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Therapeutic Innovation & Regulatory Science
2015, Vol. 49(5) 698-705

DOI: 10.1177/2168479015573586
tirs.sagepub.com

An Estimate of the Benefit-Cost Impact of the FDA Guidance on Data Monitoring Committees

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Abstract

Background: There is little information available about the impact that FDA guidances have on the clinical trial enterprise. *Objective:* To estimate the impact of the FDA's Guidance for Industry, "The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors." *Methods:* An economic model was developed to measure the costs and potential savings associated with the change in data monitoring committee (DMC) usage since issuance of the DMC guidance for industry-sponsored clinical trials. To establish the change in use following the issuance of the DMC guideline, a literature search was conducted among high-impact medical journals during publication year 2010 and compared to a similar analysis conducted during publication year 2000. Costs were obtained for DMCs and applicable clinical trials. The results were applied to an analysis of ClinicalTrials.gov completed trials during 2007 to 2013. *Results:* Review of 4200 manuscripts from publication year 2010 was compared to a similar literature search of publication year 2000. The mention of DMCs in industry-sponsored randomized controlled trials from high-impact journals increased from 24% to 47% (risk ratio = 1.9, $P < .0001$). This increased rate of DMCs is associated with an increase of 1045 DMCs for industry-sponsored phase 2 and 3 interventional trials that were commenced and completed from 2007 to 2013 and were listed in ClinicalTrials.gov. The increased cost due to these additional DMCs was approximately US$231 million, and the savings associated with early termination of clinical trials due to these DMCs was approximately US$428 million. *Conclusion:* The DMC guidance has had a net positive economic impact on the clinical trial enterprise. However, noneconomic factors need to be evaluated. ClinicalTrials.gov could be further leveraged to explore further noneconomic benefits and costs of DMCs.

Keywords

data monitoring committees, FDA guidance, impact, cost, benefit

Introduction

FDA Guidances for Industry are not binding "on the FDA or on the public." However, as they "represent the Agency's current thinking on a particular subject,"[1] guidances can significantly affect the cost of drug development.[2] Efforts have been made to model potential cost-effectiveness for both regulation[3] and for specific guidances,[4] but these types of models rely on speculative assumptions. We hypothesized that measurement of cost-effectiveness can be effectively modeled by inclusion of data from ClinicalTrials.gov, the largest aggregate database available for informing policy makers about the clinical trials enterprise.[5] This paper examines the benefit-cost impact of the March 2005 FDA Guidance for Industry "The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors."[6]

Data monitoring committees (DMCs; also known as data and safety monitoring boards [DSMBs] and independent data monitoring committees [IDMCs]) are independent committees that are chartered to provide oversight for clinical trials. Subsequent to the 1998 request of the Office of the Inspector General for the FDA to "define the types of trials for which DSMBs would be required,"[7] the March 2006 DMC guidance (first issued in draft 2001) describes which trials should empanel DMCs and how they should operate. Once empaneled, the most significant recommendation that a DMC can make is early

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Submitted 10-Dec-2014; accepted 26-Jan-2014

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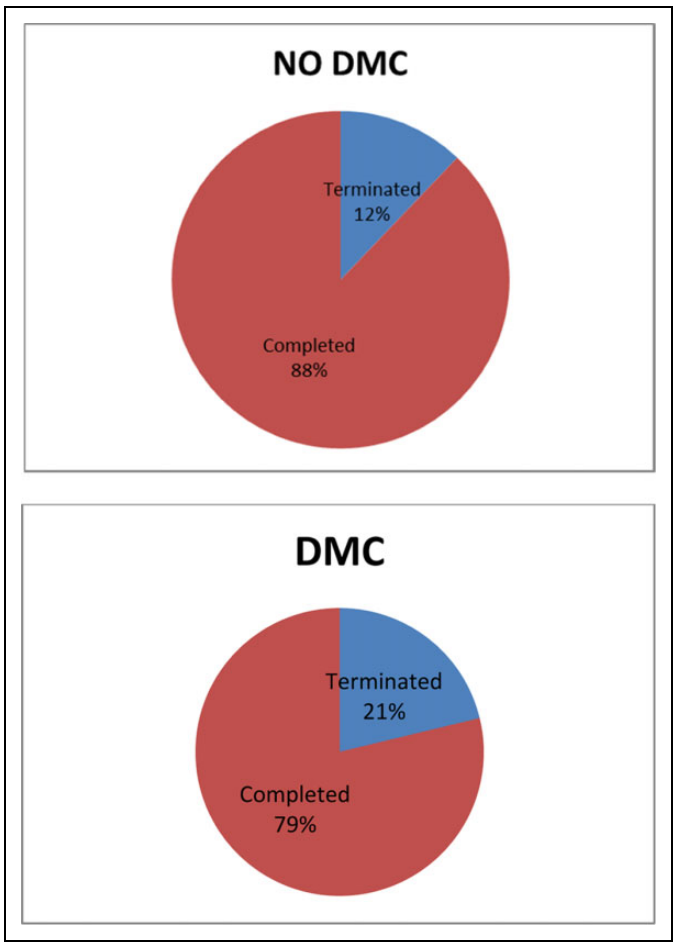

Figure 1. Trials terminated by data monitoring committees (DMCs). Source: ClinicalTrials.gov.

termination of the clinical trial for either safety or efficacy reasons (Figure 1). Termination for safety is recommended when the DMC feels that continuation of the trial will expose clinical trial participants to an unnecessary risk of morbidity and/or mortality. Termination for efficacy may be recommended if the clinical trial shows high levels of benefit or, conversely, if there is vanishingly small chance of benefit. In creating the benefit-cost framework, the clearest benefits emanate from early termination: reduced clinical trial cost, less morbidity and mortality, better allocation of sponsor resources, and, in stopping for efficacy, shorter time to market. The costs of the DMC are the out-of-pocket costs to establish and operate a DMC and the potential costs of erroneous termination.

For transparency and simplicity, this model restricts quantitative analysis to actual spending or savings due to DMCs in industry-sponsored trials. The analysis is limited to industry-sponsored trials because data on clinical trial costs and DMC costs are publicly available. Additionally, industry compliance with ClinicalTrials.gov is superior to that of other sponsors.[8] Taking this approach gives the model the advantage of using granular data available from literature as well as ClinicalTrials.gov. The model necessarily makes some assumptions about calculation of DMC use but does have the advantage of access to actual data about the use of DMCs. Due to the speculative nature of noncash costs and benefits surrounding early termination, the model specifically excludes quantitative estimates of the morbidity and mortality, potential revenues from increased speed to market, or decreased future revenues from erroneous termination. Therefore, we limited our economic analysis only to the monetary costs of DMCs versus the economic cost savings from early termination for trials that have industry as their sole source of funding (Table 1). Other benefits are discussed qualitatively.

Materials and Methods

Overall Strategy and Restrictions

Definition of overall terms used in this study are as follows:

Economic impact = attributable savings from DMC guidance − attributable costs from DMC guidance.
Attributable savings = savings from early termination of a clinical trial × excess number of clinical trials terminated attributable to the DMC guidance.
Attributable costs = economic cost of a DMC × excess number of DMCs attributable to the DMC guidance.

We were somewhat limited in assessment of the true preguidance use of DMCs, as there was no large-scale database available at that time. The first version of ClinicalTrials.gov was not released until 2000, and the International Committee of Medical Journal Editors did not require trial registration until 2005.[9,10] Therefore, for consistency, our estimate of preguidance-to-postguidance change in DMC use was provided through literature search. We adopted a method for 2010 publications similar to that used by Sydes et al,[11] who determined preguidance DMC use through literature search of high-impact journals for publication year 2000. Whereas publication bias may obscure the "true rate" of DMCs, we felt that this was a reasonable strategy to establish the relative risk of DMC use after guidance issuance. Our model therefore compared publication year 2010 to publication year 2000 to assess the "relative risk" for postguidance DMCs compared to preguidance. Determination of economic impact was determined by applying this 'literature derived' change to the "actual" DMC use in industry-sponsored trials derived from ClinicalTrials.gov.

Cost Variable Definitions

Total clinical trial cost was obtained using the self-reported 2011 phase 2 and phase 3 spending figures of the Pharmaceutical Research and Manufacturers of America (PhRMA)[12]

Table 1. Data monitoring committee guidance: economic impact analysis.

Benefits	Costs
Early termination of clinical trial	Expenses of data monitoring committee
Reduced morbidity/mortality	Erroneous termination
Increased speed to market	

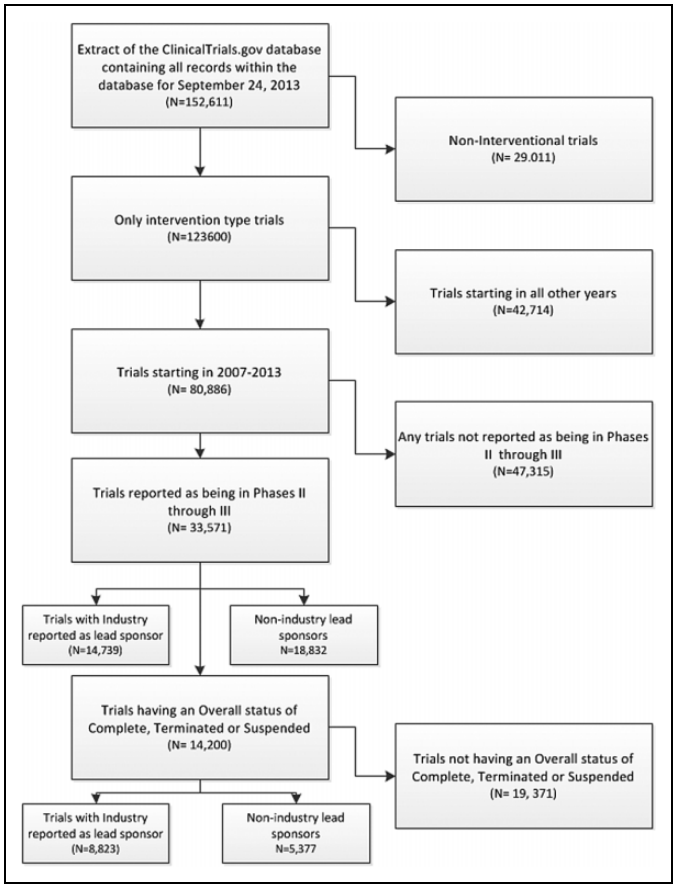

Figure 2. ClinicalTrials.gov search strategy.

across the period of the ClinicaTrials.gov extracts (January 2007–September 2013).

Mean clinical trial cost was derived by dividing the total clinical trial cost by the total number of industry trials.

Mean DMC cost was derived from a recent publication[13] that provided an economic estimate of the cost to support an industry-sponsored DMC by looking at the costs of managing a DMC in-house as well as partial and total outsourcing.

Actual DMC Usage Definitions

Total Number of Industry Trials

ClinicalTrials.gov provided an extract of the database containing all records within the database for September 24, 2013. The raw ClinicalTrials.gov database extract at that time referenced 152,611 trials by a unique National Clinical Trial Identifier number. For this analysis, trials having a reported start date year from 2007 to 2013 were selected from the database. Additional trial selections were made from the database, where "OVERALL_STATUS" = *completed*, *suspended*, or *terminated*; "Study_Type" = *interventional*; and "Phase" = *phase 2*, *phase2/phase3*, or *phase 3*. Reported use of a DMC (*yes/no/missing*) was the primary variable for analysis. Analyses were performed comparing percentages of the selected trials' overall status categories by DMC use (*yes/no*) by the primary agency class sponsorship. ("Has_DMC" was an optional field with values "yes" or "no" complete for 78% of industry-sponsored entries. If a value was missing, it was assumed to be "no" for purposes of the analysis.) The selection criteria resulted in a sample size of 14,200 trials. For this analysis, the "Agency_Class" variable was presented either as "Industry" or "Other Trial Sponsors," incorporating or grouping National Institutes of Health, other, and US government sponsors into the "Other Trial Sponsor" category. Of the 14,200 trials, 8823 were industry sponsored and 5377 were non–industry sponsored (Figure 2). The percentage and number of trials by DMC use and by the selected overall status categories are reported. A second analysis was performed tabulating and comparing the number of reported trial subject enrollment by DMC use and AGENCY_Class for OVERALL_STATUS.

Validation methodology. Data from time points described by Califf et al[14] were extracted from ClinicalTrials.gov and imported into SAS 9.2 for data manipulation and analysis. In all cases, the results from our programming reproduced those reported by Califf et al within 1 percentage point. The variation is secondary to known updates to the ClinicalTrials.gov database.

Total Number of Industry DMCs

This figure was derived from searching ClinicalTrials.gov for all interventional clinical trials selected for phase 2 or phase 3, industry as the sole sponsor, from January 2007 to September 2013, having a DMC.

Pre- and Postguidance DMC Frequency in High-Impact Journals

DMC Frequency

For publication year 2010, a comprehensive e-journal search was conducted on all articles published in the 6 high-impact general medical journals found in the comparator group as well as the 5 highest-impact specialty journals in cardiology, infection, oncology, and psychiatry, selected according to their impact factor published in the 2010 Journal Citation Report[15] (Table 2). The first round of search consisted of identifying

Table 2. Journals searched and 2010 impact factors.

Therapeutic Area: Journal Title	2010 Impact Factor
General interest	
New England Journal of Medicine	53.486
Journal of the American Medical Association	30.011
The Lancet	33.633
Annals of Internal Medicine	16.729
British Medical Journal	13.471
Archives of Internal Medicine	10.639
Cardiac and cardiovascular systems	
Circulation	14.432
Journal of the American College of Cardiology	14.293
European Heart Journal	10.052
Circulation Research	9.504
Nature Reviews Cardiology	7.467
Infectious diseases	
Lancet Infectious Diseases	16.144
Clinical Infectious Diseases	8.186
Emerging Infectious Diseases	6.859
AIDS	6.348
Journal of Infectious Diseases	6.288
Oncology	
CA-A Cancer Journal For Clinicians	94.333
Nature Reviews Cancer	37.184
Cancer Cell	26.925
Journal of Clinical Oncology	18.970
Lancet Oncology	17.764
Psychiatry	
Molecular Psychiatry	15.470
American Journal of Psychiatry	12.759
Archives of General Psychiatry	10.782
Biological Psychiatry	8.674
Schizophrenia Bulletin	8.273

interventional clinical trials through a keyword search of ''trial'' as well as the search of the involvement of human clinical research participants. The second round of search consisted of identifying the clinical trials that made use of DMCs. This was done through a keyword search for ''data,'' ''monitoring,'' ''committee,'' ''safety,'' and ''board.'' Those articles identified through keyword search were hand searched and abstracted by trained clinical data assistants. Among data points gathered were presence of a DMC, size of trial, trial design, and sponsorship. Any questions regarding interpretation of data were classified by a physician (J.S.). Trials were classified as ''industry sponsored'' if an industry source was listed as a sole sponsor. For publication year 2000, Sydes et al[11] similarly characterized the use of DMCs through literature search in the same top-6 general medical journals, as well as highest-impact cardiology, infection, oncology, and psychiatry journals. The resulting articles were hand searched for randomized controlled trials and DMC usage. ''Pharmaceutical company involvement'' was explicitly assessed, which we used as a surrogate for ''industry sponsorship.''

Although there were slight variations in the literature search strategies between our group and the Sydes et al[11] effort, there was no significant difference between the randomized clinical trials in general versus specialist journals ($P = .08$) or the distribution of the size of clinical trials ($P = .6$). In terms of trial design details, those that noted crossover or factorial designs were <5% of the total sample. Comparisons were made using odds ratios; significance was calculated with a Pearson chi-square test and 2-tailed *t* tests.

Definitions of Derived Variables

Postguidance DMC risk ratio was calculated from literature-derived (see Table 3):

= No. of 2010 trials with DMC / (No. of 2010 studies with DMC + *No*. of 2010 studies without DMC).

Attributable DMC burden was defined as the increase (decrease) in the number of DMCs due to the guidance:

= Total no. of industry DMCs / Postguidance DMC risk ratio.

Attributable DMC cost (Atr_DMC_Cost) was defined as the increase (decrease) in the cost of DMCs due to the guidance:

= Attributable DMC burden × Average DMC cost.

Trial cost savings was the amount saved when a DMC requires early termination of a clinical trial. The model assumes that, upon termination, 75% of trial funds have already been spent:

= 25% average clinical trial cost.

DMC trial termination difference—trials were considered terminated if, from ClinicalTrials.gov, their OVERALL_STATUS = ''terminated'' or ''suspended'':

= Trial termination rate for trials with DMCs − trial termination rate for trials without DMCs.

Number of trials terminated due to postguidance DMC:

= Attributable DMC burden × DMC trial termination difference.

Attributable postguidance savings:

= Number of trials terminated due to postguidance DMC × trial cost savings.

Net impact of DMC guidance:

= Attributable postguidance savings − attributable DMC cost.

Table 3. Derived variables.

Variable		Data
Mean cost of industry-sponsored trial phase 2 and phase 3 trials, 2007-2013	*A*	$17.6 million
Mean DMC cost: outsourced	*B*	$220,800
Industry trials with DMC	*C*	2205
Nonindustry trials with DMC		2694
Postguidance DMC risk ratio (from literature search)		
2010: industry-sponsored trials (total from 2010/with DMC)		292/136
Percentage		47
2000: industry-sponsored trials (total from 2000/with DMC)		304/74
Percentage		24
2010/2000 risk ratio ($P < .0001$)	*D*	1.9
Attributable DMC burden (increase in industry trials with a DMC from 2000 to 2010)		
$C - C/D$	*E*	1044
Attributable DMC cost (cost of the DMC for the increase in industry trials with a DMC from 2000 to 2010)		
$B \times E$	*F*	$231 million
Trial cost savings (25% of mean cost of industry-sponsored trial)		
$25\% \times A$	*G*	$4.4 million
Trial termination rate attributable to DMCs (increase in early termination due to DMCs)[a]		
Termination of trials with DMCs, %		21.2
Termination of trials without DMCs, %		12.1
Increase due to DMCs, %	*H*	9.1
Trials terminated due to postguidance DMC		
$E \times H$	*I*	95
Savings from postguidance terminations		
$G \times I$	*J*	$418 million
Net impact of DMC guidance		
$J - F$		$187 million

Currency is in US dollars. DMC, data monitoring committee.
[a]See Figure 1.

Results

Cost

Total clinical trial cost: Approximately $23 billion is the annual burden × 6.75 years = $155 billion.

Mean industry clinical trial cost: $155 billion / 8823 phase 2 and phase 3 trials = $17.6 million.

Mean DMC cost: Estimates are from fully outsourced DMC = $220,800 to fully "insourced" model at $458,000. $220,800, the low cost, was used in this analysis.

Actual DMC Usage

Total Number of Industry Trials

There were 14,200 trials started after January 2007 and completed, terminated, or suspended by September 2013. Of these, 8823 were industry sponsored and 5377 were non–industry sponsored. Of the industry trials, 2205 (25%) had DMCs. Of non–industry sponsored trials, 2694 (50%) had DMCs.

Pre- and Postguidance Frequency of DMCs (Literature Search Method)

A total of 4200 articles from publication year 2010 were identified that met search term criteria, 1131 from the high-impact general medical journals and 3069 from the high-impact therapeutic area journals. The manuscript abstracts were reviewed to determine if the articles were randomized clinical trials, and 816 articles were identified. (Figure 3) The result of the literature search was compared to the Sydes et al[11] analysis of the 2000 publication year. The use of DMCs was significantly greater in 2010 (risk ratio, 2.1; 95% CI, 1.8-2.6). Of the 816 randomized control studies from 2010, 292 were categorized as "industry sponsored" with 136 DMCs (Table 4). From the 2000 publication year, 304 were characterized as "pharmaceutical company involvement," 74 of which had DMCs.[14]

Discussion

The literature search methodology showed that following introduction of the FDA Guidance on data monitoring committees, the frequency of DMCs in the published literature from high-

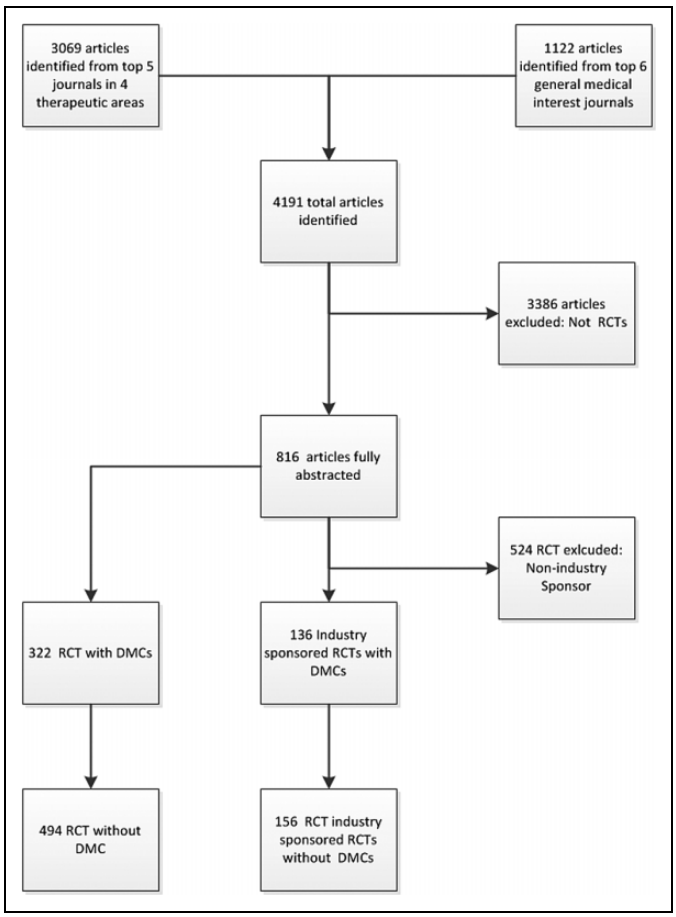

Figure 3. Literature search strategy. DMC, data monitoring committee; RCT, randomized controlled trial.

impact journals has approximately doubled (risk ratio, 1.9; 95% CI, 1.5-2.4). It is reasonable to implicate the guidance in producing this increase. ClinicalTrials.gov data provide a rough estimate of the impact of the FDA Guidance on DMCs over the entire clinical trial enterprise. Our ClinicalTrials.gov analysis shows that since 2007, 25% of completed industry-sponsored clinical trials have or have had a DMC, implying that preguidance industry-sponsored clinical trials had a DMC rate of approximately 14%. We estimate that the increase in the establishment and operation of these DMCs has added $231 million in additional clinical trial spending. However, our analysis shows that this has been a good investment; these same DMCs have been responsible for a reduction in planned trial expenditures of $418 million.

This net positive economic impact of $187 million results in a return on investment of 81%. This is independent of other benefits, such as avoidance of morbidity, mortality, or the opportunity cost of not taking a more effective therapy. These "costs" are likely not trivial—in our sample of completed trials from 2007 to 2103, a total of 158,044 subjects were enrolled in studies that were stopped or suspended that had DMCs. There is also the possibility that studies were stopped due to efficacy concerns, which might result in additional benefits of more expedient delivery of proper therapy to the population as well as a shorter "time to market," which increases revenue for industry sponsors.

However, it should be noted that the above assumes that trial termination by a DMC was properly recommended. As there are no uniform standards for recommending trial modification, DMCs may vary widely in their interpretation of patient safety. Thus, if a DMC inappropriately recommends termination, that might derail development of a promising compound. Not only would this deprive patients of needed therapy, but it might also cost industry sponsors large sums of investment capital.

Conclusions

Our model demonstrates that use of DMCs has markedly increased since issuance of the DMC guidance. Additionally, we show that the investment in DMCs has a positive return on investment for the clinical trial enterprise. However, the specific reasons for DMC action are unknown and are necessary to estimate the true value of DMCs. Specific fields in ClinicalTrials.gov would be helpful in providing a better answer to this question.

Limitations

We cannot be certain that the observed increase of DMCs in the literature is secondary to the presence of the FDA guidance. It could also be secondary to an increase in "DMC worthy" trials or perhaps a publication bias in favor of studies with DMCs. That said, application of these literature-based findings to limitations of estimating the cost savings includes estimation of the cost of clinical trials as well as that of early termination. The cost of clinical trials includes only those costs reported by PhRMA members. This may be an under- or overestimate, as not all trials selected have sponsors who are PhRMA members. Additionally, we had no hard data regarding cost savings from early termination. Our judgment to use the 25% value of trial costs was due to unpublished interviews with DMC experts who thought that termination often occurs before 50% enrollment.

From a methods perspective, in addition to the previously described limitations of the ClinicalTrials.gov database,[14] the DMC field was not a required field and was nonmissing in 78% of cases. We equated DMC use in these "missing" trials with "no DMC." We decided to do a sensitivity analysis by assuming that any missing DMC indication was a result of no DMC. As such, missing DMC values were recoded as "no DMC" and thus included in the analysis. The logistic regression results were not appreciably different from the original analysis excluding the missing DMC indication. Additionally,

Table 4. Comparison of 2000 versus 2010 literature search.

	2000			2010: All Studies			2010: Industry-Sponsored Studies				CI	
Journals	RCT	DMC	%	RCT	DMC	%	RCT	DMC	%	RR	5%	95%
High impact	282	70	25	336	175	52	122	69	57	2.0	1.7	2.6
Ann Intern Med	21	5	24	27	10	37	6	2	33	1.6	1	3.7
Arch Intern Med	28	3	11	9	0	0	0	0	0	Unable to calculate; value = 0		
BMJ	34	0	0	50	4	8	4	0	0	Unable to calculate; value = 0		
JAMA	49	12	24	42	26	62	11	7	64	2.6	2	4.4
N Engl J Med	62	22	35	125	88	70	63	41	65	2.0	1	2.8
Lancet	88	28	32	83	47	57	38	19	50	1.8	1	2.5
Therapeutic area	380	49	13	480	147	31	170	67	39	2.4	2	3.2
Cardiology	145	31	21	147	62	42	67	29	43	2.0	1	2.8
Infection	56	10	18	115	37	32	29	12	41	1.8	1	3.4
Oncology	103	8	8	159	43	27	57	24	42	3.5	2	7.1
Psychiatry	76	0	0	59	5	8	17	2	12	Unable to calculate; value = 0		
All	662	119	18	816	322	39	292	136	47	2.1	2	2.6

DMC, data monitoring committee; RCT, randomized controlled trial; RR, risk ratio.

as the use of National Clinical Trial Identifier numbers was also optional, we could not establish any reliable concordance rate between the mention of DMCs in publications and that in the ClinicalTrials.gov database.

An additional and important limitation is that there is no standardized definition of what is meant by "DMC," so there is no way to know whether the DMCs were comparable. For instance, they may be internal or external DMCs. There was no evidence, say, of the number of interim analyses. This may have an additional impact on the cost estimate, as discussed in the Conclusions section. With respect to the literature search, unlike the Sydes et al[11] publication, which focused on trial factors favoring use of DMCs, our efforts reported only on the presence or absence of DMCs and not their appropriateness; that is, this effort did not evaluate factors such as survival endpoints and study duration.

As mentioned above, "industry sponsorship" is not directly comparable. As far as the cost assumptions for the model, total clinical trial spending may have been underestimated because ClinicalTrials.gov contains industry trials from non-PhRMA members. Additionally, as some of the trials in our ClinicalTrials.gov extract were classified as phase 1/2 and phase 3/4, it is likely that some spending may not have been classified as phase 2 or phase 4. Mean clinical trial cost may have been overestimated, as some of the clinical trials spending is directed toward trials where industry is not the sole sponsor.

Acknowledgments

The author thanks the following individuals for their assistance with this study. For data abstraction: Bryan Wong, Zhising Leck, and Gloria Than Wan Hui. For analysis: Alan Smith and Mark Williams. Review and advice: Robert M. Califf.

Declaration of Conflicting Interests

The author is an employee of ACI Clinical, which facilitates data monitoring committees. He serves and has served as a data monitoring committee member.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

References

1. US Food and Drug Administration. Guidance and regulation. http://www.fda.gov/Food/GuidanceRegulation. Accessed December 9, 2014.
2. Hirshberg B, Katz A. Cardiovascular outcome studies with novel antidiabetes agents: scientific and operational considerations. *Diabetes Care*. 2013;36(suppl 2):S253-S258.
3. US Food and Drug Administration. Economic impact analyses of FDA regulations. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/. Accessed December 9, 2014.
4. Bouvy J, Koopmanschap M, Shah R, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. *Clin Pharmacol Ther*. 2012;91(2):281-288.
5. Pasquali S, Lam W, Chiswell K, Kemper A, Li J. Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov Registry. *Pediatrics*. 2012;130(5):e1269-e1277.
6. US Food and Drug Administration. The establishment and operation of clinical trial data monitoring committees for clinical trial sponsors. http://www.fda.gov/regulatoryinformation/guidances/ucm127069.htm. Published March 2006. Accessed December 9, 2014.
7. Department of Health and Human Services. Institutional review boards: a time for reform. https://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf. Accessed December 9, 2014.

8. Wadman M. FDA says study overestimated non-compliance with data-reporting laws. *Nature*. May 1, 2012.
9. US National Institutes of Health. ClinicalTrials.gov. Histories, policies, and laws. http://ClinicalTrials.gov/ct2/about-site/history. Accessed November 2015.
10. DeAngelis C, Drazen J, Frizelle F, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *JAMA*. 2004;292(11):1363-1364.
11. Sydes M, Altman D, Babikera A, Parmar M, Spiegelhalter D; DAMOCLES Group. Reported use of data monitoring committees in the main published reports of randomized controlled trials: a cross-sectional study. *Clin Trials*. 2004;1(1): 48-59.
12. Berndt E, Cockburn I. Price indexes for clinical trial research: a feasibility study. http://www.bls.gov/opub/mlr/2014/article/pdf/price-indexes-for-clinical-trial-research-a-feasibility-study.pdf. Accessed December 9, 2014.
13. Bussom D, Winter L. Data monitoring committees: implementation and sourcing model options. http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/Online+Extras/Data-Monitoring-Committees-Implementation-and-Sour/ArticleStandard/Article/detail/835338?contextCategoryId=47497. Published 2014. Accessed December 9, 2014.
14. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA*. 2012;307:1838-1847.
15. Thomson Reuters. Science citation reports 2010 (impact factor) by Journal Citation Reports. http://www.rcmishra.com/research-tools/impact-factor-2010-journal-citation-reports-by-thomson-reutors. Accessed November 2015.