

Additional outcome measures included:

1. **Surgical outcomes**: Length of surgery, hospitalization time, and blood loss.
2. **Medical outcomes**: Incidence of complications and changes in neurological function.
3. **Quality of life**: Assessed using instruments like the SF-36 PCS questionnaire and the European Quality of Life (EQ-5D) Questionnaire.
4. **Radiographic outcomes**: Evaluating fusion status, device placement, and morphologic changes in treated intervertebral discs through MRI and X-ray assessments.

This distribution shows a balance between patient-centric outcomes (pain relief, improved function) and structural outcomes (achievement of solid fusion or maintaining spinal alignment). Many trials also tracked both kinds of outcomes as secondary endpoints, even if one domain was primary. This reflects an increasing recognition that successful treatment of IDD should demonstrate both radiographic success and meaningful patient benefit.

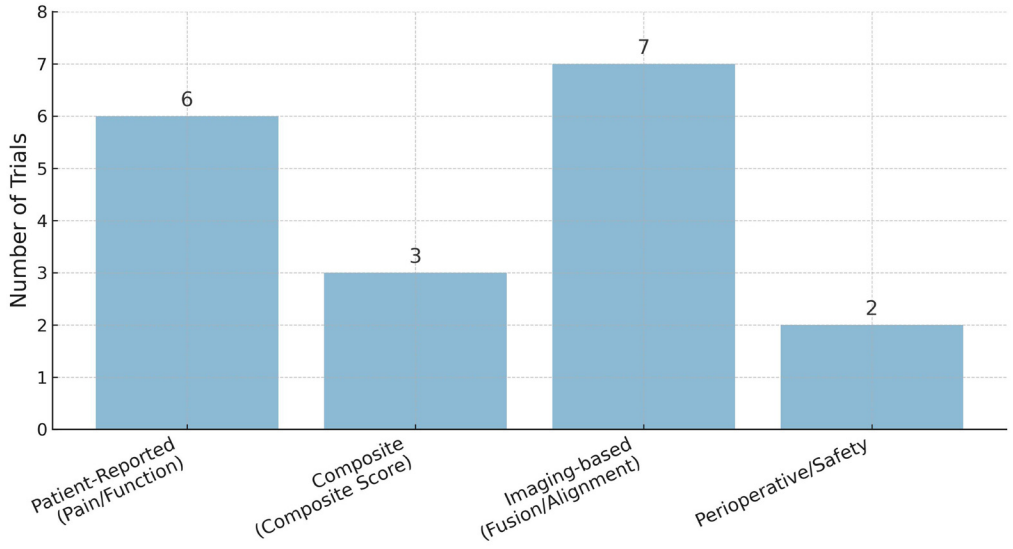

Figure 3. Primary outcome measure categories.

Trial phases

Consistent with the nature of the interventions, most trials were not classical drug trials and therefore did not have a phase designation. Thirteen of the studies were categorized as "N/A" for phase (these include device trials and procedure studies which are not assigned Phase 1–4). Among the 5 trials with an official phase, there was 1 Phase 3 trial (the MSC injection trial for chronic low back pain), 1 Phase 2 trial (tranexamic acid in spinal fusion), 1 Phase 1/2 trial (a pilot stem cell injection study), and 2 Phase 4 trials (post-market studies: one evaluating a biologic allograft in cervical fusion and another comparing analgesic regimens).

The dominance of "Phase N/A" (72% of trials) underscores that many studies were device or surgical technique evaluations typically conducted under IDE (Investigational Device Exemption) regulations rather than the drug trial phase system. The presence of a large Phase 3 program in regenerative medicine (Mesoblast's trial) indicates a mature effort to bring a biologic therapy through regulatory approval. The Phase 4 studies suggest that the corresponding interventions (e.g., allograft bone substitutes, new analgesics) were already in clinical use and were further studied, to gather additional evidence.

Discussion

This systematic review of registered trials provides a comprehensive overview of research efforts aimed at treating intervertebral disc degeneration. The trials are diverse, spanning cutting-edge biologic therapies to incremental improvements in surgical technique, which reflects the multifactorial nature of degenerative disc disease and the lack of a single definitive cure. Several important insights emerge:

Emphasis on fusion and biomechanical solutions

A significant portion of trials focus on improving spinal fusion outcomes for IDD with75% of device trials targeting fusion enhancement. This includes novel interbody cages (often 3D-printed or with enhanced porosity) intended to improve bony integration, and biologic graft substitutes (like cellular allografts or growth-factor-rich tissues) to stimulate fusion. The rationale is that a solid fusion can stabilize the segment and alleviate pain from an unstable degenerated disc.

The prevalence of fusion-oriented trials indicates that, despite the availability of motion-preserving artificial discs, fusion remains a mainstay for advanced IDD and there is ample room for optimizing it. Recent systematic reviews confirm that lumbar fusion for degenerative disease remains effective, though outcomes vary significantly based on patient selection and surgical technique[33,34]. The use of new material and structures (titanium alloys with trabecular structure, etc.) and biologics addresses known problems like pseudoarthrosis (failed fusion). Especially, current evidence suggests that 3D-printed porous titanium cages demonstrate superior fusion rates and significantly lower subsidence rates (3.03% vs. 10–20% for traditional cages) compared to conventional cage structures[35–37].

If these innovations succeed in increasing fusion rates or speeding fusion, patients could benefit from more reliable pain relief and possibly shorter recovery. However, it also underscores that current fusion surgery, while effective for many, is not uniformly successful, hence the ongoing search for enhancements. Adjacent segment degeneration remains a concern, affecting up to 25% of patients within 10 years following fusion[38].

Exploration of regenerative therapies

Parallel to mechanical solutions, there is clearly a strong interest in restoring disc function biologically. The presence of high-profile trials using mesenchymal stem cells (MSCs) or other cell products reflects a hope that disc degeneration could be treated rather than simply bypassed with fusion. These trials target patients with chronic discogenic back pain who might avoid or delay surgery if an injection could reduce their pain by halting or reversing degeneration.

Recent systematic reviews and meta-analyses demonstrate that MSC therapy can significantly reduce pain scores (VAS reduction SMD = -0.50, 95%CI = -0.68 to -0.33, $P < 0.00001$) and disability indices (ODI reduction SMD = -0.27, 95%CI = -0.44 to -0.09, $P = 0.003$) in patients with degenerative disc disease[39,40]. Early-phase trials have shown safety of intradiscal MSC injections, and preclinical studies suggest such cells can modulate inflammation and matrix content in degenerating discs[41,42]. The FDA approval of late-stage trials for stem cell products represents a significant milestone, with Phase 3 trials now underway involving up to 400 patients[43].

The European RESPINE project, a H2020-funded Phase 2b clinical trial, demonstrated promising results with allogenic mesenchymal stromal cells in 112 patients with DDD, showing functional and pain improvements of 50% within 6 months and 65–78% after 1 year[44]. However, as noted by Vadalà and colleagues, the hostile microenvironment of the degenerated disc (avascularity, hypoxia, low pH, hyperosmolarity) poses significant challenges for both resident and exogenously administered cells, which must be carefully considered in regenerative therapy design[45].

However, recent critical perspectives, including concerns raised by leading researchers in the field, emphasize that cell therapy for disc degeneration faces significant challenges beyond initial promising results. The avascular nature of the disc, combined with its unique nutritional environment, creates conditions that may limit cell survival and therapeutic efficacy. The increased metabolic demands of delivered cells in a nutrient-poor environment may paradoxically worsen the degenerative process rather than improve it[46].

Notably, regenerative trials face challenges such as appropriate patient selection (they likely work best in moderate degeneration, not complete collapse) and demonstrating durable benefits. The fact that the large trial required a composite endpoint of pain and function improvement without additional

interventions speaks to stringent efficacy criteria. Clinical studies remain relatively limited, with only 6 eligible clinical trials identified in recent bibliometric analyses, suggesting that further randomized controlled studies are needed to improve the evidence level[47].

Shift in pharmacological approaches

There is a clear trend toward multimodal pain management and alternatives to opioids, as evidenced by the trials investigating extended-release local anesthetics like Exparel© (liposome-encapsulated bupivacaine). This shift has been significantly influenced by the opioid crisis, prompting medical professionals to explore alternative strategies for managing post-surgical pain[48–50].

The development of advanced mesenchymal precursor cell therapies like Rexlemestrocel-L also represents innovation in pharmacological approaches, aiming to address inflammation at its source rather than merely masking symptoms. These therapies may offer longer-lasting relief by modulating the inflammatory processes that contribute to pain in IDD. Current evidence suggests that tranexamic acid reduces perioperative blood loss and transfusion requirements in spinal fusion procedures, representing one successful pharmacological adjunct[32].

Patient-centered outcomes gaining importance

We observed that many trials incorporated patient-reported outcomes (pain, disability indices) either as primary or key secondary endpoints (33% of trials used PROs as primary endpoints). This aligns with the broader trend in spine research to ensure that radiographic success translates to patient benefit. Traditionally, device trials focused heavily on fusion rates or angular motion achieved, but newer trials (e.g., those for FDA approval of arthroplasty devices or stem cell therapies) often require demonstration of improvement in patient pain and function.

The frequent use of composite endpoints that include a clinical improvement component (such as 15-point improvement in ODI or NDI) underscores this patient-centric approach. It is encouraging that trials are not solely reporting "fusion achieved on CT" without considering how the patient feels. The consistency of including validated scales like ODI, VAS, NDI, SF-36, or EQ-5D across these studies will allow future meta-analyses to compare efficacy in terms of quality of life improvement. In the long run, patients with IDD seek pain relief and restored function – the ultimate success of any new intervention will be judged by those outcomes.

Motion-preserving strategies: Balancing innovation with risk

While motion-preserving devices represented 25% of device trials, these interventions face unique challenges that merit careful consideration. Cervical disc arthroplasty, while promising for maintaining spinal motion, requires complex anterior surgical approaches with inherent risks including vascular injury, esophageal perforation, and recurrent laryngeal nerve damage[51,52].

Long-term studies of cervical disc arthroplasty show variable outcomes, with 20-year follow-up data demonstrating that while both cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF) are effective, CDA shows lower reoperation rates but comparable functional outcomes[53,54]. However, complications including heterotopic ossification, implant subsidence, and device migration can impact long-term function[55]. Recent meta-analyses at 10-year follow-up show that while CDA demonstrates statistically significant improvements in neck disability scores and fewer secondary surgeries compared to ACDF, the clinical significance of these differences remains debatable[56].

The risk-benefit profile must be carefully weighed against fusion procedures, which, while eliminating motion, offer more predictable outcomes and lower perioperative morbidity in many cases. The complex surgical exposure required for disc arthroplasty, particularly in obese patients, has been associated with increased neurologic complications, pulmonary embolism, and wound infections[57].

Trial quality and research challenges

A concerning finding from this review is the high early termination rate (33%, 6 out of 18 trials), which significantly exceeds the general clinical trial termination rate of approximately 12% reported in the broader literature[58,59]. This suggests significant challenges in conducting IDD research. Common reasons for early termination across clinical research include insufficient accrual (57% of terminated trials), safety concerns, and futility[60]. Studies in orthopedic research have reported termination rates as high as 40%, with inadequate recruitment being the leading cause[61].

This high attrition rate underscores the need for more robust trial design, better patient stratification, and potentially more collaborative multi-center approaches to ensure adequate statistical power. The diversity in outcome measures and trial designs limits the ability to synthesize evidence across studies, further emphasizing the need for standardization of protocols and outcome measures in IDD research.

Conclusion

This systematic review reveals a dynamic field actively investigating diverse approaches to IDD treatment, from advanced fusion technologies to regenerative therapies. While fusion-centric approaches remain predominant (75% of device trials), the research landscape reflects both innovation and significant challenges. The high early termination rate (33%) highlights critical issues in IDD research methodology and execution. This concerning trend, which exceeds general clinical trial termination rates, suggests that future studies require more thorough design standards, improved patient selection criteria, and enhanced multi-center collaboration to ensure adequate enrollment and statistical power. The development of standardized

protocols and outcome measures could significantly improve the consistency and reliability of IDD clinical research.

Motion-preserving strategies, while representing 25% of device trials, require careful consideration of their risk-benefit profile. The complex surgical approaches required for disc arthroplasty and uncertain long-term advantages over fusion demand evidence-based selection criteria and patient counseling about realistic expectations. On the other hand, the promising developments in regenerative medicine, particularly MSC therapy, show clinically meaningful improvements in pain and function. However, the limited number of high-quality clinical trials necessitates continued investigation with larger, well-designed studies. The recent FDA approval of Phase 3 stem cell trials represents a crucial step toward establishing regenerative therapies as viable treatment options.

Engineering innovations in fusion technology, particularly 3D-printed porous titanium cages with their superior fusion rates and reduced subsidence risk, demonstrate the potential for improved surgical outcomes. However, the higher costs and technical complexity of these technologies require careful economic evaluation alongside clinical benefits. The balance between structural and patient-reported outcomes observed across trials is encouraging, reflecting the field's evolution toward patient-centered care. However, the diversity in outcome measures and trial designs limits the ability to synthesize evidence across studies, further emphasizing the need for standardization.

For clinicians, emerging evidence from completed trials will inform critical decisions about stem cell therapies, advanced implant technologies, and optimal surgical approaches. However, the high termination rate serves as a cautionary reminder that not all promising interventions will translate to clinical practice. The research activity documented reflects a field in transition, moving beyond traditional fusion approaches toward comprehensive solutions that address both structural and biological aspects of disc degeneration. Success will depend not only on technological innovation but also on improved research methodology, standardized protocols, and collaborative efforts to overcome the recruitment and design challenges that have hindered progress. Ultimately, advancing IDD treatment requires both scientific innovation and methodological thoroughness to ensure that promising therapies reach patients safely and effectively.

Ethics and consent

Ethical approval and consent were not required

Data availability

Underlying data

Zenodo: "Dataset of Clinical Trial Protocols for Intervertebral Disc Degeneration Management (2013-2024) (1.0)," can be accessed at https://doi.org/10.5281/zenodo.16605934[62].

The project contains the following underlying data:

- clinicaltrialprotocols.csv (extracted data from 18 clinical trial protocols including study characteristics, interventions, outcomes, and sponsor information)

Extended data

No extended data are associated with this article.

Reporting guidelines

Zenodo: PRISMA 2020 checklist for 'Overview of intervertebral disc degeneration clinical trial protocols'. https://doi.org/10.5281/zenodo.16605934[62].

Data are available under the terms of the Creative Commons Zero Attribution 4.0 International license (CC-BY-4.0).

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The authors have conducted a systematic review of intervertebral disc degradation associated clinical trials with regard to study designs and protocols. After a stringent selection process, eighteen studies were analyzed. While there is considerable value in conducting this sort of review, there are several weaknesses in the manuscript.
One of the most valuable observations is regarding the 33% of analyzed trials that were terminated early compared to 12% reported in the broader literature.
The first weakness is a minor terminology-clarity issue. This analysis is about clinical trials focused on back pain associated with intervertebral disc degeneration, not management of disc degeneration. Many of the selected studies do not attempt to address the disc degeneration itself, or "IDD management strategies", but solely address the chronic pain associated with disc degradation. Better clarity is needed throughout the paper - these trials are targeting IDD associated back pain. To be clear, pharmacological treatments in particular are not addressing the progressive degradation of the disc. Degenerative disc disease (DDD) is a term that typically encompasses both the disc degeneration and the associated disease symptoms, but IDD, as the authors correctly stated, refers to the disc degeneration which "is a significant contributor to chronic back pain and disability".

A more fundamental weakness in this paper is what appears to be an (incorrect) assumption that IDD associated pain interventions are addressing a single or generally similar cohort of patients. Grouping together cervical interventions with lumbar interventions, drugs with devices, earlier-stage patients with later-stage patients, discogenic pain versus post-herniation or stenosis or slip or osteophytes etc., and assuming that it is somehow inappropriate that there would be diversity of outcome measures and protocols seems flawed. The diversity of outcome measures and protocols reflects the diverse nature of the disorder across the broad spectrum of this progressive disorder. Treatments and therefore protocols that address earlier stages of the disorder should look different from those that address specific variants of degeneration related pain on the other end of the spectrum (or in a different region of the spine). Therefore standardization is not necessarily beneficial as suggested repeatedly by the authors. I would proffer that primary outcomes matched the patient cohorts. There should be no expectation that conservative care

and drugs would have the same endpoints as fusions and artificial discs.

There is a related weakness in this analysis considering the diversity of clinical cohorts and functional needs of these patients - looking at a mere 18 clinical trials is not sufficient to make many useful observations. It is somewhat of an exaggeration to state that "this systematic review of registered trials provides a comprehensive overview", on the basis of 18 studies. It seems that many of the conclusions that were made would be better made by analyzing the 160 interventional studies, the vast majority of which were excluded because they didn't have results and protocols. Study results were not included in the analysis so the reason for this exclusion is not clear. There are other inconsistencies in study selection criteria: active, not recruiting not to be included but Tranexamic Acid study was included. The authors excluded "trials that did not primarily address intervertebral disc degeneration (for example, studies focusedd on acute disc herniation... " This suggests that the authors do not agree that disc degradation always precedes a herniation. There is structural damage in all of our lumbar discs by our late teens and tears in our lumbar discs for 100% of us by age 30 (Boos 2002, Vernon-Roberts 2007). The authors need to more clearly explain why treatments for low back pain post-herniation were excluded (or include them and re-analyze).
The authors claim that there is an "evolution toward patient-centered care". It seems that the authors presume that fusion success studies are done without the foreknowledge that pseudoarthrosis rates are highly correlated with poor patient outcomes from an abundance of studies. Objective endpoints (i.e. radiological assessments) and subjective endpoints (i.e. patient reported outcomes) both have their intrinsic strengths and weaknesses in evaluating innovative solutions. Similarly, structural endpoints are always based on evidence or at least a hypothesis that the structural endpoint will beniefit the patient, sometimes in ways that would not be reflected in patient reported outcomes. It's not necessarilly true that patient reported outcomes are gaining in importance. While there are studies that focus on the new functionality of a new device, these studies are not in place of patient outcome studies, but supplementary and often a prerequisite.

The authors conclude that more thorough design standards and improved patient selection criteria will address the issue of high early termination rate. It is not clear what is meant by "more thorough design standards". By "improved patient selection criteria" do the authors mean less restrictive? As noted by the authors, early study termination often has to do with enrollment difficulties, which is influenced by several factors including cross-over timepoints, which is in turn strongly influenced by regulatory bodies' required endpoint timelines. Enrollment difficulty also involves excessive regulatory requirements, including numbers of required patient visits/imaging which can discourage participation.

In this reviewer's opinion, the summaries of related studies are not of interest or necessary. Instead, features of similar analyses that are relevant to the present analysis could be summarized in a few sentences.

There are several other corrections and clarifications that are needed in the paper, but this review will not delve into them.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

No

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I have 40 years of comprehensive research expertise involving disc degeneration associated low back pain.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 06 October 2025

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Satyajit Pandurang Kulkarni
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This article titled "*A systematic review of intervertebral disc degeneration clinical trial protocols*" offers a comprehensive examination of intervertebral disc degeneration (IDD) and the existing protocols, which are in close alignment with the F1000 research journal. Nevertheless, I propose several modifications. Your research specifically addresses the management of IDD; however, the title fails to incorporate the terms management or treatment. I recommend including one of these terms to clarify your focus or review topic. The heading that follows the abstract is labeled "plan language summary," which I believe should be corrected to "plain language summary." Additionally, please clarify at the outset what you mean by "Intervertebral Disc Degeneration"; specifically, provide the diagnostic criteria (or ICD code) and explicitly state that the review is focused solely on the treatment aspect. In the introduction section, please elucidate the rationale behind conducting this study. What prompted you to undertake a systematic review on IDD? In other words, please elaborate on the knowledge gap that your study aims to address. I found the inclusion of "related studies" to be unclear; please connect this section with the final paragraph, as these studies appear to be unrelated to IDD. Therefore, it is essential to explain the reasoning behind their inclusion. Is your study protocol registered with PROSPERO? In the study design section, please articulate the specific question you intend to answer through this review. The results and discussion sections are well composed; however, I suggest condensing the conclusion

section. The tables and figures are well presented and appropriately labeled.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
No

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: spine and alternative treatment

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.