The Spine Journal 15 (2015) 1133–1140

Technical Report

Spine device clinical trials: design and sponsorship

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Received 11 June 2014; revised 13 November 2014; accepted 21 January 2015

Abstract

BACKGROUND CONTEXT: Multicenter prospective randomized clinical trials represent the best evidence to support the safety and effectiveness of medical devices. Industry sponsorship of multicenter clinical trials is purported to lead to bias.

PURPOSE: To determine what proportion of spine device-related trials are industry-sponsored and the effect of industry sponsorship on trial design.

STUDY DESIGN: Analysis of data from a publicly available clinical trials database.

METHODS: Clinical trials of spine devices registered on ClinicalTrials.gov, a publicly accessible trial database, were evaluated in terms of design, number and location of study centers, and sample size. The relationship between trial design characteristics and study sponsorship was evaluated using logistic regression and general linear models.

RESULTS: One thousand six hundred thrity-eight studies were retrieved from ClinicalTrials.gov using the search term ''spine.'' Of the 367 trials that focused on spine surgery, 200 (54.5%) specifically studied devices for spine surgery and 167 (45.5%) focused on other issues related to spine surgery. Compared with nondevice trials, device trials were far more likely to be sponsored by the industry (74% vs. 22.2%, odds ratio (OR) 9.9 [95% confidence interval 6.1–16.3]). Industry-sponsored device trials were more likely multicenter (80% vs. 29%, OR 9.8 [4.8–21.1]) and had approximately four times as many participating study centers ($p<.0001$) and larger sample sizes. There were very few US-based multicenter randomized trials of spine devices not sponsored by the industry.

CONCLUSIONS: Most device-related spine research is industry-sponsored. Multicenter trials are more likely to be industry-sponsored. These findings suggest that previously published studies showing larger effect sizes in industry-sponsored vs. nonindustry-sponsored studies may be biased as a result of failure to take into account the marked differences in design and purpose.

Key Words: Spine surgery; Medical devices; Implants; Industry sponsorship; Bias; Multicenter clinical trials

Introduction

The number and variety of devices for spine surgery are increasing. Both novel devices and devices representing incremental improvements in preexisting technology are commonly the subject of clinical trials aiming to establish or confirm their safety and effectiveness. Although single-arm trials may suffice in some situations, the gold standard for proving safety and effectiveness is a randomized clinical trial (RCT). An even higher standard is the multicenter RCT (MRCT). Multicenter RCTs play an important role in surgical devices for several reasons. First, multiple centers may be required to achieve adequate trial sample sizes in reasonable time frames. Perhaps, more importantly, MRCTs show that the surgical intervention can be performed adequately by a reasonably large number of physicians, not just a single physician.

Multicenter RCTs are difficult, time-consuming, and expensive, often requiring a team of trained personnel, as opposed to a single coordinating investigator, to implement,

FDA device/drug status: Not applicable.

Author disclosures: ***DJC:*** Nothing to disclose. ***RAC:*** Nothing to disclose.

The authors are employees of SI-BONE, Inc. SI-BONE, Inc., sponsored this research. Two of the trials retrieved in the ClinicalTrials.gov data set that comprises the focus of the analysis reported herein were sponsored by SI-BONE, Inc. All databases, analysis code, and analyses are available on request. No funding was received in support of this work.

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http://dx.doi.org/10.1016/j.spinee.2015.01.027
1529-9430/

oversee, and report the study. Human research carries a liability risk that an individual physician or hospital may not want or be able to assume [1]. Additionally, public sector funding for clinical trials has significantly declined over the past two decades, increasing the competition for research dollars [2]. The time, financial burden, and liability risk required to conduct multicenter clinical trials markedly limits the ability of an individual physician to develop a medical device without outside support [1]. Not surprisingly, many trials are sponsored by the industry.

Several recent articles [3–5], including a Cochrane summary [6], have concluded that trials sponsored by the industry are more likely to report positive results, suggesting that these trials are biased. However, none of the authors of these comparisons took into account the component studies' interventions, designs, or purposes. In the scientific spirit of reproducibility of results through replication, device-related spine trials could be repeated in the nonindustry setting, allowing a direct comparison of the potential effect of industry sponsorship. As noted above, several factors make nonindustry trial replication difficult.

The aim of this study was to determine the type and frequency of clinical trial sponsorship and determine if the sponsor type systematically affects the scope and design of device-related spine surgery clinical trials.

Materials and methods

No publicly available database provides a complete picture of currently existing clinical trials. For many reasons, Clinicaltrials.gov is a reasonable proxy. ClinicalTrials.gov is a federally funded and publicly available database run by the US National Institutes of Health and is part of the World Health Organization International Clinical Trials Registry Program. Listing a trial in a publicly accessible trials database is a United States federal requirement for premarket studies. Moreover, journals adhering to the International Committee on Medical Journal Editors clinical trials reporting requirement require trial listing in a publicly accessible database to consider a trial for publication. Typically, listings in trial repositories are reserved for prospective clinical studies; retrospective studies are rarely listed.

Using its web-based search interface, we queried (March 6, 2014) the ClinicalTrials.gov database using the search term "spine." All entries were downloaded in individual Extensible Markup Language format and concatenated into a single file. An Extensible Stylesheet Language file was written to extract relevant information from the Extensible Markup Language document. The resulting data table was imported into R [7], which was used for all analyses.

Both authors individually reviewed each trial listing. Any disagreements were resolved by discussion. Trials were characterized as follows: not about spine pathology, specifically about osteoporosis treatment or prevention, and about spine pathology but not about spine surgery. The remaining studies where then categorized as either about spine surgery but not about specific devices used to address specific spine pathology (eg, sealants, blood measurement devices during spine surgery, etc.) or about spine surgery using devices. Trials were excluded if, according to the study's status field, they were terminated, suspended, or withdrawn. Using ClinicalTrials.gov's study design field, trials were divided into RCTs and non-RCTs (eg, prospective parallel group nonrandomized studies) or other (eg, single-arm cohorts). Based on the listed study locations, trials were further divided into single center or multicenter. Trials were characterized as multicenter if more than one study center was listed or the term "multicenter" was used in the title or description. In the event no study site was listed, the record was reviewed for subject enrollment. Sponsorship was initially determined based on ClinicalTrials.gov's sponsor type field as "industry," "federal," or "other." Further review was undertaken to ensure accurate reporting of sponsor. Trial location was characterized as either conducted in the United States only, outside the United States (OUS) only, or both.

Logistic regression was used to determine the odds that a trial listing was associated with a particular characteristic. Log-linear models were used to estimate the effect of industry sponsorship on the number of centers and sample size. The database used for the analysis reported herein, the analysis code, and the complete results are available on request.

Results

A search of ClinicalTrials.gov using the term "spine" yielded 1,638 records. Of these, 531 were not specifically about spine pathology, 222 focused on osteoporosis treatment or prevention, and 465 involved the spine but were not surgical in nature. Of the remaining 420 studies, 52 were suspended, terminated, or withdrawn, leaving 367 studies for analysis. Of the 367 trials that focused on spine surgery, 200 (54.5%) specifically involved devices for the surgical treatment of spine-related conditions and 167 (45.5%) focused on issues unrelated to devices (Table 1). Twelve (3.3%) studies were federally sponsored, 170 (46.3%) were sponsored primarily by academia, and 185 (50.4%) were industry-sponsored (Table 2). A strong association was seen between trial focus and sponsor type; 74% of device trials were industry-sponsored versus 22.2% of nondevice trials (odds ratio [OR] 9.9, 95% confidence interval [CI] 6.1–16.3, $p<.0001$). Among the 200 surgical device trials, the proportion of trials that were RCTs was smaller for industry-sponsored studies than other sponsor types: 41.2% for industry, 63.3% for academia, and 100% for federally funded studies (OR 0.41, 95% CI 0.21–0.79, industry vs. academia, $p=.008$). However, this relationship was attenuated and not statistically significant when considering trials that had at least one site in the United States (OR 0.93; 95% CI 0.31–2.94, $p=.89$).