



Contents lists available at ScienceDirect

## North American Spine Society Journal (NASSJ)

journal homepage: [www.elsevier.com/locate/xnsj](http://www.elsevier.com/locate/xnsj)

## Basic Science

## Sponsorship of clinical trials related to the spine: Trends over time and comparative analysis of trial characteristics by sponsorship type



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## ARTICLE INFO

## Keywords:

Spine  
Clinical trials  
Interventional studies  
Sponsorship  
Study sponsorship  
Blinding  
Randomization  
Trial initiation  
Spine trials

## ABSTRACT

**Background:** Clinical trials are crucial to advance products and procedures related to the spine. ClinicalTrials.gov is an internet-based registry and results database that catalogs trial characteristics, such as intervention types, phase, randomization, and blinding. Sponsorship trends have not been specifically evaluated for spine-related clinical trials, nor have trial characteristics been compared among spine-related trials sponsored by institutions, industries, and federal agencies. The purpose of this cross-sectional analysis of spine-related clinical trials was to characterize the types and trends of sponsorship for spine-related clinical trials, and compare trial characteristics among trials sponsored by institutions, industries, and federal agencies.

**Methods:** ClinicalTrials.gov was queried for clinical trials started from the launch of ClinicalTrials.gov (February 29, 2000) through December 31, 2022, using the term “spine.” Trial characteristics were abstracted, including start year, intervention type, phase, randomization, and blinding. Univariate and multivariate analyses were performed to determine associations between sponsorship type and other trial characteristics.

**Results:** A total of 4,484 clinical trials were identified, of which 78 trials were excluded due to incomplete reporting of trial registration data. From 2000 through 2022, the number of spine-related trials initiated annually markedly increased (from 21 to 453, representing an increase of 2,057%). This was predominantly driven by an increase in the number of institutionally sponsored trials. Relative to trials with institutional sponsorship, industry sponsorship was independently associated with different intervention types, phases of study, lack of randomization, and lack of blinding. Relative to trials with institutional sponsorship, federal sponsorship was independently associated with intervention type, and phase of study.

**Conclusions:** From 2000 through 2022, the number of spine-related clinical trials initiated annually markedly increased, driven by an increase in institutionally sponsored trials. Specific trial characteristics were more or less likely for industrially or federally sponsored trials relative to institutionally sponsored trials suggesting the types of clinical trials are shifting over time.

## Introduction

Clinical trials are crucial to the advancement of products and procedures related to the spine. The Food and Drug Administration Modernization Act of 1997 required the United States Department of Health and Human Services, acting through the National Institutes of Health (NIH), to establish a registry of clinical trial information for both federally and privately funded trials, resulting in the creation of the Clinical-

Trials.gov, an internet-based registry and results database that became publicly available in February 2000 [1,2].

Registration and results data are reported to ClinicalTrials.gov by sponsors and investigators, and the database is maintained by the NIH through the National Library of Medicine [1]. Registration data cataloged by ClinicalTrials.gov includes trial characteristics, such as the intervention type under active investigation, phase, randomization, and blinding.

FDA device/drug status: Not applicable.

Author disclosures: **DLC:** Author received research support in the form of investigator salary at Level B (\$1,001-\$10,000) from Yale University Fellowship for Medical Student Research Fund during the time at which the research was conducted. **WJ:** Nothing to disclose. **AE:** Nothing to disclose. **JNG:** Nothing to disclose.

Given his role as Editor in Chief, Jonathan Grauer, MD had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Tobias Mattei.

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<https://doi.org/10.1016/j.xnsj.2023.100296>

Received 12 November 2023; Received in revised form 18 November 2023; Accepted 20 November 2023

Available online 27 November 2023

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Previous studies analyzing spine-related clinical trials registered with ClinicalTrials.gov have focused on publication rates and factors related to publication of trial results as well as the rates, reasons, and predictors of trial termination [3,4]. However, sponsorship trends have not been specifically evaluated for clinical trials related to the spine, nor have trial characteristics been compared among spine-related trials sponsored by institutions, industries, and federal agencies.

This study sought to characterize the types and trends of sponsorship for spine-related clinical trials and to compare trial characteristics among trials sponsored by institutions, industries, and federal agencies.

**Methods**

*Study sample*

The ClinicalTrials.gov database was queried on January 3, 2023, for clinical trials (investigational studies) started from the launch of ClinicalTrials.gov (February 29, 2000) through December 31, 2022, using the search term “spine.” Use of these data was deemed exempt from review by our Institutional Review Board.

*Trial characteristics*

Trial characteristics were abstracted from ClinicalTrials.gov as categorical variables. Some were grouped to facilitate interpretation, and definitions are provided below. Trial characteristics were abstracted, including start year, intervention type, phase, randomization, and blinding.

ClinicalTrials.gov defines the trial sponsor as “the organization or person who initiates the study and who has authority and control over the study [5]”. Categories of study sponsorship were federal (ie, sponsorship by the NIH or another United States federal agency), industrial, and institutional, which included sponsorship by individuals, universities, and community-based organizations.

Trial intervention is defined according to the “process or action that is the focus of a clinical study [5].” Intervention types were categorized as procedure, device, drug, biological, behavioral, or other (other included the following intervention types: combination product, diagnostic testing, dietary supplementation, genetic, radiation, and others).

As defined by ClinicalTrials.gov, the phase of a clinical trial reflects “the stage of a clinical trial studying a drug or biological product, based on definitions developed by the U.S. Food and Drug Administration. The phase is based on the study’s objective, number of study participants, and other characteristics [5].” Phase 4 captured what was included in the data set as early phase 1 and phase 1 studies. Phase 2 captured what was included in the data set as phase 2 and 1/2 studies. Phase 3 captured what was included in the data set as phase 3 and 2/3 studies.

Studies were also characterized as randomized (ie, yes or no) and blinded (ie, yes or no). Blinding was abstracted as a dichotomous variable to indicate whether or not the participant, care provider, investigator, and/or outcomes assessor was blinded.

*Data analyses*

Univariate chi-square analyses were performed for spine-related clinical trials to compare the distribution of trial characteristics among trials sponsored by federal agencies, industry, and institutions. Pairwise multivariate logistic regressions were used to determine associations between sponsorship type(s) and other trial characteristics.

Statistical analyses were performed with RStudio [6]. Significance was set to 0.05. Forest plots were generated in Microsoft Excel [7] and used to present the results of multivariate analyses.

**Results**

*Sponsorship trends*

A total of 4,484 clinical trials were identified, of which 78 trials were excluded due to incomplete reporting of trial registration data (Fig. 1). Of the 4,406 clinical trials included in the study sample, institution-sponsored 3,398 (77.1%), industry-sponsored 942 (21.4%), and federally sponsored 66 (1.5%).

From 2000 through 2022, the number of spine-related trials initiated annually markedly increased (from 21 to 453, representing an increase of 2,057% (Fig. 2). This was predominantly driven by an increase in the number of institutional-sponsored studies from 12 trials initiated in 2000 to 389 initiated in 2022 (a 3,142% increase), and the percentage of spine-related clinical trials sponsored by institutions increased from 57.1% in 2000 to 85.9% in 2022 (Fig. 3). Comparatively, the percentage of spine-related clinical trials sponsored by industry fell from 33.3% of trials initiated in 2000 to 12.6% of trials initiated in 2022. The percentage of spine-related clinical trials sponsored by federal agencies also decreased from 9.5% of trials initiated in 2000 to 1.5% in 2022. These decreases represent relative trends in the percentages of spine-

**Flowchart for Eligible Clinical Trials**

ClinicalTrials.gov queried January 3, 2023 for interventional studies (clinical trials) started on or after February 29, 2000 through December 31, 2022 using search term "spine"

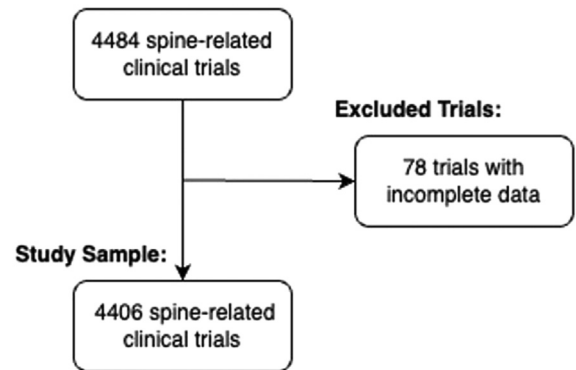


Fig. 1. Flowchart for selection clinical trials related to the spine eligible for inclusion in the study sample resulting from query of ClinicalTrials.gov on January 3, 2023.

**Sponsorship of Spine-Related Clinical Trials by Start Year**

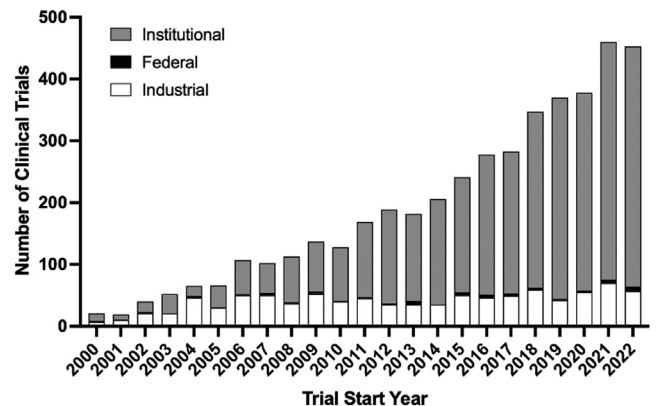


Fig. 2. Sponsorship of spine-related clinical trials started from 2000 through 2022.

**Sponsorship of Spine-Related Clinical Trials by Start Year**

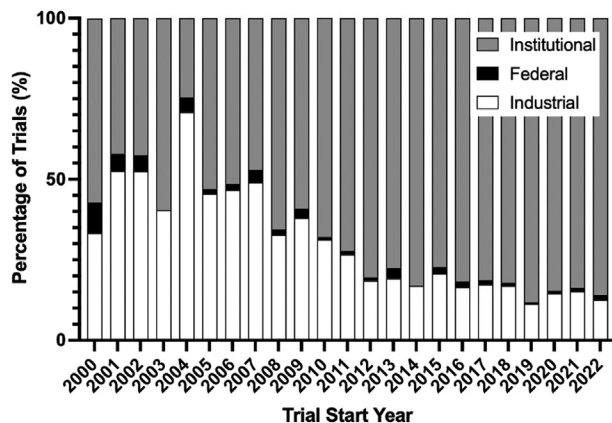


Fig. 3. Percentage of trials by sponsorship type for clinical trials related to the spine initiated annually from 2000 through 2022.

related clinical trials sponsored by industry and federal agencies and are largely due to the disproportionate increase in spine-related clinical trials initiated annually by industry while increases, albeit lesser, were also observed in the numbers of industry and federal spine-related trials initiated in the year 2022 relative to in the year 2000.

*Association of trial characteristics with sponsorship types*

Trial characteristics for spine-related clinical trials are summarized in Table 1. On univariate analysis of the study sample, all trial characteristics assessed (intervention type, phase, randomization, and blinding) were found to be correlated with sponsorship type ( $p < .05$  for each).

Multivariate analyses were performed to evaluate whether trial characteristics were independent associated with sponsorship types; that is, trial characteristics were compared first among trials sponsored by industry relative to institutionally sponsored trials then among trials sponsored by federal agencies relative to institutionally sponsored trials (Table 2).

Relative to trials with institutional sponsorship, industry sponsorship was independently associated with intervention type (relative to procedure studies, studies related to devices odds ratio [OR] = 12.03, biologics OR = 11.94, drugs OR = 5.89, behavioral interventions OR = 0.11), phase of study (relative to phase 1, phase 2 OR = 1.89, phase 3 OR = 5.13, not applicable OR = 0.61), nonrandomized trials OR = 1.36, trials without blinding OR = 1.28 ( $p < .05$  for each) (Fig. 4).

Relative to trials with institutional sponsorship, federal sponsorship was independently associated with intervention type (relative to procedure studies, studies related to behavioral interventions OR = 3.62) and phase of the study (relative to phase 1, phase 4 OR = 0.09, not applicable OR = 0.27) ( $p < .05$  for each) (Fig. 5).

**Discussion**

Clinical trials are critical to the advancement of science and technologies in all clinical areas, including those related to conditions of the spine. The current study is a cross-sectional analysis of spine-related clinical trials registered with ClinicalTrials.gov that found that the number of spine-related clinical initiated annually increased by 2,057% from the time ClinicalTrials.gov went public (February 29, 2000) through December 31, 2022. The total number of spine-related clinical trials initiated during the year 2020 was only slightly greater than the number of trials initiated in 2019, owing to a possible impact of the COVID-19 public health emergency on the clinical research infrastructure of the United States during the year 2020; however, the number of spine-related clinical trials in 2021 was also noted to be greater than the number of spine-related clinical trials in 2022 (Fig. 2). This suggests that the COVID-19 public health emergency may have delayed the initiation of clinical trials slated to start in 2020 until the year 2021, accounting for the unusual increase in trials initiated in 2021 above those initiated in 2022.

The increase in spine-related clinical trials initiated annually is mainly accounted for by the increase in institutionally sponsored clinical trials (ie, clinical trials sponsored by individuals, universities, and community-based organizations not otherwise categorized as industry or as a federal agency). This finding supports the need to better understand the reasons for this increase in institutionally sponsored clinical trials related to the spine that has not been matched by increases in spine-related clinical trials sponsored by industry and federal agencies.

**Table 1**

Univariate chi-square analysis for trial characteristics distributed among spine-related clinical trials sponsored by institutions, industry, and federal agencies.

	Sponsorship: N (%)			p value
	Institutional	Industrial	Federal	
Total trials = 4,440	3398 (76.5%) *	942 (21.2%) *	66 (1.5%) *	–
<i>Intervention type</i>				
Procedure	648 (19.1%)	33 (3.5%)	9 (13.6%)	<.0001
Device	503 (14.8%)	291 (30.9%)	4 (6.1%)	
Biological	49 (1.4%)	77 (8.2%)	1 (1.5%)	
Drug	732 (21.5%)	489 (52.0%)	35 (53.0%)	
Behavioral	203 (6.0%)	1 (0.1%)	9 (13.6%)	
Other	1263 (37.2%)	50 (5.3%)	8 (12.1%)	
<i>Phase</i>				
1	117 (3.4%)	42 (4.5%)	7 (10.6%)	<.0001
2	266 (7.8%)	153 (16.2%)	23 (34.8%)	
3	220 (6.5%)	338 (35.9%)	9 (13.6%)	
4	331 (9.7%)	91 (9.7%)	2 (3.0%)	
N/A	2464 (72.5%)	318 (33.8%)	25 (37.9%)	
<i>Randomized?</i>				
Yes	2626 (77.3%)	660 (70.1%)	43 (65.2%)	<.0001
No	772 (22.7%)	282 (29.9%)	23 (34.8%)	
<i>Blinded?</i>				
Yes	2036 (59.9%)	501 (53.2%)	33 (50.0%)	.0004
No	1362 (40.1%)	441 (46.8%)	33 (50.0%)	

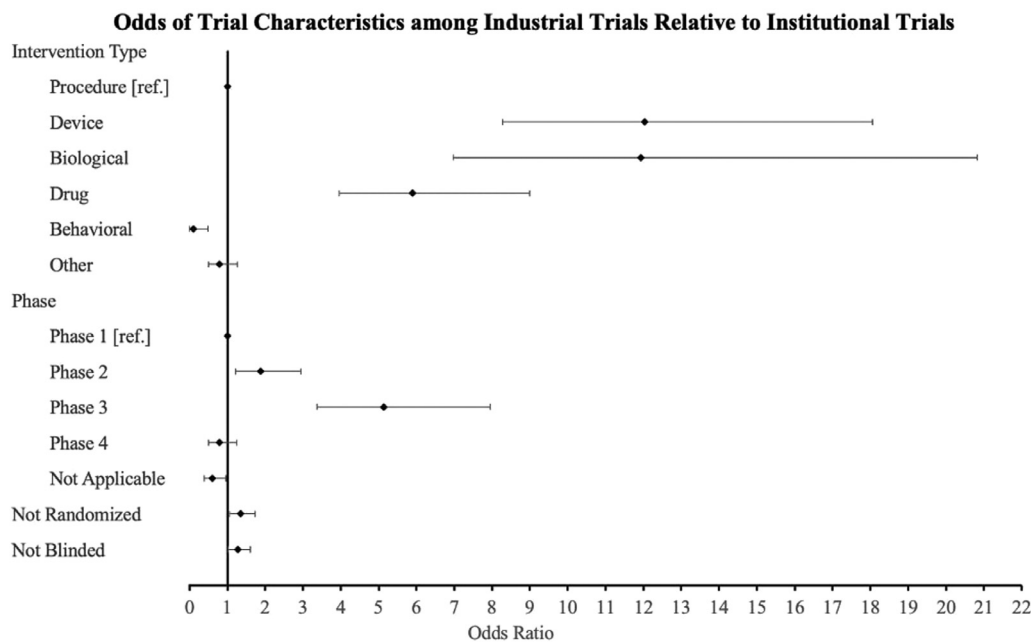
CI, confidence interval.

Percentage values accompanied by asterisk (\*) reflect the percentage of the total clinical trials in the study sample (N = 4,406 trials).

**Table 2**  
Results of pairwise multivariate analyses for trial characteristics among spine-related clinical trials with industrial, institutional, and federal sponsorship.

Sponsorship:	Institutional [ref.]	Industrial		Federal	
		OR (95% CI)	p value	OR (95% CI)	p value
<i>Intervention type</i>					
Procedure [ref.]	–	1.00	–	1.00	–
Device	–	12.03 (8.27, 18.05)	<.0001	0.58 (0.16, 1.82)	.3755
Biological	–	11.94 (6.97, 20.82)	<.0001	0.52 (0.03, 3.13)	.5466
Drug	–	5.89 (3.96, 9.00)	<.0001	2.06 (0.92, 5.08)	.0944
Behavioral	–	0.11 (0.01, 0.50)	.0271	3.62 (1.38, 9.52)	.0079
Other	–	0.79 (0.50, 1.26)	.3220	0.46 (0.17, 1.20)	.1091
<i>Phase</i>					
1 [ref.]	–	1.00	–	1.00	–
2	–	1.89 (1.23, 2.94)	.0044	1.37 (0.58, 3.60)	.4933
3	–	5.13 (3.37, 7.94)	<.0001	0.70 (0.24, 2.08)	.5039
4	–	0.79 (0.50, 1.25)	.3051	0.09 (0.01, 0.39)	.0034
Not applicable	–	0.61 (0.39, 0.96)	.0292	0.27 (0.11, 0.78)	.0100
<i>Randomized?</i>					
Yes [ref.]	–	1.00	–	1.00	–
No	–	1.36 (1.06, 1.74)	.0159	1.37 (0.68, 2.82)	.3796
<i>Blinded?</i>					
Yes [ref.]	–	1.00	–	1.00	–
No	–	1.28 (1.02, 1.60)	.0334	1.21 (0.61, 2.28)	.5734

CI, confidence interval; OR, odds ratio; ref., reference.



**Fig. 4.** Results of multivariate analysis for industrially sponsored clinical trials relative to institutionally sponsored clinical trials; *ref.*, reference.

Previously, the odds of termination for spine-related clinical trials were higher for trials with industry sponsorship relative to trials sponsored by institutions, even after accounting for other clinical trial design characteristics [4]. This independent increase in odds of trial termination has also been shown for shoulder-related clinical trials [8]. Commonly reported reasons for termination of spine-related clinical trials include insufficient rate of participant accrual, business decisions or strategic reasons, regulatory or conduct issues, and scientific data from the trial [4]. It is possible that industry is not initiating as many clinical trials related to conditions of the spine relative to institutions due to a higher risk of trial termination, more critical appraisal of difficulties with clinical trials that have been reported as reasons for trial termination, and/or difficulties associated with the different types of clinical trials initiated by industry versus industry—for which univariate and multivariate analyses were used. Alternatively, it is also possible that there are now fewer barriers and/or more support (eg, grant funding,

technical support, collaboration, and/or corporate support) available for the initiation of spine-related clinical trials by institutions.

When the registration characteristics were compared among spine-related clinical trials sponsored by industry, institutions, and federal agencies, all trial characteristics (intervention type, phase, randomization, and blinding) were correlated with sponsor type; that is, univariate analysis revealed differences in the types of studies initiated by industry, institutions, and federal agencies. To investigate more rigorously whether trial characteristics would be independently associated with sponsorship types, multivariate analysis was performed with federal and industry-sponsored trials compared in a pairwise manner to institutionally sponsored trials.

Regarding trials with institutional sponsorship, industry sponsorship was independently associated with different intervention types, phases of study, lack of randomization, and lack of blinding (open-label). For example, with the procedure as the reference for trial intervention type,

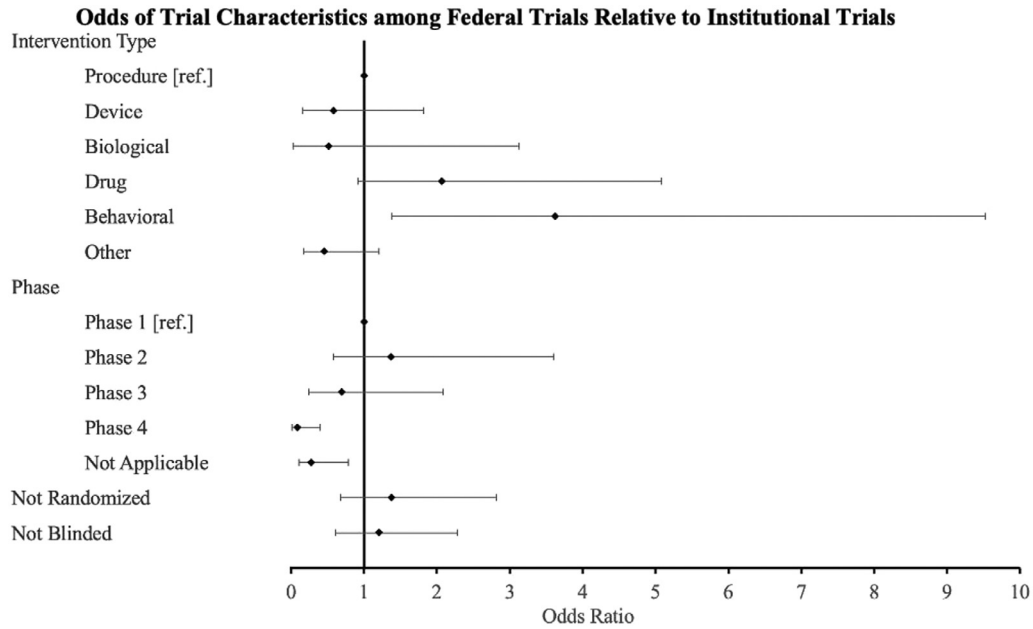


Fig. 5. Results of multivariate analysis for federally sponsored clinical trials relative to institutionally sponsored clinical trials; *ref.*, reference.

spine-related trials sponsored by industry were more likely to investigate devices, biological agents, and drugs relative to those sponsored by institutional trials whereas trials investigating a behavioral intervention tended to be funded primarily by institutions rather than by industry. These differences in trial design characteristics may help to explain prior findings by Caruana et al. [4] that clinical trials sponsored by industry are more likely to result in termination relative to those sponsored by institutions. Increased attention to the challenges faced by industry sponsors, as well as policies to support device-, biological-, and drug-related clinical trials may help industry sponsors avoid clinical trial termination, ultimately facilitating the advancement of new products and procedures for diseases and disorders of the spine.

Relative to trials with institutional sponsorship, federal sponsorship was independently associated with intervention type, phase of study. For example, relative to studies of procedures and phase 1 studies, behavioral interventions, and phase 4 trials were more closely tied to federal sponsorship as opposed to institutional sponsorship. These results, in combination with the increase of trials initiated annually by institutions relative to trials initiated by industry and federal agencies, suggest that the type(s) of spine-related clinical trials performed has been shifting over the years from the launch of ClinicalTrials.gov in 2000 through 2022.

There are several limitations to this study. A cross-sectional sampling of trials registered at ClinicalTrials.gov limits data collection to a single time point (ie, January 3, 2023—the date the ClinicalTrials.gov database was queried) as well as to “applicable clinical trials” defined by the Final Rule for Clinical Trials Registration and Results Information Submission (ie, generally, phase 2 through 4 trials investigating FDA-regulated interventions that are conducted in the United States) [9]. There are likely to be clinical trials advancing science and technologies related to conditions of the spine that were registered with ClinicalTrials.gov in addition to those captured in the study sample but that did not include the term “spine” in any of the following trial registration data elements and, thus, were not captured: title, condition/disease, or intervention(s). Therefore, this study likely captures only a subset of clinical trials related to the spine but undoubtedly underestimates the true number of clinical trials related to interventions under active investigation for diseases and disorders of the spine. Moreover, given that registration of clinical trials with the NIH was not required until 1997 by the Food and Drug Administration Modernization Act and ClinicalTrials.gov was not

made publicly available until February 29, 2000, [1] which precludes analysis of trends in spine-related clinical trials prior to FDA-mandated registration of clinical trials with the NIH.

## Conclusions

Over the period from February 2000 (corresponding to the launch of the database) through December 31, 2022, the number of spine-related trials initiated annually markedly increased (from 21 to 453, representing an increase of 2,057%). This was predominantly driven by an increase in the number of institutionally sponsored trials. However, institutionally sponsored trials were found to differ in trial design characteristics that included the type of intervention under active investigation, phase of study, blinding, and randomization. When differences in trial characteristics are interpreted in combination with the increased proportion of spine trials sponsored by institutions relative to those sponsored by industry and federal agencies, the types of clinical trials—the main mechanism for advancing products and procedures related to diseases and disorders of the spine—can be understood to be shifting over time. This has important implications for surgeons and patients, as industry-sponsored spine-related clinical trials report positive results at a higher rate [10]—which may reflect bias in study design and complicate interpretation of surgical outcomes—and differences in trial characteristics are shown here to be linked to differences in, for example, randomization and blinding on the basis of sponsorship type, suggesting differences in rigor of study design.

## Permission to reproduce copyrighted materials or signed patient consent forms

Not applicable.

## IRB approval/research ethics committee

Yale Institutional Review Board deemed the current study exempt from IRB review and approval.

## Levels of evidence

Not applicable.

### Declaration of competing interests

One or more of the authors declare financial or professional relationships on ICMJE-NASSJ disclosure forms.

### Acknowledgments

The authors acknowledge that this work would not have been possible without the ongoing efforts by the National Library of Medicine in collecting trial registration data from sponsors/investigators and in maintaining ClinicalTrials.gov database.

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