Author's Clinical Specialty: A Competing Interest in Economic Analysis of Surgical Interventions, Reality or Fiction?

A thesis

submitted by

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Abstract

A well-developed literature suggests that financial conflicts of interest are associated with results reported in published health economic analyses. This study investigates the association between the clinical specialty of publishing authors and the favorability of reported incremental cost effectiveness ratios (ICERs). We aim to examine and evaluate surgical interventions catalogued in the Tufts Medical Center Cost Effectiveness Analysis (CEA) Registry (www.cearegistry.com). We used the Tufts CEA Registry, a comprehensive database of cost-utility analyses that have been performed for a wide variety of diseases, conditions and treatment options. Eligible studies were articles and ratios labeled as "surgical" studies between 1976 and 2011. Logistic regression models were used to examine the multivariate relationship between the primary outcome (favorable ICER) and the primary author's clinical specialty while controlling for confounders, including the source of funding for the published analysis and the type of treatment option to which the intervention was compared. Our primary results showed that CEAs comparing surgical interventions with alternative treatment options using the $50,000 per QALY benchmark did not show a significant association between primary author being a surgeon and ICER favorability (adjusted OR= 1.25, 95% CI= 0.78- 1.99, p=0.38). When compared relative to the weighted median ICER in our sample there was a strong trend to producing favorable ICER when the primary author is a surgeon (OR= 1.60, 95% CI=1.06 - 2.40, p= 0.02 and adjusted OR= 1.50, 95% CI= 0.99- 2.30, p= 0.06). The "surgeon" effect was more evident with the increased proportion of surgeons per article (OR =2.43, CI=1.36 - 4.41, p = 0.003, adjusted OR= 2.22, CI=1.22-4.09, p = 0.01). Our study is the first to show an evidence that non-financial competing interests may represent an important source

of bias that has not yet been systematically addressed. Understanding this source of bias may guide stakeholders when utilizing this literature.

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Table of Contents

List of tables

List of Figures

List of abbreviations

QALY: Quality Adjusted Life Year

ICER: Incremental Cost Effectiveness Ratio

CEA: Cost Effectiveness Analysis

CUA: Cost Utility Analysis

OR: Odds Ratio

CI: Confidence Intervals

Introduction

1.1 Background

In recent years, the issue of conflict of interest has generated a great deal of uneasiness in the biomedical research community. Reviewers and governing organizations have been putting considerable effort into trying to limit the disquieting influence of secondary gains – real or perceived – on reported research results. To address this issue, medical institutions, research facilities, and academic journals have amplified their disclosure requirements for financial conflicts of interest. Nonetheless, financial gain is not the sole cause of undue influence. Secondary interests -- which we refer to as "non-financial competing interests" -- include a variety of factors that may bias the professional judgment of researchers, including career advancement, academic recognition and political, personal or religious association, all of which could pose a compelling influence beyond the mere prospect of financial gain. The degree to which non-financial competing interests can undermine the integrity of biomedical research has not yet been systematically evaluated in the medical literature (1).

This study was designed to investigate one potential source of non-financial competing interests specifically originating from the author's clinical specialty. We hypothesize that the clinical specialty of the author might influence the favorability of published cost effectiveness ratios. While most investigators view themselves as objective and vigilant in their efforts to protect the integrity of their research and deliver the best unbiased evidence, the truth is that when individuals must make decisions, they employ both reason and emotions to determine the expected utility of alternative options (2, 3). This preset collective of emotions and cognitive skills is determined by past experience and perceived reward and risk expectations. In a similar way, authors might adopt or endorse one technology over the other, based on their personal preferences or how much time and effort they invested in developing an intervention, regardless of financial support or incentive (4, 5).

The lack of comprehensive research into non-financial competing interests could be due, in part, to the more challenging nature of intellectual conflicts of interest on many levels. Analyzing this type of bias is complicated by the lack of a reliable methodology. An Institute of Medicine report addressed how difficult it could be to assess and infer motives in the context of non-financial competing interests, describing studies in this area as intrusive (1).

Readers, journal reviewers, and policy makers are typically skeptical of results from economic analyses sponsored by a pharmaceutical or device manufacturer (6, 7). This skepticism is prudent in the context of cost-effectiveness analyses, as several reports have identified an association between favorable ICER values and industry sponsorship (8-11). In contrast, most readers would consider sponsorship by a professional society a stamp of validity and authenticity. They might therefore disregard the potential role of competing interests beyond financial gain in these cases.

The concern about real or perceived conflicts of interest has been discussed previously by multiple medical and surgical panels with little reassurance that such conflicts are being managed appropriately (5). For example, the consensus statement of the American Academic Society (AAS) and Society of University Surgeons (SUS) joint task force noted that competing interests indeed exist and may transcend the financial relationships to industry. Moreover, elimination of all conflicts would be difficult at best (12). On one hand, the partnership between academic surgical practices and industry is pivotal to advance surgical innovation, and a complete severance of this relationship would likely have a detrimental impact on progress in the field. On the other hand, producing biased recommendations jeopardizes the integrity and transparency of academic research and renders it less credible and less valid. Despite the development of standards to limit financial conflicts of interest, the joint task force failed to craft an accepted method to identify and control intellectual and personal competing interests. A similar dilemma was highlighted by a different research groups led by Bion (13).

We investigated non-financial competing interests by analyzing published cost effectiveness ratios catalogued in the Tufts Cost-Effectiveness Analysis (CEA) Registry. We focused our analysis on surgical interventions because this field has a large number of new devices and rapidly evolving technologies. Adapting a new technology can be alluring to surgeons because it is considered innovative, offers an advantage for academic advancement, or places the practitioner in a prestigious position as a provider of state-of-art surgical services. These factors are merely examples of potential motives that can subconsciously sway authors who are trained in surgical specialties to produce economic analyses that conclude a new technology is a superior and cost effective treatment option.

To the best of our knowledge, there has been no original research examining the role of the author's clinical specialty as a source of non-financial competing interests. Many authors have examined the relationship between financial support and the favorability of reported incremental cost-effectiveness ratios(8, 10, 14-16). Others have examined the involvement of authors in guidelines development(17, 18). On the other hand, intellectual and specialty specific bias has not been addressed in the context of economic analysis.

1.2 Economic Impact of Intervention

Cost effectiveness analysis utilizes the following formula to calculate incremental cost effectiveness ratios (

$$\text{ICER}= \frac{\text{COST intervention} - \text{COST comparator}}{\text{QALY intervention} - \text{QALY comparator}}$$

The resulting values can conceptually be summarized in the following plot (Figure.1) -- which illustrates the relationship between change in cost and change in health outcomes.

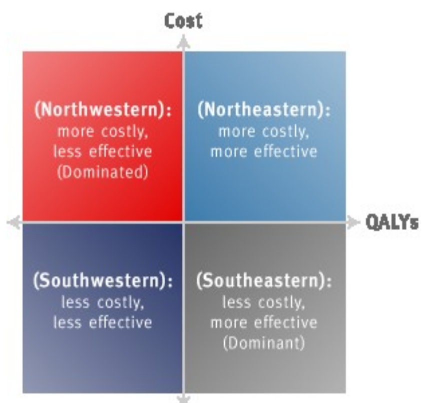

Figure 1. The cost-effectiveness plane, Source: www.cearegistry.com (12)

Most economic analyses yield CERs that fall in the Northeast quadrant in the cost-effectiveness plane. These interventions increase cost but improve health. Technologies and treatment options in the Northeast quadrant are the basis of most cost-utility tradeoff debates. The small number of interventions reported in the Southwest quadrant sacrifice health but save money. If the health sacrifice is sufficiently small and the saving is sufficiently large, the intervention is referred to as “decrementally cost-effective" (10)

The Southeast is the most favorable of all quadrants, where better outcomes are achieved at a lower cost. The Northwestern quadrant encompasses the dominated interventions, i.e., more expensive and worsens health outcomes

Materials and Methods

2.1 Data Source

To evaluate our hypothesis, we used the Tufts Medical Center Cost Effectiveness Analysis Registry (www cost-utility analyses performed to evaluate interventions for a wide variety of disease conditions. CEVR collects data for the registry using a pre-specified methodology that starts with a search of MEDLINE using the terms "QALYs," "quality-adjusted," "cost utility."

Two trained readers independently review retrieved studies. The readers then meet and reach consensus on what to record about this article in the registry. Collected information includes study methods, authorship information (including sponsorship), study focus (intervention evaluated, what it was compared to, and the relevant population), and the incremental cost-effectiveness ratio (ICER), which is the incremental monetary cost per quality adjusted life year (QALY) gained by an intervention, relative to a designated comparator(19). A QALY is one year of life in a hypothetical state of perfect health. No QALYs are gained following death. In general, a year of life in any other health state is worth between 0 and 1 QALY, with more preferred health states worth more than less preferred states. A "small" cost-effectiveness ratio implies that an intervention is favorable (i.e., efficient) because it indicates that relative to its comparator, the incremental cost per QALY gained (the "price" of each QALY) is small. One article may evaluate more than one intervention, compare that intervention to more than one comparator, or conduct analyses for more than one population. For these reasons, individual articles in some cases report more than one cost-effectiveness ratio.

2.2 Inclusion & Exclusion Criteria

We included all articles and ratios designated as surgical in the CEA Registry that were published between 1976 and 2011. Two researchers independently reviewed descriptions of the comparator and intervention for all ratios. The two reviewers then compared the intervention type designations ("surgical" or "non-surgical"). Eighty-nine ratios among 972 reviewed were designated non-surgical. In a few instances there were minor discrepancies, but these were resolved by consensus. Further review identified 20 additional articles as not evaluating surgical interventions (see Figure 2). We excluded these articles from further consideration.

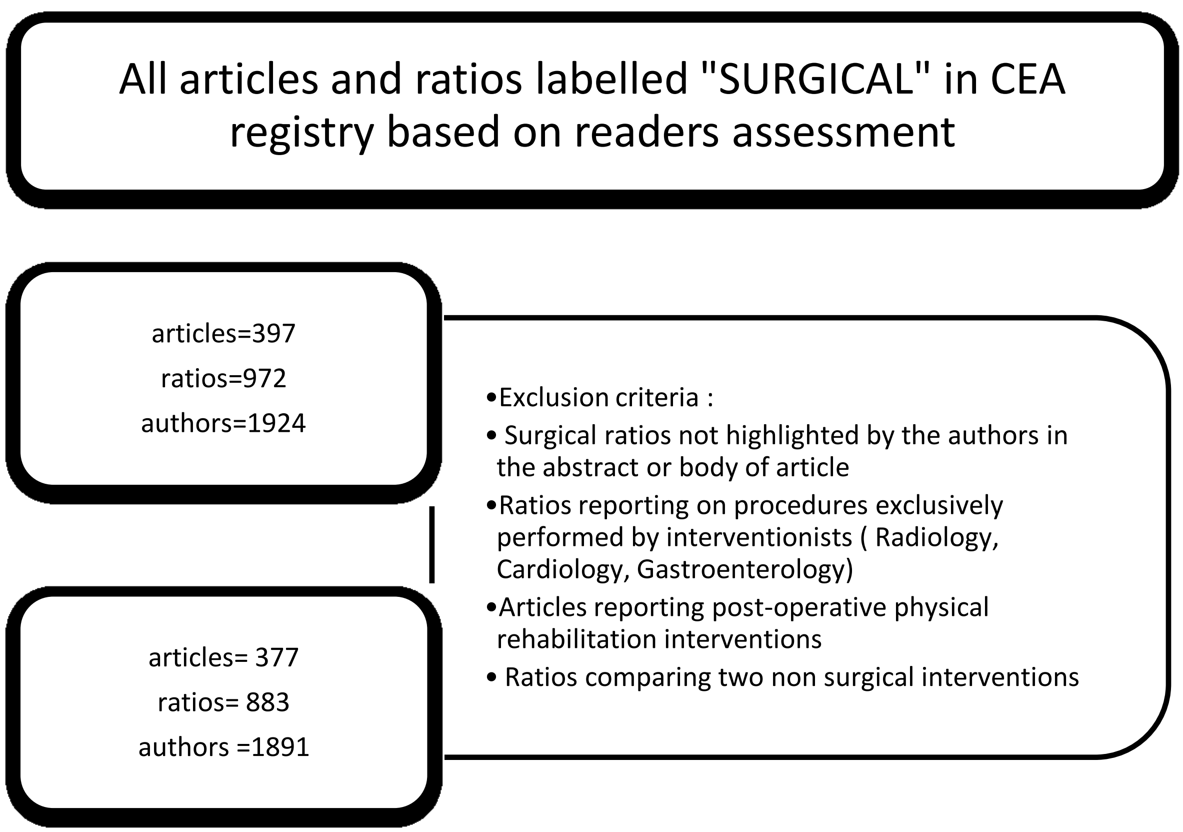

Figure 2. Exclusion Criteria of Non-Surgical Articles and Ratios.

2.3 Variable Definitions

We manually reviewed the 377 retained articles, extracted and recoded the information described below using a Microsoft Excel data capture form developed by our team. Based on article reviews conducted by 2 researchers, we collected information on each study's primary exposure variable (author clinical specialty) and primary outcome (ICER favorability). The following items were documented:

A. Exposure variable (primary author with surgical training):

To ascertain exposure (a function of author surgical training), one researcher reviewed each article and extracted the field of training for all authors. If an author was identified as a medical doctor, additional details were collected pertaining to his/her training in surgical specialties and/or subspecialties. For non-medical authors, we documented only the primary field of training. Training information for each author was obtained from one of the following public sources: (i) the article's list of author affiliations, (ii) a review of the listed credentials at the institution each author was affiliated with, or (iii) a review of credentials described on professional association websites. We also designated each major author's role as "first listed", "last listed" (senior author), or the corresponding author. For our analyses, only authors who were board certified as surgeons or enrolled in a surgical training program when the economic analysis was published were considered surgeons. Medical students and researchers who went on to acquire surgical training after the date of publication were considered undeclared.

Our primary analysis examined the influence of having a surgeon as a primary author, defined as either first, last or corresponding author (compared to not having a surgeon as a primary author). In secondary analyses, we explored the effect of having a surgeon as a author in any position. Finally, the proportion of authors with surgical training was also used as an alternative (continuous) measure of exposure.

Classifying "exposed" articles was conducted by a member of the research team who was blinded to the outcome of interest (ICER favorability).

B. Outcome variable (ICER favorability):

The study outcome depends on whether an ICER is more favorable than a benchmark (i.e., less than that benchmark, implying that the intervention improves health at a relatively low "price"), or less favorable. An ICER was considered to be primary if it was highlighted in the article's abstract. We attempted to identify a single primary ICER in each article. In many cases, however, we were unable to identify a single ICER for each article because abstracts highlighted multiple ratios (see Figure 3). To ensure each article was equally represented in this analysis, we assigned a statistical weight to each ICER of $1/n$, where n was the number of ICERs reported in the article from which the ICER was extracted.

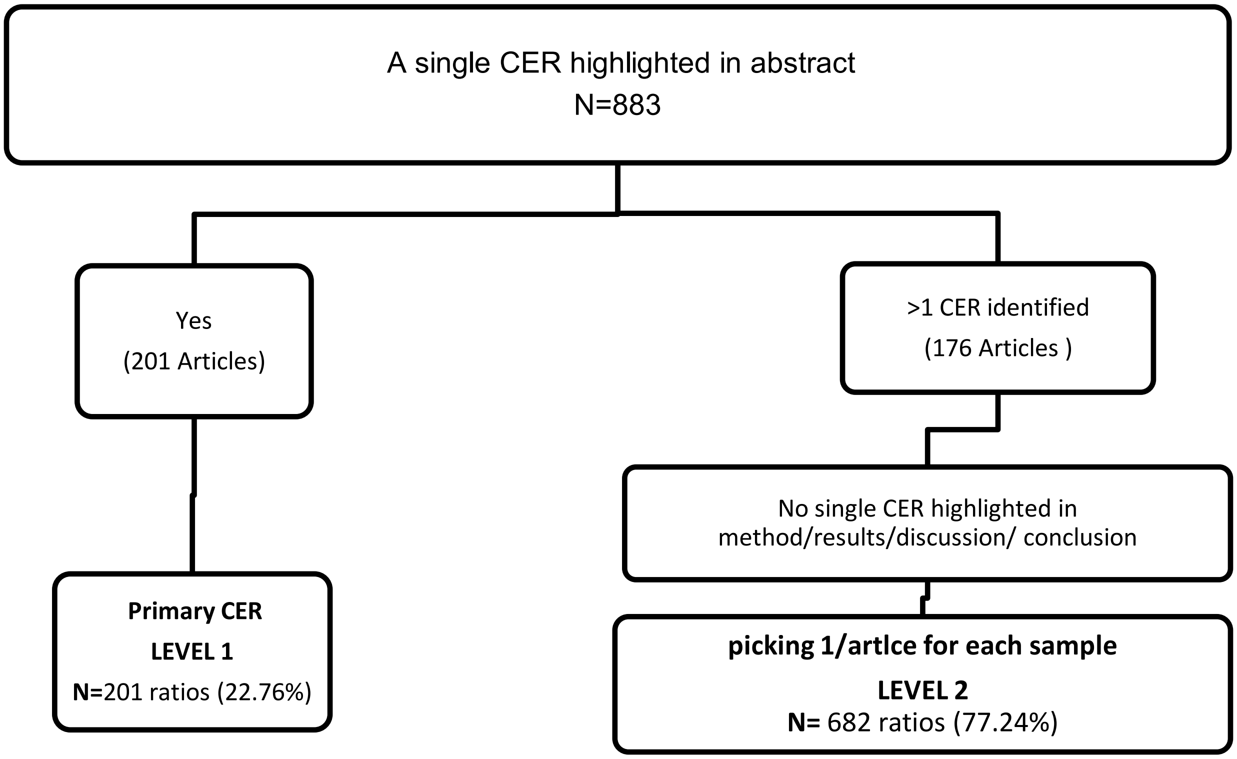

Figure 3. Algorithm Used to Identify Primary Surgical Ratio

C. Benchmark values:

A commonly used benchmark value for identifying ICERs as favorable in the US is \$50,000/QALY (20-22) . We used this benchmark and also the median ICER from our dataset as benchmarks for the purpose of classifying ICERs as either "favorable" (below the benchmark) or "unfavorable" (above the benchmark). Comparing each ICER to our sample's median provides an indication of favorability within the context of the interventions targeted by our analysis. To determine the weighted median ICER, we once again used the previously assigned statistical weight of $1/n$.

D. Standardization of variables:

We standardized ICERs in our dataset so the surgical treatment therapy is the intervention and the non-surgical therapy is the comparator. That is, we calculated the ICER as $ICER = \frac{QALY_{surgery} - QALY_{non-surgery}}{Cost_{surgery} - Cost_{non-surgery}}$. This adjustment ensured that the ICER represents the value of surgical intervention (rather than the non-surgical intervention). For ICERs comparing two surgical interventions, we designated the more recently developed option as the "intervention". Two research team members with surgical training determined which procedure was most recent.

Next, we revised some of the ICER values to ensure that they would be appropriately classified as "favorable" or "unfavorable" relative to the benchmark. For ICERs with positive numerators and denominators, no change is needed since the ICER can be directly compared to the benchmark (e.g., \$50,000 per QALY). Negative ICERs, on the other hand, might indicate *either* favorable cost-saving health improving ("dominant") interventions or unfavorable cost-increasing health decreasing ("dominated") interventions. We thus assigned dominated interventions an arbitrarily large value of \$1 trillion per QALY to ensure that they were classified as unfavorable in all analyses; "dominant" interventions were assigned a value of negative \$1 per QALY to ensure they would always be classified as "favorable".

2.4 Statistical Analysis

We used logistic regression to examine the multivariate relationships between our primary independent variable of interest (primary author specialty) and our primary outcome (ICER more favorable than the benchmark of \$50,000 per QALY) while controlling for potentially confounding variables, including: comparator category (alternative surgical procedure, new device, new medical treatment, or watchful waiting), and funding source (industry- supporting intervention, Industry- supporting comparator, government agency or professional association, funding not specified, industry- others). We retained the potential confounding variables in the multivariate model; regardless of the P values for their coefficients.

Again, because some articles reported multiple primary ICERs, and because our primary analysis used the ratio as the unit of analysis, we used the pre-assigned statistical weights of each ratio in these logistic regression models.

The analysis just described treats all retained ratios from each article as equally relevant. We explored the uncertainty associated with the selection of a single primary ICER for each article using a resampling algorithm. For these analyses we first created 1000 copies of our database, where each copy included only one randomly selected primary ICER per article. Next, a (non-weighted) logistic regression model was run on each of the 1000 dataset instances, yielding 1000 odds ratios and corresponding p-values. We summarized our findings by presenting summary statistics (median, 85^{th}, 90^{th}, and 95^{th} percentile confidence intervals) for the odds ratios and p-values.

A set of secondary analyses used the weighted sample median ICER from our sample in place of the convention $50,000 per QALY benchmark to categorize ICERs as favorable or unfavorable.

Finally, we conducted sensitivity analyses to examine the impact of changing the exposure variable definition to reflect all surgical authors and the proportion of surgeons listed on each article. we repeated the analysis scheme on a subset of the data excluding all ratios comparing two surgical treatment options.

Results

3.1 Primary Results

We identified 377 surgical articles that contributed 883 primary surgical ratios. In 194 (51.5%) article the primary author was a surgeon and in 258 articles (68.4%), at least one of the authors was a surgeon (see Table 1.A).

When it comes to funding source, 48% of included studies were funded by a government agency or a professional association,39% had no specified funding source, and 13% were funded by industry sponsorship.

Two hundred one (201) articles had a single primary ICER and 176 had multiple primary ICER values. Based on the weighted analysis, 269 (71%) of primary ICER values were equal to or less than $50,000 per QALY.

Among the 883 ICERs, 37% (unweighted) compared a new surgical procedure to an older surgical procedure, 38% compared surgery to watchful waiting, 20% compared surgery to a new medical treatment, and the remaining 5% compared surgery using conventional approaches to the use of a new surgical device. Table 1.B summarizes these results and also reports the corresponding distribution developed using the weighted ratios which were very similar to the unweighted results.

There were a total of 1891 authors on all articles collectively, of which 1593 were unique. Among the 1593 authors, we classified 548 as surgeons (34.4%), and of these, we classified 249 (15.6% of all authors) as a primary surgical author. Table 1.C shows the distribution of authors based on the number of articles they contributed to our sample.

For the primary analysis, using the $50,000 per QALY benchmark, both the unadjusted and adjusted models failed to show a significant association between ICER favorability and having a surgeon as a primary author (adjusted OR= 1.25, 95% CI= 0.78- 1.99, p=0.38).

In the secondary analysis, using the median CER of $19,859 as the benchmark, there was a significant association between ICER favorability and the primary author being a surgeon (OR= 1.60, 95% CI=1.06 - 2.40, p= 0.02). Adjusting for covariates related to source of funding and type of comparator yielded a similar trend, although the regression was just shy of achieving statistical significance (OR=1.50, 95%= 0.99 - 2.30, p=0.06) (see Table 3).

The resampling analysis, yielded results consistent with the results from the weighted analysis. We examined the distribution of odds ratio values generated by the bootstrap and reported the proportion of these ratios exceeding 1.0 (see Appendix- exhibit 1-2). We also reported the proportion of P-values that were significant (< 0.05).

None of the covariates adjusted for in the multivariate model seemed to have a major impact on the main odds ratio of interest.

3.2 Sensitivity Analysis

We repeated our analysis, using an alternative exposure definition. In this case, an article was designated as exposed if any author had surgical training. Neither the adjusted nor the unadjusted analysis showed a statistically significant association between authorship status and ICER favorability (see Table 4, Appendix exhibit 3-4).

The analysis was repeated using a third definition of "exposure" as a continuous variable equal to the proportion of authors of each article who were surgeons. The results showed that the increased proportion of surgeons per article yielded a strong association with ICER favorability at the median ICER benchmark even after adjusting for confounders (unadjusted OR =2.43, CI=1.36 - 4.41, p = 0.003 and adjusted OR= 2.22, CI=1.22-4.09, p = 0.01) (see Table 5, Appendix exhibit 5-6).

Additional sensitivity analysis used a subset of the data where studies that compared two surgical treatment options were excluded. The weighted logistic model was applied and the results showed similar trends compared to the results observed in the previous analyses using different author definitions and benchmark values (see appendix exhibit 7-9)

Table 1. Distribution of Articles, Cost Effectiveness Ratios, and Authors

A. Number of articles	**N= 377 Articles**
Articles with surgical training	
Articles where Any author is a surgeon	258(68.44%)
Articles where Primary author is a surgeon	194 (51.46%)
Articles where None of the authors is a surgeon	119 (31.57%)
Funding Source for article	
Professional/Government Agency	182(48%)
Industry- Supporting Intervention	32(8%)
Industry -Supporting Comparator	10(3%)
Industry - Others	6(2%)
Not Specified	147(39%)
Number of Primary CER in the article	
Single CER	201(53%)
2 CER	69 (18%
3 CER	46 (12%)
4 CER	25 (7%)
5-10 CER	29 (8 %)
>10 CER	7 (2%)

B. Number of Cost Effectiveness Ratios (CER)	N=883 CERs	N=377 CERs (1 per article)
	Crude	Weighted
Distribution of CERs		
CERs from articles with only a Single primary CER	201(22.76%)	201 (53.32%)
CERs from articles with Multiple primary CERs	682 (77.24%)	176 (46.68%)
Favorable CER per ≤$50,000 benchmark	644 (72.93%)	269(71.35%)
Median CER	$17,281	$19,858
Favorable CER per ≤$median benchmark	441 (50%)	188 (49.87%)
Comparator Category		
New Surgical procedure	323(37%)	146.13 (39%)
New Device	48(5%)	26.33(7%)
New Medical Treatment	174(20%)	67.44(18%)
Watchful waiting	338(38%)	137.11(36%)

C. Number of Authors	N= 1891 All authors N= 1593 Unique authors
Number of Surgical Authors	548 (34.40%)
Number of Surgical Authors on only 1 article	474
Number of Surgical Authors on only 2	52
Number of Surgical Authors 3-4 articles	15
Number of Surgical Authors on ≥5 articles	5
Number of Primary Surgical Authors	249 (15.63%)
Number of Surgical Authors on only 1 article as Primary author	217
Number of Surgical Authors on only 2 articles as Primary author	24
Number of Surgical Authors 3 articles as Primary author	7
Number of Surgical Authors on ≥5 articles as Primary author	1

Table 2. Relationship of Article Authorship (Surgeon vs. non-Surgeon) and Primary CER status (below or above benchmark)

	Benchmark Value				
	$50,000		$19,600*		Total # of articles
	≤$50,000	>$50,000	≤$19,600	>$19,600	
Articles where at least one primary author is a surgeon	**144 (74.23%)**	50 (25.77%)	**108 (55.67%)**	86 (44.33%)	194
Primary author not a surgeon	**125 (68.31%)**	58 (31.69%)	**80 (43.72%)**	103 (55.28%)	183
Articles where at least one author is a surgeon	**188 (72.87%)**	70 (27.13%)	**134 (51.94%)**	124 (48.06%)	258
No author is a surgeon	**81 (68.07%)**	38 (31.93%)	**55 (46.22%)**	64 (53.78%)	119

* Weighted primary ICER

Table 3. Weighted Analysis: Primary Author is a Surgeon

	Benchmark Value					
		19,858			50,000	
	OR	95% CI	P-Value	OR	95% CI	P-Value
<u>Unadjusted Model</u>						
Primary author is a surgeon	1.60*	1.06 - 2.40	0.02	1.31	0.84 - 2.05	0.23
<u>Adjusted Model</u>						
Primary author is a surgeon	1.50	0.99 - 2.30	0.06	1.25	0.78- 1.99	0.38
Comparator Category						
New Surgical procedure	1			1		
New Device	1.02	0.44 - 2.40	0.94	0.53	0.22 - 1.27	0.14
New Medical Treatment	1.01	0.55 - 1.86	0.95	1.01	0.53 - 2.01	0.86
Watchful waiting	1.28	0.79 - 2.07	0.25	1.15	0.67 -1.96	0.60
Funding Source						
Industry- Supporting Intervention	1			1		
Industry- Supporting Comparator	0.24	0.03 -1.26	0.09	0.21	0.04 - 1.08	0.09
Professional/Government Agency	0.94	0.43 - 2.04	0.83	0.49	0.17 - 1.24	0.15
Not Specified	1.06	0.48 - 2.32	0.90	0.57	0.19 - 1.45	0.25
Industry - Others	0.60	0.08 - 3.67	0.57	1.11	0.13- 23.97	0.96

Table 4. Weighted Analysis: Any Author is a Surgeon

	Benchmark Value

	$19,858			$50,000		
	OR	95% CI	P-Value	OR	95% CI	P-Value
<u>Unadjusted Model</u>						
At least one author is a surgeon	1.27	0.82-1.96	0.29	1.20	0.74 - 1.92	0.45
<u>Adjusted Model</u>						
At least one author is a surgeon	1.19	0.76 -1.87	0.42	1.18	0.74 - 1.97	0.51
Comparator Category						
New Surgical procedure	1			1		
New Device	1.02	0.44 - 2.39	0.95	0.52	0.22 - 1.25	0.13
New Medical Treatment	0.97	0.53 - 1.78	0.96	1.01	0.55 - 2.07	0.88
Watchful waiting	1.27	0.79 - 2.05	0.26	1.14	0.68 - 1.95	0.61
Funding Source						
Industry- Supporting Intervention	1			1		
Industry- Supporting Comparator	0.20	0.02 - 1.08	0.06	0.20	0.04 - 1.01	0.08
Professional/Government Agency	0.87	0.40 - 1.86	0.66	0.48	0.16 - 1.20	0.13
Not Specified	1.03	0.47 - 2.25	0.96	0.57	0.19 - 1.46	0.25
Industry - Others	0.56	0.07 - 3.36	0.51	1.09	0.13-23.48	0.97

Table 5. Weighted Analysis: Proportion of Surgical Authors

	Benchmark Value					
	19,858			50,000		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Unadjusted Model						
Proportion of surgical authors	2.43*	1.36 - 4.41	0.003	1.60	0.84 - 3.12	0.18
Adjusted Model						
Proportion of surgical authors	2.22*	1.22 - 4.09	0.01	1.54	0.79- 3.07	0.21
Comparator Category						
New Surgical procedure	1			1		
New Device	1.05	0.45 - 2.46	0.91	0.53	0.21 - 1.21	0.14
New Medical Treatment	1.06	0.58- 1.95	0.85	1.01	0.54 - 2.05	0.86
Watchful waiting	1.30	0.81 - 2.10	0.28	1.15	0.64 - 1.86	0.60
Funding Source						
Industry- Supporting Intervention	1			1		
Industry- Supporting Comparator	0.20	0.02 -1.00	0.08	0.21	0.05 - 1.21	0.09
Professional/Government Agency	0.82	0.38 - 1.76	0.62	0.49	0.16 - 1.18	0.15
Not Specified	0.93	0.42 - 2.02	0.85	0.57	0.18 - 1.35	0.25
Industry - Others	0.48	0.06 - 2.92	0.43	1.11	0.12- 20.95	0.96

Discussion

By examining the association between author clinical specialty and the favorability of reported ICER values relative to a benchmark, we attempted to determine if clinical specialty is a form of non-financial competing interests and potentially influence the outcome of cost-effectiveness studies. This is the first study to demonstrate that author clinical specialty tends to be associated with the results reported by published cost-effectiveness analyses.

To date, most of the work attempting to characterize the impact of non financial competing interests on publication findings has not used a unified measurable outcome or a quantifiable exposure measure. We compared ICERs to pre-specified benchmarks and could hence define a comparable measure of result favorability applicable to all studies in our dataset. We believe this method can be successfully used to assess bias for other specialties. author clinical specialty was used as a surrogate for exposure leading intellectual bias.

Our analysis did not detect a statistically significant association between authorship characteristics and ICER favorability when assessed relative to the conventional benchmark value of $50,000 per QALY. This finding might be explained by a potential bias against publishing results with ICERs exceeding the $50,000 per QALY benchmark. Bell et al.(10) observed this phenomenon, reporting that most published cost-effectiveness analyses tend to report ICERs in the acceptable range of $20,000 to $50,000 per QALY, or "expensive" ICERs exceeding $100,000 per QALY. Relatively few ICERs have "middle range" values. Our sample exhibited the same pattern: 71% of the reported surgical ICERs were less than $50,000 per QALY which could have compromised the power of our data to detect a statistical difference at this particular benchmark value.

The resampling sensitivity analysis made it possible for us to quantify the uncertainty introduced by the selection of one ICER to represent each study in our sample. The non-parametric percentile intervals confirmed that the majority of the odds ratios exceeded the threshold of 1.0 when the p value was statistically significant.

We recognize that our definition of “surgeon” may misclassify some authors, since some procedures could be performed by both surgeons and non-surgeon interventionists. Additionally, medical students aspiring to go into surgical training may be influenced by similar biases as declared surgeons. These misclassification errors may bias our study toward the null.

One point to highlight is the small proportion of industry-sponsored economic analyses in our sample (13%) relative to proportion of studies that received funding from a government agency or professional association (48%). The limited sponsorship by industry seems to be inconsistent with the prevailing perception in the biomedical community that industry sponsorship may influence a relatively large number of studies. This distribution is consistent with previous results from a meta analysis that compared all the published cost effectiveness analysis catalogued in the CEA Registry (10) .

A review of literature to ascertain the effect of financial competing interests on the published CEA articles confirmed that studies funded by pharmaceutical companies and device manufacturers are 50-100% more likely to report a favorable ICER at the $20,000 benchmark value (9, 10). The effect of non-financial competing interest arising from the author clinical specialty in our sample seems to be comparable and just as important to scrutinize upon evaluating the quality of the reported economic analysis.

In light of our results, we concur with the previous reports suggesting that non-financial competing interests might strongly influence the results of published literature and guidelines. We propose some measures that might help mitigate this source of bias. First, researchers should be educated about non-financial competing interests and trained to identify potential sources of this bias within their team early in the course of a project. Second, project contributors with the most expertise with the intervention under evaluation could be assigned a consultant or expert role, rather than be listed as an author. Publications could encourage openness and enhance disclosure of possible non-financial conflicts of interest by ensuring collection of information on each author's specialty, years of training, and role in developing or testing the new procedure, device, or therapy.

Following initial publication, electronically available articles could be updated with new information on the professional affiliation of authors to convey how previous research may have influenced their career advancement.

In addition, more polices must be designed and implemented to alleviate the effect of intellectual/non-financial bias during the process of disseminating results. For example, author involvement in a professional society that might use research for guideline development should be clearly disclosed and whenever such a conflict is strongly evident the governing committees should attempt to reduce the involvement of intellectually conflicted individuals in guideline development.

These recommendations are preliminary formative suggestions and must still be examined, evaluated and further refined before implementation. To further quantify the sources of non-financial competing interests, studies investigating the potential sources of influence in the context of work conducted by different specialties must be conducted, including studies that prospectively collect information on author motives using validated questionnaires or standardized interviews.

In conclusion, we found some evidence that physician specialty may influence the favorability of cost effectiveness studies, and therefore may need to be taken into account when considering the results of these analyses. More transparent methods to report non-financial competing interests should be considered.

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Appendix

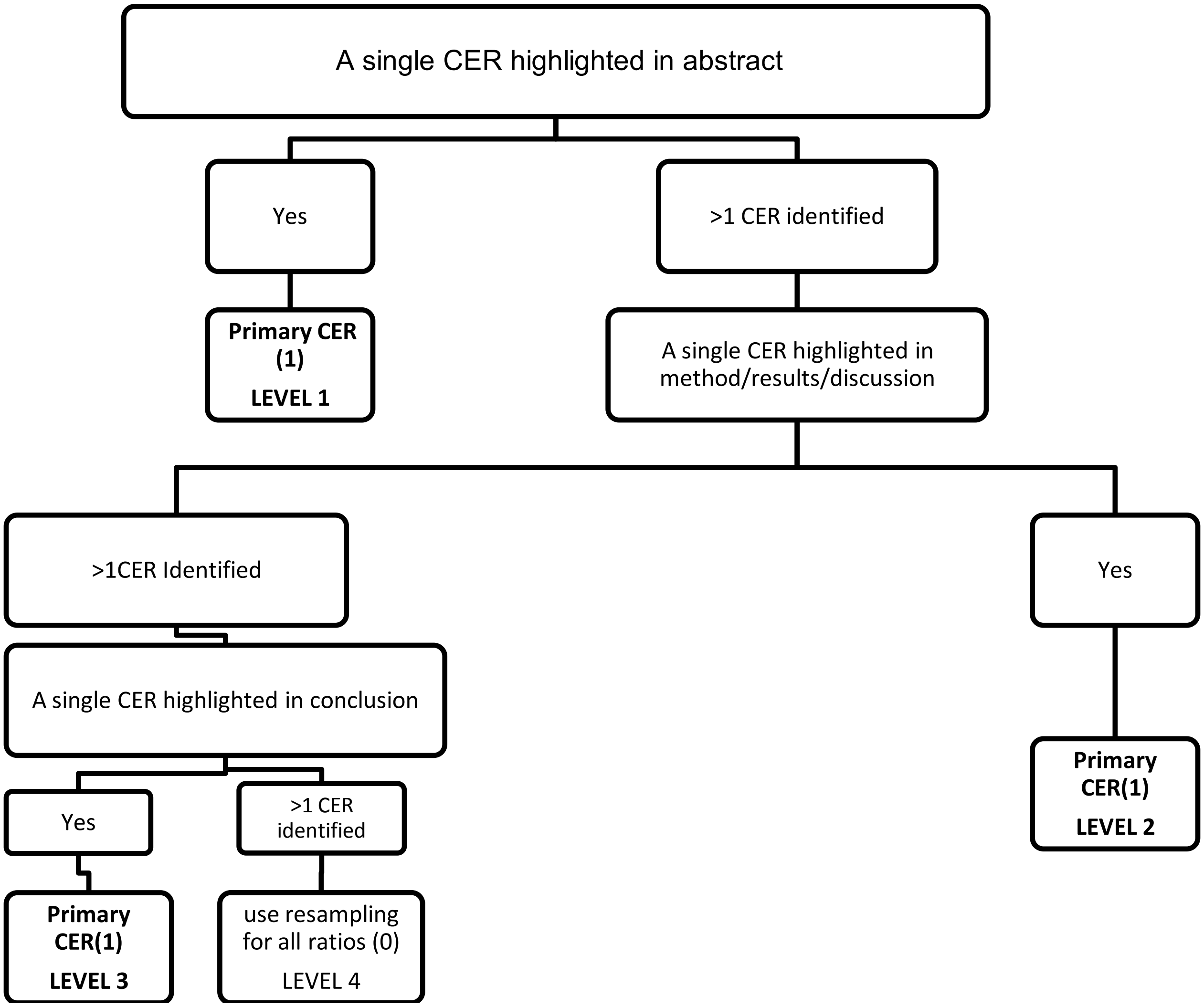

Figure 1. Initial algorithm to identify primary surgical ratios(failed)

Exhibit 1. Sensitivity analysis using re-sampling method:
A. Outcome: Benchmark Value $19,858 B. Exposure: Primary author is a Surgeon

	Benchmark Value				
	$19,858				
	Median OR	Median P-value	95 Percentile Intervals	90 Percentile Intervals	85 Percentile Intervals
Unadjusted Model					
Primary author is a surgeon	1.59* (%OR>1= 100)	0.03 (%P <0.05= 77.6)	(1.36 - 1.88)	(1.39 - 1.84)	(1.42 -1.80)
Adjusted Model					
Primary author is a surgeon	1.50 (%OR>1= 100)	0.06 (%P <0.05= 42.6)	(1.27 - 1.78)	(1.30 - 1.73)	(1.33 - 1.70)
Comparator Category					
New Surgical procedure	1(Ref.)				
New Device	1.03	0.75	(0.69 - 1.55)	(0.74 - 1.48)	(0.77 - 1.40)
New Medical Treatment	1.02	0.71	(0.73 - 1.38)	(0.77 - 0.33)	(0.80 - 1.29)
Watchful waiting	1.33	0.25	(1.04 - 1.69)	(1.08 - 1.62)	(1.10 - 1.58)
Funding Source					
Industry-Supporting Intervention	1(Ref.)				
Industry-Supporting Comparator	0.20	0.10	(0.09 - 0.32)	(0.10 - 0.31)	(0.10 - 0.30)
Professional/Government Agency	0.92	0.78	(0.72 - 1.21)	(0.74 - 1.15)	(0.76 - 1.11)
Not Specified	1.06	0.80	(0.81 - 1.37)	(0.85 - 1.32)	(0.88 - 1.27)
Industry - Others	0.58	0.55	(0.17 - 1.31)	(0.19 - 1.21)	(0.20 - 1.17)

Exhibit 2. Sensitivity analysis using re-sampling method:
A. Outcome: Benchmark Value $50,000, B. Exposure: Primary Author is a Surgeon

	Benchmark Value				
	$50,000				
	Median OR	Median P-value	95 Percentile Intervals	90 Percentile Intervals	85 Percentile Intervals
Unadjusted Model					
Primary author is a surgeon	1.30 (%OR>1=99.9)	0.25 (%P <0.05 = 4.1)	(1.09 - 1.60)	(1.11 - 1.56)	(1.14 - 1.52)
Adjusted Model					
Primary author is a surgeon	1.25 (%OR>1=98.2)	0.35 (%P<0.05= 1.4)	(1.02 - 1.56)	(1.05 - 1.50)	(1.08 - 1.47)
Comparator Category					
New Surgical procedure	1(Ref.)				
New Device	0.53	0.15	(0.37 - 0.77)	(0.40 - 0.73)	(0.41 - 0.70)
New Medical Treatment	1.08	0.69	(0.57 - 1.57)	(0.79 - 1.46)	(0.81 - 1.39)
Watchful waiting	1.17	0.56	(0.88 - 1.54)	(0.92 - 1.50)	(0.95 - 1.45)
Funding Source					
Industry-Supporting Intervention	1(Ref.)				
Industry-Supporting Comparator	0.26	0.09	(0.19 - 0.41)	(0.20 - 0.39)	(0.20 - 0.38)
Professional/Government Agency	0.49	0.16	(0.38 - 0.63)	(0.39 - 0.61)	(0.40 - 0.60)
Not Specified	0.56	0.25	(0.43 - 0.72)	(0.43 - 0.70)	(0.46 - 0.68)
Industry - Others	1.07	0.92	(0.81 - 1.40)	(0.85 - 1.36)	(0.87 - 1.32)

Exhibit 3. Sensitivity analysis using re-sampling method.
A. Outcome: Benchmark value $19,858 B. Exposure: Any Author is a Surgeon

	Benchmark Value				
	$19,858				
	Median OR	Median P-value	95 Percentile Intervals	90 Percentile Intervals	85 Percentile Intervals
Unadjusted Model					
At least one author is a surgeon	1.26 (%OR>1=99)	0.30 (%P <0.05=1.5)	(1.07 - 1.51)	(1.09 - 1.46)	(1.11 - 1.44)
Adjusted Model					
At least one author is a surgeon	1.20 (%OR>1=98)	0.42 (%P <0.05=0.2)	(1.01 - 1.45)	(1.03 - 1.40)	(1.05 -1.37)
Comparator Category					
New Surgical procedure	1(Ref.)				
New Device	1.03	0.75	(0.70 - 1.52)	(0.75 - 1.47)	(0.77 - 1.39)
New Medical Treatment	0.98	0.72	(0.71 - 1.33)	(0.75 - 1.29)	(0.77 -1.25)
Watchful waiting	1.32	0.26	(1.03 - 1.67)	(1.07 - 1.61)	(1.09 - 1.57)
Funding Source					
Industry-Supporting Intervention	1(Ref.)				
Industry-Supporting Comparator	0.21	0.07	(0.08 - 0.28)	(0.09 - 0.27)	(0.09 - 0.26)
Professional/Government Agency	0.84	0.66	(0.66 - 1.09)	(0.68 - 1.05)	(0.70 - 1.02)
Not Specified	1.02	0.82	(0.79 - 1.31)	(0.82 - 1.25)	(0.84 - 1.23)
Industry - Others	0.52	0.50	(0.16 - 1.18)	(0.18 - 1.11)	(0.19 - 1.07)

Exhibit 4. Sensitivity analysis using re-sampling method:
A. Outcome: Benchmark Value $50,000, B. Exposure : Any Author is a Surgeon

	Benchmark Value				
	$50,000				
	Median OR	Median P-value	95 Percentile Intervals	90 Percentile Intervals	85 Percentile Intervals
Unadjusted Model					
At least one author is a surgeon	1.21 (%OR>1=98.5)	0.43 (%P<0.05= 0.3)	(0.97 - 1.49)	(1.01 - 1.44)	(1.03 - 1.39)
Adjusted Model					
At least one author is a surgeon	1.21 (%OR>1=91.5)	0.45 (%P<0.05= 0.3)	(0.96 - 1.51)	(1.00 - 1.44)	(1.03 - 1.41)
Comparator Category					
New Surgical procedure	1(Ref.)				
New Device	0.52	0.14	(0.37 - 0.76)	(0.39 - 0.72)	(0.40 - 0.70)
New Medical Treatment	1.07	0.70	(0.75 - 1.55)	(0.79 - 1.44)	(0.81 - 1.38)
Watchful waiting	1.16	0.57	(0.88 - 1.54)	(0.92 - 1.49)	(0.94 - 1.44)
Funding Source					
Industry-Supporting Intervention	1(Ref.)				
Industry-Supporting Comparator	0.24	0.07	(0.18 - 0.38)	(0.19 - 0.37)	(0.19 - 0.35)
Professional/Government Agency	0.48	0.14	(0.73 - 0.61)	(0.38 - 0.59)	(0.39 - 0.58)
Not Specified	0.56	0.25	(0.44 - 0.71)	(0.45 - 0.70)	(0.46 - 0.68)
Industry - Others	1.05	0.93	(0.78 - 1.37)	(0.82 - 1.31)	(0.85 - 1.30)

Exhibit 5. Sensitivity analysis using re-sampling method:
A. Outcome: Benchmark Value $19,858 B. Exposure: Proportion of surgical authors

	Benchmark Value				
	$19,858				
	Median OR	Median P-value	95 Percentile Intervals	90 Percentile Intervals	85 Percentile Intervals
Unadjusted Model					
Proportion of surgical authors	2.42* (%OR>1= 100)	0.003 (%P <0.05=99.9)	(1.93 - 3.04)	(2.00 - 2.96)	(2.05 -2.86)
Adjusted Model					
Proportion of surgical authors	2.21* (%OR>1= 100)	0.01 (%P <0.05=94.4)	(1.76 - 2.79)	(1.82 - 2.71)	(0.38 - 0.54)
Comparator Category					
New Surgical procedure	1(Ref.)				
New Device	1.00	0.74	(0.66 - 1.58)	(0.70 - 1.47)	(0.73 - 1.41)
New Medical Treatment	1.24	0.61	(0.82 - 1.90)	(0.89 - 1.79)	(0.93 - 1.71)
Watchful waiting	0.96	0.75	(0.64 - 1.42)	(0.68 - 1.34)	(0.71 - 1.27)
Funding Source					
Industry-Supporting Intervention	1(Ref.)				
Industry-Supporting Comparator	1.12	0.63	(0.95 - 1.32)	(0.97 - 1.28)	(0.98 - 1.27)
Professional/Government Agency	0.28	0.11	(0.12 - 0.34)	(0.12 - 0.33)	(0.12 - 0.32)
Not Specified	0.54	0.50	(0.17 - 1.19)	(0.18 - 1.14)	(0.19 - 1.12)
Industry - Others	1.21	0.63	(0.92 - 1.55)	(0.97 - 1.50)	(1.00 - 1.47)

Exhibit 6. Sensitivity analysis using re-sampling method:
A. Outcome: Benchmark Value $50,000 B. Exposure: Proportion of surgical authors

	Benchmark Value				
	$50,000				
	Median OR	Median P-value	95 Percentile Intervals	90 Percentile Intervals	85 Percentile Intervals
Unadjusted Model					
Proportion of surgical authors	1.55 (%OR>1= 100)	0.19 (%P <0.05= 3.8)	(1.19 - 1.99)	(1.24 - 1.91)	(1.26 -1.86)
Adjusted Model					
Proportion of surgical authors	1.48 (%OR>1= 100)	0.25 (%P <0.05=1.4)	(1.12 - 1.94)	(1.17 - 1.86)	(1.20 - 1.81)
Comparator Category					
New Surgical procedure	1(Ref.)				
New Device	2.03	0.15	(1.37 - 3.07)	(1.44 - 2.89)	(1.47 - 2.77)
New Medical Treatment	2.19	0.08	(1.53 - 3.21)	(1.60 - 2.99)	(1.67 - 2.87)
Watchful waiting	1.88	0.15	(1.30 - 2.66)	(1.37 - 2.51)	(1.42 - 2.43)
Funding Source					
Industry-Supporting Intervention	1(Ref.)				
Industry-Supporting Comparator	1.13	0.61	(0.91 - 1.43)	(0.93 - 1.39)	(0.95 - 1.35)
Professional/Government Agency	0.52	0.33	(0.41 - 0.81)	(0.42 - 0.78)	(0.44 - 1.35)
Not Specified	2.11	0.51	(1.61 - 2.71)	(1.69 - 2.62)	(1.74 - 2.55)
Industry - Others	2.15	0.13	(1.70 - 2.81)	(1.75 - 2.73)	(1.79 - 2.66)

Exhibit 7. Weighted Analysis: Primary Author is a Surgeon (excluding ratios comparing two surgical treatment options)

	Benchmark Value					
	19,858			50,000		
	OR	95% CI	P-Value	OR	95% CI	P-Value
<u>**Unadjusted Model**</u>						
Primary author is a surgeon	1.88*	1.12 - 3.18	0.02	1.60	0.90 - 2.86	0.11
<u>**Adjusted Model**</u>						
Primary author is a surgeon	1.61	0.94 - 2.78	0.09	1.45	0.78- 2.65	0.24
Comparator Category						
New Device	1			1		
New Medical Treatment	0.93	0.36 - 2.42	0.88	2.02	0.75 - 5.45	0.16
Watchful waiting	1.24	0.52 - 2.98	0.63	2.18	0.89 -5.25	0.09
Funding Source						
Industry-Supporting Intervention	1			1		
Industry-Supporting Comparator	0.14	0.01 -1.93	0.07	0.12	0.01 - 0.82	0.04
Professional/Government Agency	0.54	0.19 - 1.45	0.23	0.23	0.03 - 0.87	0.06
Not Specified	0.91	0.32 - 2.46	0.86	0.34	0.05 - 1.30	0.17
Industry - Others	0.40	0.04 - 2.37	0.37	0.50	0.04 - 12.48	0.61

Exhibit 8. Weighted Analysis: Any Author is a Surgeon (Excluding ratios comparing two surgical treatment options)

	Benchmark Value					
	$19,858			$50,000		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Unadjusted Model						
At least one author is a surgeon	1.38	0.97-2.26	0.26	1.20	0.65 - 2.18	0.56
Adjusted Model						
At least one author is a surgeon	1.23	0.69 -2.21	0.49	1.14	0.59 - 2.14	0.70
Comparator Category						
New Device	1(Ref.)			1(Ref.)		
New Medical Treatment	0.89	0.34 - 2.31	0.81	1.94	0.72 - 5.22	0.19
Watchful waiting	1.23	0.52 - 2.93	0.63	2.17	0.89 - 5.24	0.09
Funding Source						
Industry-Supporting Intervention	1			1		
Industry-Supporting Comparator	0.13*	0.01 - 0.83	0.05	0.12	0.11 - 0.73	0.31
Professional/Government Agency	0.50	0.18 - 1.34	0.18	0.22*	0.02 - 0.82	0.05
Not Specified	0.91	0.32 - 2.45	0.85	0.33	0.05 - 1.29	0.16
Industry - Others	0.38	0.04 - 3.73	0.35	0.47	0.04 -11.78	0.58

Exhibit 9. Weighted Analysis: Proportion of Surgical Authors (Excluding ratios comparing surgical treatment options)

	Benchmark Value					
	19,858			50,000		
	OR	95% CI	P-Value	OR	95% CI	P-Value
<u>**Unadjusted Model**</u>						
Proportion of surgical authors	3.13*	1.47 - 6.83	0.003	1.79	0.78 - 4.24	0.18
<u>**Adjusted Model**</u>						
Proportion of surgical authors	2.62*	1.19 - 5.90	0.02	1.61	0.67 - 4.03	0.29
Comparator Category						
New Device	1			1		
New Medical Treatment	0.96	0.37 - 2.50	0.93	2.01	0.75 - 5.38	0.16
Watchful waiting	1.20	0.51 - 2.88	0.67	2.14	0.88 - 5.18	0.09
Funding Source						
Industry- Supporting Intervention	1			1		
Industry- Supporting Comparator	0.14	0.01 - 0.91	0.07	0.11*	0.01 - 0.75	0.03
Professional/Government Agency	0.49	0.17 - 1.30	0.16	0.21*	0.03 - 0.80	0.05
Not Specified	0.80	0.28 - 2.16	0.66	0.31	0.05 - 1.20	0.14
Industry - Others	0.30	0.03 - 2.27	0.26	0.43	0.03 -10.80	0.54