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Clinical Trial Quality Assessment in Adult Spinal Surgery: What Do Publication Status, Funding Source, and Result Reporting Tell Us?

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Abstract

Study Design: Narrative Review

Objectives: The objective of this study was to compare publication status of clinical trials in adult spine surgery registered on ClinicalTrials.gov by funding source as well as to identify other trends in clinical trials in adult spine surgery.

Methods: All prospective, comparative, therapeutic (intervention-based) trials of adult spinal disease that were registered on ClinicalTrials.gov with a start date of January 1, 2000 and completion date before December 17, 2018 were included. Primary outcome was publication status of published or unpublished. A bivariate analysis was used to compare publication status to funding source of industry vs non-industry.

Results: Our search identified 107 clinical trials. The most common source of funding was industry (62 trials, 57.9% of total), followed by University funding (26 trials, 24.3%). The results of 76 trials (71.0%) were published, with industry-funded trials less likely to be published compared to non–industry-funded trials (62.9% compared to 82.2%, $P = .03$). Of the 31 unpublished studies, 13 did not report any results on ClinicalTrials.gov, and of those with reported results, none was a positive trial.

Conclusions: Clinician researchers in adult spine surgery should be aware that industry-funded trials are less likely to go on to publication compared to non–industry-funded trials, and that negative trials are frequently not published. Future opportunities include improvement in result reporting and in publishing negative studies.

Keywords

clinical trials, publication bias, trial database, funding, study design, intervention type

Introduction

Surgery for the adult spine has the potential to alleviate pain and improve quality of life in appropriately selected patients. Given an aging population as well as advances in surgical technique and implant selection, the number of surgeries performed each year is increasing.[1,2] Concurrently, non-operative treatment options for spine pathology are also increasing in number, timing, and complexity.[3] With the increase in the number of operative and non-operative treatment options comes an increasing responsibility for the surgeon to understand the risks and benefits of each particular treatment. Ideally, this understanding is based on evidence that has proven that one clinical decision is superior to another. Such evidence is often derived from prospective clinical trials.

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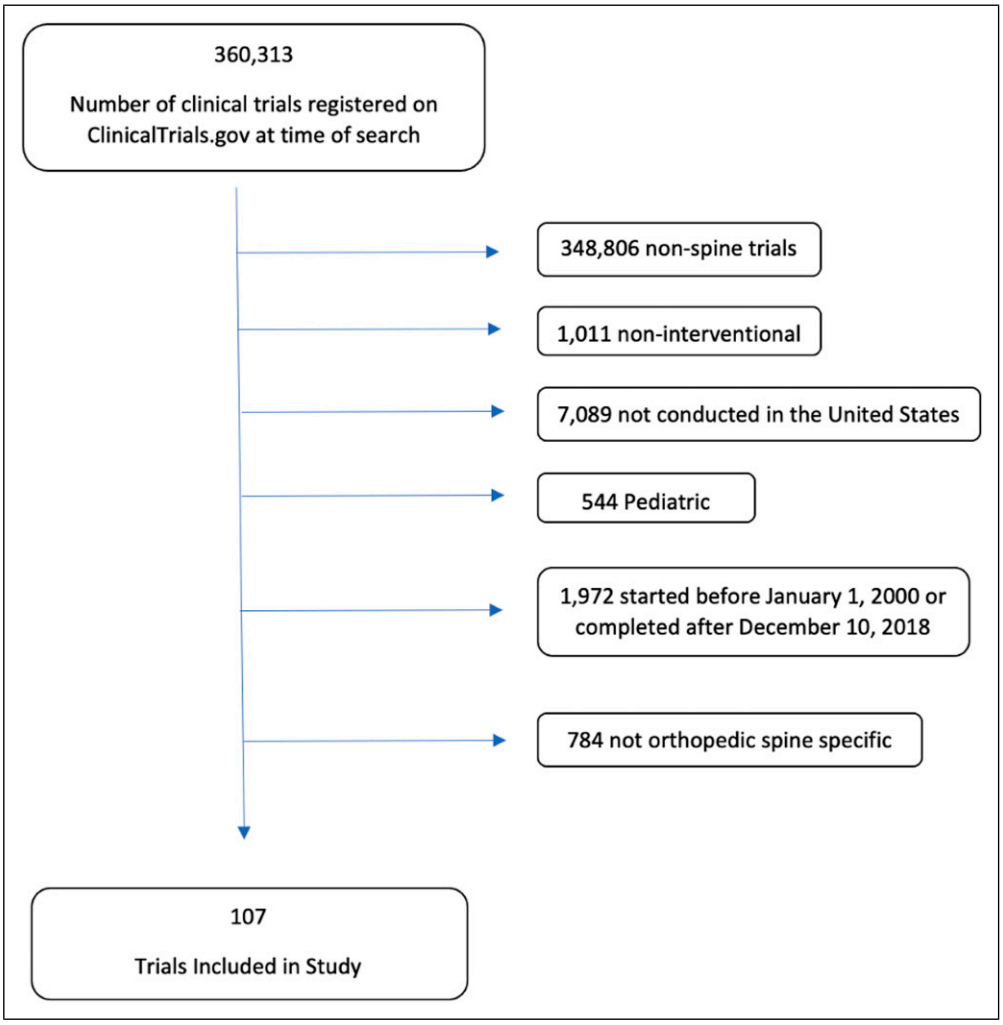

Figure 1. Flow diagram of included studies.

Within adult spine surgery, prospective clinical trials have had a profound impact on how patients are treated.[4] For instance, the Spine Patient Outcomes Research Trial (SPORT) aids clinicians in the management of patients with intervertebral disc herniation, degenerative spondylolisthesis, and stenosis.[5–7] Yet not all prospective clinical trials in adult spine surgery are equal in design. There is significant variability in study parameters including randomization, blinding, and crossover. The clinical questions that a given trial aims to answer may be related to a pharmacological, procedural, device, or behavioral intervention.

The source of funding varies from study to study as well. For instance, SPORT was government-sponsored, while other influential trials have received industry support. Berenson et al. performed a prospective-randomized trial funded by Medtronic Spine. Their results suggested that balloon kyphoplasty for painful vertebral compression fractures in patients with cancer may improve self-assessment of disability compared to non-surgically treated patients.[8] In addition to trial design and funding, the results of some trials are published, while others are not. While the reason for this is multifactorial, certain studies in spine surgery have found an association between failure to publish and source of funding, with the results of industry-funded studies less likely to be published compared to the results of non–industry-funded studies.[9] Other studies suggest that there is no such association between failure to publish and source of funding.[10]

In light of the complexity of interpreting prospectively collected data and the previous, the objective of this study was to compare publication status of clinical trials in adult spine surgery registered on ClinicalTrials.gov by funding source as well as to identify other trends in clinical trials in adult spine surgery. We hypothesized that studies funded by industry were less likely to be published than those with non-industry funding.

Materials and Methods

Data Source

A search of trials registered on ClincalTrials.gov was conducted with the search terms “spine” and “spinal” (data search algorithm is available as a Supplement). Studies were included

Table 1. Funding Source of Clinical Trials.

Funding source	Frequency	Percent, %
Industry	62	57.9
University	26	24.3
NIH	11	10.3
Medical society	6	5.6
Private	2	1.9
Total	107	100.0

Table 2. Intervention Type by Funding Source.

Intervention	Industry	Non-industry	Total	P Value*
Device	34	7	41	.003
Drug	13	15	28	
Procedure	8	7	15	
Behavioral	0	7	7	
Other	6	9	15	
Total	62	45	107	

*Chi-squared analysis, *P*-value of less than .05 is considered significant

if 2 independent reviewers (MS and VB) agreed upon inclusion of a study into the final analysis. Trials pertaining to adult spine surgery were isolated to identify prospective, therapeutic trials with a completion date greater than or equal to 24 months prior to our search to allow adequate time for publication of trial results (December 17, 2018). This timeframe is similar to previously established methodology of clinical trial evaluation.[11,12] ClinicalTrials.gov was founded in 1997, and it is a database of privately and publicly funded clinical studies conducted around the world, and is maintained by the United States National Library of Medicine, part of the National Institute of Health. Currently. It currently lists 368,659 research studies conducted in all 50 United States and 219 countries.[13] Any controlled clinical investigation of a Food and Drug Administration (FDA)-regulated drug and any study of an FDA-regulated medical device must be registered with ClinicalTrials.gov as part of section 402(j) of the Public Health Service Act.[14]

Inclusion/Exclusion Criteria

Inclusion criteria were prospective, therapeutic (intervention-based) clinical trials with a start date after January 1, 2000 and a completion date before December 17, 2018 that investigated the effect of a drug, procedure, medical device, or behavioral intervention on pathology of the adult spine. Exclusion criteria were pediatric trials (patient age less than or equal to 18 years), observational studies, trials completed after December 17, 2018, and trials that were conducted outside the United States.

Data Collection and Analysis

Variables recorded were trial title, national clinical trial (NCT) identification number, year of trial start, year of completion, and, if results were published, the journal in which results were published. Outcome variables assessed were spinal pathology for which the trial was performed (lumbar degenerative disease, lumbar disc herniation, cervical degenerative disease, adult deformity, vertebral compression fracture, infection, kyphosis, pain, neuromonitoring, osteoporosis, other or mixed disease), spinal level for each procedure (cervical, lumbar, or multiple; no trial focused on thoracic pathology exclusively), trial design (randomized or not randomized, blinded or not blinded, parallel or crossover), source of funding, intervention type (drug, procedure, device, behavioral, other), procedure type (lumbar fusion, lumbar decompression, anterior cervical decompression and fusion) number of enrolled patients, trial phase, publication status (published or not published), and number of citations for original research articles that were published based on trial results. Publication status was determined by a PubMed search of trial titles and principal and/or co-principal investigator names. Number of citations was obtained by a Google Scholar search performed on March 27th, 2021. If trial results yielded more than one publication, we selected the publication with the highest number of citations. For unpublished results, we recorded whether results were available on ClinicalTrials.gov, the result type (positive trial, negative trial, no significance reported), the percent of patients starting but not completing the study, follow-up timing, and whether or not any primary or secondary outcome variable was recorded. Because we were not comparing clinical outcomes, we did not assess risk of study bias or certainty in the body of evidence.

Statistical analysis were descriptive statistics of the frequency of each outcome variable and the percentage of total that each outcome variable represented. Fisher's exact test was utilized to determine the significance of association for categorical variables between groups. A one-way analysis of variance (ANOVA) test was used to compare means among multiple (greater than 2) groups. A *P*-value of less than .05 was considered statistically significant.

Results

Included Studies

Our search revealed 107 prospective, comparative, intervention-based clinical trials in adult spine surgery that were completed in the United States between January 1, 2000 and December 17, 2018. (Figure 1) The year with the most trials completed was 2012 (14 trials), and the year with the least was 2004 (zero trials). The most common source of funding was industry (62 trials, 57.9% of total), followed by intramural or University funding (26 trials, 24.3%). The NIH funded 11 trials (10.3%). There was a mean of 155.5 ± 211.5 enrolled patients per trial (range 6 to 1874). (Table 1)

Intervention Type

The most common type of intervention was related to device or implants (42 trials, 39.3%), followed by drug (31 trials, 29.0%), procedure (22 trials, 20.6%), and behavioral intervention (12 trials, 11.2%). There was a significant association between funding source and intervention type, with industry-funded studies more likely to fund device trials compared to other funding sources (P = .003). (Table 2) Of the devices studied, the most common was for disc arthroplasty, which accounted for seven of 42 devices (16.7%). The most common spine pathology investigated was lumbar degenerative disease (32 trials, 30.0%). Cervical degenerative disease and adult deformity trials accounted for 17 (15.9%) and 4 (3.7%) trials, respectively. Of the 12 behavioral related trials, common interventions included physical therapy, cognitive behavioral therapy, coaching, and chewing gum.

Clinical Trial Design

Trial design was most frequently parallel, with 81 trials (75.7%) employing a parallel design. Randomization was more common than no randomization, with 83 randomized trials (77.6%) and 24 non-randomized (22.4%). A majority of studies did not employ double blinding (73 studies, 68.2%) (Table 3).

Table 3. Clinical Trial Study Characteristics.

Characteristic	Frequency	Percent, %
Randomized		
Yes	83	77.6
No	24	22.4
Double blinded		
Yes	34	31.8
No	73	68.2

Clinical Trial Publication Outcomes

Of the 107 trials, the results of 76 were published (71.0%), while the results of 31 (29.0%) were not published. (Table 4) There was no significant difference when comparing proportion of trials completed between 2000 and 2010 that went onto publication (18 of 24 trials, 75%) vs trials completed between 2011 and 2018 that went onto publication (68 of 83 trials, 81.9%, P = .65). (Table 5) 11 studies received funding from the NIH, and all ultimately went onto subsequent publication (100.0%). 39 of 62 (62.3%) industry-funded studies went onto subsequent publication, which was a significantly smaller proportion compared to non–industry-funded studies (37 of 45 studies, 82.2%, P = .03). (Table 5). Of the 31 unpublished trials, 13 (41.9%) did not report outcome data on ClinicalTrials.gov. Of the 18 unpublished trials with available results, there were no positive trials (.0%), 8 (44.4%) negative trials, and 10 (55.6%) trials for which neither a positive nor negative result was reported. (Table 6)

The most common journal of publication was *Journal of Neurosurgery: Spine* (16 publications) followed by *Spine* (15 publications). Six trials were published in *The Journal of Bone and Joint Surgery*, and 4 were published in *The New England Journal of Medicine*.

When analyzed by funding source, studies funded by the NIH had the highest mean number of citations per publication compared to studies funded by industry, medical societies, or university. Studies funded by the NIH had a mean of 270 citations compared to mean of 65.5 citations for industry-funded studies, 24.3 for studies funded by university, and 8.6 for studies funded by medical societies (P = .004). (Table 7) The overall mean number of citations per study was 81.5 (range 0 to 1217). The most highly cited NIH-funded study was SPORT. Of the numerous publications from this trial, the most cited had 1217 citations at the time of search.[8] The most-commonly cited industry-funded study was the Cancer Patient

Table 4. Publication Outcome of Adult Spine Surgery Clinical Trials.

Journal name	Number of trials	Percent of trials, %
Journal of Neurosurgery: Spine	16	15.0
Spine	15	14.0
Published abstract	6	5.6
The Journal of Bone and Joint Surgery	6	5.6
Neurosurgery	6	5.6
New England Journal of Medicine	4	3.7
Pain physician	4	3.7
International Journal of Spine Surgery	3	2.8
Anesthesia and Analgesia	2	1.9
Anesthesiology	2	1.9
Other journals	12	11.2
Unpublished	31	29.0
Total	**107**	**100**

Table 5. Comparison of Trials Based on Publication Status.

	Trial published		Trial not Published	*P*-Value
Trial completed after 2010	Yes	68	15	.650
	No	18	6	
Industry-funded	Yes	39	23	.030 *
	No	37	8	

**P*-value less than .05 is considered significant.

Table 6. Result Reporting for Unpublished Clinical Trials.

Trial Results Available on ClinicalTrials.gov	Yes (%)	18 (58.1)
	No (%)	13 (41.9)
Trial result	Positive (%)	0 (0)
	Negative (%)	8 (44.4)
	No significance reported (%)	10 (55.6)
Follow up in months, mean (range)		6.9 (0 to 24)
Funding source	Industry	23
	University	7
	Medical society	1
	Private foundation	0
	Medical society	1
	NIH	0

The total number of unpublished trials was 31; NIH: National institute of health

Table 7. Comparison of Number of Citations per Publication Based on Funding Source.

	Funding source				
	Industry	**Medical society**	**NIH**	**University**	**P-value**
Publications (N)	38	5	9	18	
Number of citations (mean ± SD)	65.6 ± 88.6	8.6 ± 6.8	270 ± 445	24.3 ± 22.6	.004*

**P*-value less than .05 is considered significant.
Abbreviation: NIH, National institute of Health; SD, Standard deviation

Table 8. Procedure Type, Pathology, and Spinal Level by Publication Rate.

Procedure type		**Published**	**Not published**	***P*-value***
	Lumbar fusion	8	7	.31
	ACDF	9	2	
	Lumbar decompression	9	4	
Pathology				
	Degenerative disease	50	19	.56
	Non-degenerative disease	35	13	
Spinal level**				
	Cervical	13	4	.57
	Lumbar	22	10	

Abbreviation: ACDF, anterior cervical decompression and fusion.
*Chi-squared analysis. P-value less than .05 is considered significant. **No trial focused exclusively on thoracic spinal pathology.

Fracture Evaluation (CAFE) study, with 426 citations.[8] The second most-commonly cited industry-funded study was the Prestige Cervical Disc Study. It was the fifth most-cited study overall, with 287 citations at the time of search.[8] Of the ten most-commonly cited studies, only one was a study of a behavioral intervention, the Yoga for Kyphosis Trial.[15]

When trials were analyzed by procedure type (lumbar fusion, anterior cervical decompression and fusion, lumbar

decompression), spinal level (cervical or lumbar), or pathology (degenerative disease or non-degenerative disease), there was no significant association between these variables and rate of publication (Table 8).

Discussion

Our hypothesis that clinical trials funded by industry were less likely to go on to publication than trials that were not funded by industry was validated. In this current analysis, NIH-funded studies had significantly higher rates of publication compared to industry-sponsored research, which was more likely to go unpublished. Prior studies have demonstrated a significant association between funding source and publication of clinical trials for spine surgery, with trials funded by industry less likely to be published.[9] Industry-sponsored research can benefit the field of spine surgery, but it can also bias both publication of results as well as presentation of data and its interpretation.[16] In general, industry-sponsored research is associated with more favorable efficacy results, more favorable study conclusions, and lower agreement between study results and conclusions when compared to non–industry-funded research.[17] The physician tasked with interpreting and applying clinical research to treatment decisions must be aware of these associations. The significant association we found between funding source and number of citations per publication, with NIH-funded studies more likely to be cited than industry-cited studies, may suggest that clinician researchers are aware of such associations and put more faith in data from non–industry-funded studies.

We do emphasize that investigators can and do perform high-quality clinical trials regardless of funding source. SPORT for intervertebral disc herniation was government funded and has produced numerous impactful publications. It is a multi-center, prospective, randomized study of 501 patients with minimum 2-year follow-up and a primary endpoint of 2 commonly used patient-reported outcome measures (the 36-item Short-Form Health Survey bodily pain and function scales, and the Oswestry Disability Index).[18] The most frequently cited industry-sponsored study, the Cancer Patient Fracture Evaluation (CAFE) study, cited 426 times, is also a prospective-randomized trial, with 134 patients, and a follow up of 1 month, which is an adequate timeframe for cancer patients for whom pain relief is important.[8] Another example of a quality industry-funded trial is the Prestige Cervical Disc Study, which enrolled 541 patients at 32 investigational cites and reported results at 60 months. It is the second most-commonly cited industry-funded study.[19]

Our data also showed that failure to publish trial results was common (71.0% of trials published, 29.0% of trials unpublished). Other orthopedic subspecialties including adult arthroplasty and orthopedic trauma have reported similar publication rates for trials registered at ClinicalTrials.gov.[20,21] Low publication rates raise a concern for publication bias, as studies with positive results are more commonly published than studies with negative results, with 1 analysis showing that positive studies had a 3.3 times higher rate of being published when compared to negative studies.[16,22] Our data reflects this propensity to withhold negative results. Of the 31 clinical trials that were unpublished, 13 did not report any results, none were a positive study, eight were negative, and 10 reported results but did not report whether the study was positive or negative (Table 6). When studies do reach publication, they tended to be published in journals with high impact factors (Table 4). This may indicate that the studies we identified are in general higher quality than other studies that reach publication.

Not only is publication bias a problem from an ethical standpoint, but it also affects future research, as meta-analyses adopt the biases of the data that they analyze.[23] In turn, physicians may interpret data incorrectly and make treatment decisions that data does not in fact justify. Finally, if results from negative studies are not published, other investigators may waste valuable resources recreating research that has already been performed. There are numerous potential methods to increase the publication rate of negative trials. Based on our data, one potential solution is to separate study sponsorship (funding) from implant, device, or drug companies, which would allow investigators to collect, analyze, and publish data without influence of industry. Other methods are for leaders in the field of spine surgery research to publish opinion pieces or letters to the editor stressing the importance of publishing negative trials. Journal editors could publish special issues (supplemental issue, for example) dedicated to negative trials. Finally, a task force or new branch of the NIH could be formed as a watchdog group that ensures negative results from trials registered on clinicaltrials.gov are published.

The current study identified trends in design, methodology, and result reporting of prospective clinical trials that investigate treatment for adult spinal pathology. These trends help clinician-researchers appreciate the state of evidence in adult spine surgery and anticipate future development in it. While analyses of trends in prospective clinical trials have helped investigators in other specialties understand their respective fields, our study is the first to do so in a comprehensive manner for the field of adult spine surgery.[11,24–28] Other investigations in the field of spine surgery have been more limited in scope. For example, Ohnmeiss et al. analyzed 72 spine-related trials from ClinicalTrials.gov to determine their fate with regard to publication, but did not determine important aspects including trial design, randomization status, blinding, and industry influence on results.[9] Son et al. investigated publication bias for spine-related studies registered on ClinicalTrials.gov, but likewise did not describe important elements of trial design.[29] Our data shows a high rate of randomization (77.6% of trials), a low rate of blinding (68.2% of trials), and trials designed more commonly as parallel as opposed to single group or crossover studies (75.7% compared to 21.5% and 2.8%, respectively).

One weakness of this current study is the heterogeneity of our data. For example, the number of spinal pathologies present within our study was quite variable such that the most common pathology, lumbar spinal stenosis, was studied in only 32 trials (30.0%) and there were no studies that focused exclusively on thoracic spinal pathology. Moreover, within a certain pathology or within a certain intervention category, there was heterogeneity of data. Within the behavioral intervention category alone, treatments ranged from different iterations of physical therapy to yoga to chewing gum. Over the timeframe that we investigated, surgeries and procedures were more commonly investigated than behavioral interventions and drugs. We believe the heterogeneity revealed by our data is useful in its own right, as it shows the broad spectrum of spinal pathology and the even broader spectrum of attempts to address it. Furthermore, this study was limited to adult patients only in an effort to maintain sample homogeneity and may not be applicable to a pediatric population. Another weakness of our study is that data from ClinicalTrials.gov may not be completely accurate, as the National Library of Medicine does not have an established means of policing accuracy of data entry, which is dependent on the principal investigator. We associated trials that went on to publication with publication titles on PubMed, which helped mitigate this weakness. Another weakness is our reliance on PubMed to identify trials that went on to publication, as this may fail to capture studies not indexed in this registry. However, PubMed is one of the most used and dependable libraries of published medical literature.[17] Finally, we did not have data regarding the amount of funding received per trial. Future research may be directed toward identifying reasons for not publishing data as well as limitations in study design, such as barriers to randomization and other aspects of trial design that can improve the quality of a given study. Future opportunities may be in fields that are less well-represented in the current landscape of prospective trials, such as adult spinal deformity.

Conclusion

Clinician researchers in adult spine surgery should be aware that industry-funded trials are less likely to go on to publication compared to non–industry-funded trials, and that negative trials are frequently not published. Future opportunities include improvement in result reporting and in publishing negative studies.

Declaration of Conflicting Interests

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IRB Statement

This study utilized national, de-identified data and is exempt from IRB review.

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Supplemental Material

Supplemental material for this article is available online.

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