Publication Bias: Assessment and Impact

William J. Canestaro

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Reading Committee:

Joshua J. Carlson, Chair

Emily E. Devine

Aasthaa Bansal

Sean D. Sullivan

Program Authorized to Offer Degree:

Pharmacy

University of Washington

Abstract

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William J. Canestaro

Chair of the Supervisory Committee:
Joshua J. Carlson, MPH, PhD
Professor
Department of Pharmacy

Publication bias is the systematic missingness of scientific results from the academic literature. In healthcare, the problem is sizable with nearly half of all studies that collect data never reaching full publication. This has the potential to result in systematic misdirection that can influence clinical decision making. The objectives of our study were three-fold. First we conducted a systematic literature review and meta-analysis to better understand what study characteristics influence their likelihood of publication and whether these interact with one another. Second, we evaluated whether this systematic misdirection resulted in a time differential from when meaningful evidence could have been available to when it actually reached researchers. The case study for this was the drug rosiglitazone. Finally, we developed a framework for evaluating the health and economic impacts of unpublished information. The results of our meta-analysis supported much of the previously published literature. A secondary analysis also highlighted an interaction between industry funded trials and result favorability. For our second objective, we found that for rosiglitazone, publication bias resulted in a 36 month differential between when meaningful evidence could have been available and when it was published. Currently available methods of adjustment were unable to mitigate this effect. Finally, for our last aim we developed a framework for assessing the impact of unpublished research and applied it to two case studies: rosiglitazone and rofecoxib. For rosiglitazone we found that this unpublished research resulted in significant wasted drug spend but no clinical events. For rofecoxib, publication bias was found not to affect decision making.

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DEDICATION

This work is dedicated to the those who work to practice and sustain evidence-based medicine.

Chapter 1. INTRODUCTION

If we consider medical research as an industry, it is a sizable one. Global expenditures on medical research have been estimated to exceed $200B annually.[1] In the US alone over $100B is spent on medical research representing roughly 5% of annual healthcare spending.[2] If we consider medical research to be an industry, than its product or output is well-conducted studies that can be used and built upon by others. Ultimately, all of our investments in clinical research result in an extraordinarily large number of publications. Recent bibliometric analysis has suggested that global scientific output as measured by number of publications grows at a rate of 8-9% annually[3] meaning that the number of scientific publications more than doubles every ten years. In healthcare alone, the National Library of Medicine's bibliographic database, MEDLINE, adds over 800,000 new citations every year.[4]

And yet, we do not hold this industry to the same expectations of efficiency and output as others. Recently, claims have been made that this medical research is unacceptably inefficient, with some groups estimating as much as 85% of this research is wasted.[5] If we consider the output of the medical research industry to be publication, than the incomplete dissemination or selective reporting of research, especially for clinical trials is a key driver for inefficiency in the industry.[6] An economically efficient system would provide a return on this extensive investment in research in the form of clear and well conducted trials that are accessible to the scientific community at large.

Publication bias represents a threat to the central tenet of evidence-based medicine: that systematic review of published evidence can create an accurate estimate of the true safety and efficacy of an intervention. Failure to publish or disseminate trial results limits the impact of these studies on individuals who could possibly use them to make informed choices for patients or to plan future research. Limited publication is pervasive in medicine; almost half of studies monitored by Institutional Review Boards (IRBs) remain unpublished even after the study is completed and results are available,[7-13] and nearly 60% of trials received by the US Food and Drug Administration (FDA) for approval of new treatments are never published in a peer-reviewed journal.[14] Not only does incomplete or selective reporting hamper the process of evidence synthesis but it also introduces bias in the synthesis of these results to inform decisions.

To address this problem, we have undertaken a series of three research objectives. First, we have completed a systematic review and meta-epidemiological analysis to quantify how characteristics of studies influence their likelihood of publication and whether these characteristics interact with one another. Next we use the frame of cumulative meta-analysis to determine if publication bias in the case of rosiglitazone delayed the time to reach a meaningful level of evidence that would have influenced prescribing decisions. Additionally, we evaluated whether currently available methods for adjustment of publication bias could be used to mitigate any potential time differential. Finally, we developed a framework to quantify the health and economic impact of unpublished research and applied it to the two cases of rosiglitazone and rofecoxib.

Chapter 2. PREDICTORS OF PUBLICATION FOR BIOMEDICAL RESEARCH: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 INTRODUCTION:

Publication bias represents a threat to the central tenet of evidence-based medicine: that systematic review of published evidence can create an accurate estimate of the true safety and efficacy of an intervention. In fact, many studies go unpublished and those studies that do go unpublished are likely systematically different from those that are published.[15-17] The problem is widespread in medicine: only half of studies monitored by Institutional Review Boards (IRBs) are widely disseminated once results are available[7-13] and nearly 60% of all trials submitted to the US Food and Drug Administration (FDA) for marketing approval never reach full publication.[14] Less than complete publication of all studies might be explained as representing a random sampling of all studies conducted, were it not for the fact that those studies that have positive, significant, or novel results are much more likely to be published than studies with negative, null, or replicated results.[15-17] This has the effect of creating a sample of studies that may overstate the effectiveness and safety of many interventions.

This phenomenon is compounded when the available trials are compiled in a systematic review and meta-analysis. The need for access to complete clinical trial data for systematic reviews is such that the National Academy of Medicine has recently published its report titled, “Sharing Clinical Trial Data”. As the academy explained “Clinical trials are essential to determining the safety and efficacy of new health treatments, but limited data sharing prevents maximum utilization of knowledge gained". In short, the current system fails to provide an adequate return on the investments of trial participants, investigators, and sponsors."[18]

Failure to publish has strong implications for researchers, clinicians, and patients. We know that publication is strongly correlated with the study treatment's effect size, direction and significance,[15-17] as well as sponsorship.[19] To the extent that we can predict the likelihood that a systematic review will be biased, we can adjust for this misdirection. To better understand these relationships, we performed a systematic review of manuscripts that followed cohorts of studies from one of five stated pre-publication milestones. A previous review[16] has attempted a similar objective but it is over six years old and does not include many of the most recent investigations on this topic. Additionally, previous reviews have only evaluated the effect of one study characteristic at a time. While this form of analysis is helpful, it presents a limited picture. To address these shortcomings, we have conducted an updated and comprehensive review that includes seven study characteristics that may influence publication.

2.2 Material and Methods:

This systematic review targeted published manuscripts that report on cohorts of studies that estimate the proportion of included studies published by a specified time point, and identified study characteristics of the studies in each cohort associated with publication in a peer-reviewed journal. The unit of analysis was a clinical study. Manuscripts were eligible for inclusion if they assessed a cohort of studies systematically identified and tracked using one of five pre-publication milestones (tracking methods) and then tracked these studies forward to publication (considered as a binary outcome rather than time to publication) in a peer-reviewed journal. All manuscripts included in our review included both published and unpublished studies in the cohorts they reported on.

As a study is planned and moves into execution and ultimately analysis, it creates numerous records that can be identified and tracked over time. For our analysis, we defined five methods of pre-publication study tracking, herein after referred to as 'tracking method': funding record, ethics committee approval, clinical trial registration, abstract presentation at a conference, and submission to a regulatory authority. (Figure 1: Study Identification) Before a trial begins to recruit patients it is funded, the organization providing the funding (manufacturer, government agency, or non-profit funding organization) will be aware of the progress of the trial and track its progress to results, even when it goes unpublished. Studies tracked using this method can be combined in a cohort of studies. After receiving funding, trial investigators receive initial approval and oversight from an IRB or ethics committee. The IRB will have a thorough record of the study that allows for assessment of eventual publication. A third source for identifying and tracking cohorts of studies is registries such as clinicaltrials.gov which, as a consequence of having been made mandatory in recent years, has records on a large number of studies, although the amount of information reported may be limited.[20,21] The fourth source of identification and tracking is abstracts presented at conferences. These abstracts provide partial and sometimes interim results limited to a certain scientific area, and are one of the few reliable sources of results of studies that do not proceed to publication. Finally, there are submissions for new products to regulatory agencies such as the US Food and Drug Administration or the European Medicines Agency. Consistent with the work of others, [22] our method for categorization of study tracking used these five methods, and we sub-grouped studies by these five methods to determine if these methods of identification and tracking influenced the proportion of studies in each cohort that were published.

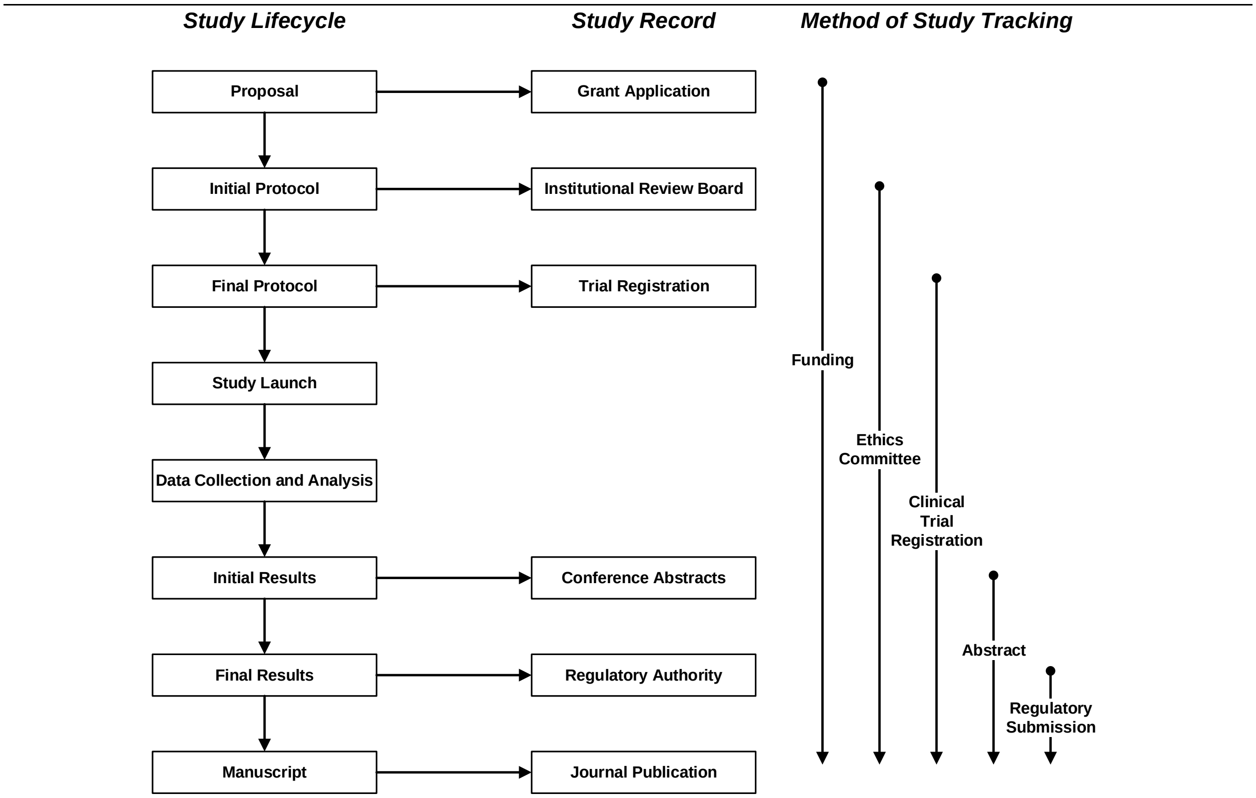


Figure 1: Study Identification

While publication bias can be defined in many ways,[23] for the purposes of this study, we used the binary outcome of publication in a peer-reviewed journal. We did not consider grey literature publication as a means of dissemination as these reports are often less accessible, more difficult to extract, and not used in most systematic reviews. To be considered for quantitative pooling, each identified manuscript was required to follow a cohort of studies from inception to publication. Each manuscript was only included if it reported study characteristics (predictor variables) for both the published and unpublished studies. The seven study characteristics included in our analysis as independent variables were: result favorability (defined as in previous studies as a positive result for the experimental arm, with or without statistical significance[16]), statistical significance of primary outcome for any treatment ($p<0.05$; $p\geq0.05$), trial sponsorship (industry-sponsored or not), number of study centers (multicenter or not), study phase (3/4 versus 1/2), study design (randomized controlled trial or not), trial size, study phase, and country of origin (North American or not). The conduct of this systematic review and meta-analysis complied, whenever possible, with the standards outlined by the Cochrane Collaboration[24] and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses).[25]

2.2.1 *Data Sources and Searches*

We performed our literature search in MEDLINE, EMBASE, Web of Science, CINAHL and Cochrane databases (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Cochrane Reviews, Cochrane Health Technology Assessment Database) using a broad and simple search string optimized for sensitivity rather than specificity (See Appendix). This search string was previously used by another set of investigators for a similar review.[16] We conducted our search in October of 2016 and we placed no exclusions on the time of publication. Additionally, an ancestry search was performed using review articles from our initial search.

2.2.2 *Inclusion Review*

All records underwent abstract review by a single reviewer (WC). To test for reproducibility of this inclusion review, a randomly selected sample of 1,000 records was reviewed by a second reviewer (NH). Inter-rater reliability was tested via Cohen's kappa.[26] In the case of poor agreement ($\kappa<0.80$) between the two reviewers a full review of all records by both reviewers was planned. Full text review was conducted for included abstracts. We excluded studies that did not follow a cohort of studies from completion to publication, did not include publication in a peer-reviewed journal as an endpoint, did not capture study characteristics predictive of publication, were not performed in humans, were not about medicine or healthcare, or were written in a language other than English. Studies published only in abstract form were included if they provided enough detail to be abstracted.

2.2.3 *Data Extraction*

Studies that met inclusion review underwent a data extraction process of the seven, predetermined potential predictors of publication. In addition, we took note of the time from completion of data collection to publication in peer-reviewed journal used to define publication or not within each cohort. For example, if an analysis defined the time point of interest to publication at 5 years, a study published at 6 years, although ultimately published would be categorized as unpublished for the purposes of that cohort analysis. Beyond time and average number of patients enrolled in each study within the larger cohort (study size), which was measured continuously, all other variables were converted into binary count format. This allowed for the use of the largest number of reports.

2.2.4 *Statistical Analysis*

We conducted traditional meta-analysis with dichotomized independent variables of result favorability, statistical significance, trial sponsorship, number of study centers, study phase, study design, trial size, study phase, and country of origin. Our outcome of interest was full publication in a peer-reviewed journal and our comparison groups were based on method of tracking. To test for systematic differences by method of study tracking we first performed a descriptive analysis to investigate the percent of studies published within each cohort stratified by method of study tracking and overall, average years of follow-up from completion of data collection (defined as the time when outcomes are no longer being collected on patients) to the threshold for defining publication, and the average number of studies within each cohort. Differences in percent of studies published between our method of study tracking subgroups were assessed via the one-way analysis of variance (ANOVA) model. We next conducted a traditional meta-analysis where the unit of analysis was cohorts of studies, the outcome variable was a binary variable indicating publication. The seven study characteristics were also dichotomized and each served as a separate predictor variable. For each study characteristic, we conducted our analysis both among all studies and stratified by method of study tracking. An odds ratio for the effect of each of our study characteristics on publication was calculated for each cohort of studies (See Appendix for example). For each tracking method, we pooled this evidence using a random effects model (DerSimonian and Laird). As a secondary analysis, a fixed effects meta-analysis using an inverse variance weighted odds ratio was also performed to determine if this substantially altered results.[27] Between cohort heterogeneity was measured and reported using the I^2 statistic.[28]

As an additional exploratory analysis, we performed a meta-regression to assess the effects of a one-way interaction term of each pair of study characteristics on the probability for publication. Importantly, this allows us to test the robustness of our assumptions about the association between two variables as well as magnitude of difference in association based on a third variable. The first factor that we evaluated under this framework was the effect of time of follow-up from completion of data collection to defining a study as published or not. This allowed us to determine if this threshold significantly confounded the results we observed in our traditional meta-analyses. All analyses were conducted using Stata version 12 (College Station, TX) using several publically available add-on software packages.[29-31]

2.3 RESULTS:

Our literature review identified 34,471 unique studies from the database search with an additional twelve identified via ancestry search of previous reviews. Ultimately, 85 cohorts of studies qualified for inclusion (Figure 2: Literature Search Results, additional study details in Appendix). The majority of studies excluded did not track cohorts of studies to publication. Additionally, a large number of studies was excluded at the point of full text review as they did not report characteristics of studies associated with publication. Tests of reproducibility between the two reviewers showed a strong to almost perfect level of agreement with $\kappa = 0.89$.[26] All discrepancies between the two reviewers were easily resolved upon full text review.

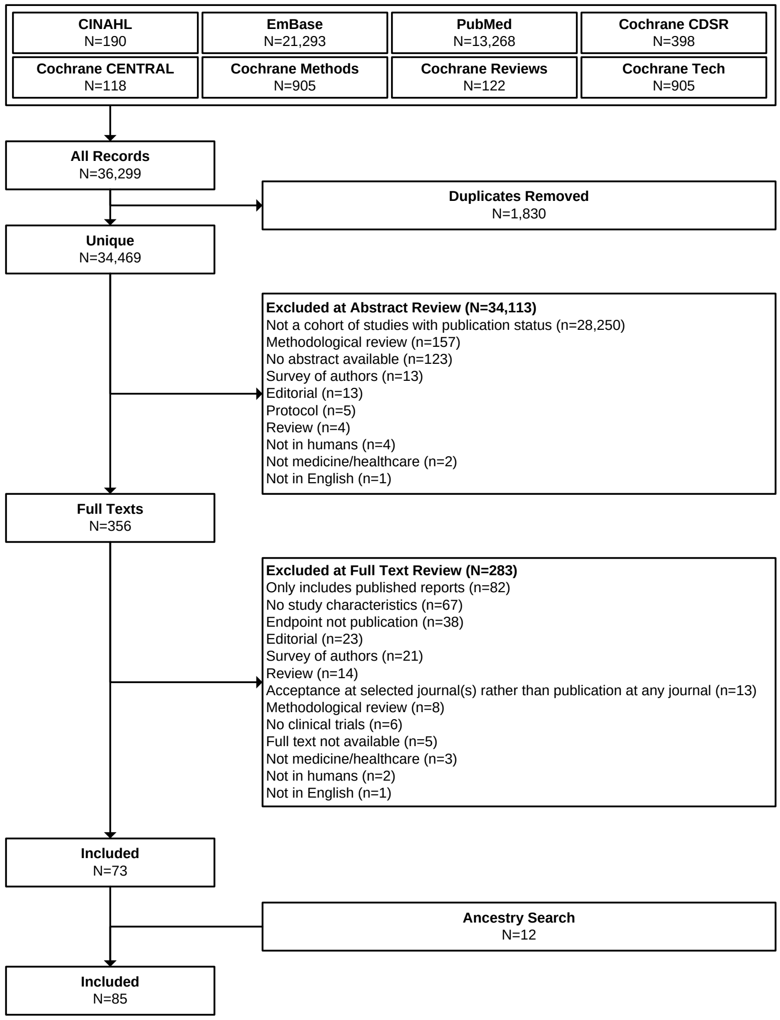


Figure 2: Literature Search Results

2.3.1 *Tracking Method*

Approximately 43% of cohorts used presentation of an abstract at a conference as their method of study tracking (Table 1: Cohort Characteristics, by Method of Study Tracking). The percent of completed studies that was published varied from roughly 42% for clinical trial registration cohorts to 74% for follow-up of funder's records, a difference that was strongly statistically significant via a one-way analysis of variance (ANOVA) model. Additionally, the time from completion of data collection to publication varied based on method of study tracking with those cohorts identified via funder's records having the longest time period for defining publication at 6.4 years (sd=2.3 years) and those cohorts identified via clinical trial registration having the shortest time period 2.5 years (sd=2.1 years). The number of studies included in each cohort also varied widely with funders reports having the smallest average cohort size (mean of 126 studies per cohort, sd=89) and clinical trial registrations having the largest (mean of 8,487 studies per cohort, sd=33,277). Notably, the number of studies included in clinical trials registry subgroup was larger than other methods of study tracking due to some outlying cohorts that evaluated the entire clinicaltrials.gov registry.

Table 1: Cohort Characteristics, by Method of Study Tracking

	Ethics Committee	**Abstract**	**Clinical Trial Registration**	**Regulatory Submission**	**Funding**	**Total**	
Total Number of Cohorts, n (% of total)	15 (18)	36 (43)	17 (20)	12 (14)	5 (6)	85 (100)	
Average Percent of Studies within each Cohort Published (sd)	54.3 (14.7)	48.9 (15.5)	42.0 (20.0)	68.6 (18.0)	74.1 (13.9)	52.7 (18.9)	<0.05
Average Years of Follow-up Used to Define Publication within each Cohort (sd)	6.13 (2.1)	4.8 (1.1)	2.5 (2.1)	4.7 (2.6)	6.4 (2.3)	4.6 (2.2)	<0.05
Average Percent of Studies within each Cohort Published by Study Characteristics, % (sd)							
Favorable	78.5 (51.4)	62.7(20.0)	61.3 (0)	61.5 (8.5)	48.1 (10.4)	62.2 (20.9)	
Significant	67.2 (14.6)	41.9 (17.3)	N/A	47.5 (0)	59.3 (4.7)	49.8 (18.7)	
Industry Funded	56.4 (29.4)	23.0 (18.3)	59.4 (21.9)	85.4 (14.9)	16 (0)	51.8 (29.1)	
Multicenter	57.5 (19.3)	33.5 (28.1)	N/A	73.4 (0)	39.4 (0)	42.1 (27.2)	
Phase 3/4	64.2 (11.9)	N/A	50.6 (23.9)	52.7 (24.0)	N/A	54.9 (21.0)	
RCT	48.0 (14.4)	36.4 (41.7)	57.9 (22.8)	88.5 (19.3)	56.5 (47.4)	48.6 (36.0)	
North American	100 (0)	58.4 (30.1)	67.6 (16.3)	N/A	100 (0)	63.2 (29.5)	
Average Number of Studies within each Cohort (sd)	278.4 (203.2)	414.8 (347.2)	8487 (33277)	275.4 (306.0)	125.6 (88.9)	1968.5 (14891.3)	NS

Reporting of statistical significance performed via ANOVA as the proportion of each cohort published, across methods of study tracking, sd=standard deviation, N/A=not applicable as calculations were not possible due to low sample size, NS=not significant

2.3.2 *Meta-Analysis*

Results from our analysis showed a significant effect for favorability, significance, industry funding, multicenter status and study phase (Table 2: Meta-Analysis Results (Odds Ratio, 95%CI) by Method of Study Tracking). Favorability showed a significant positive association with publication, with favorable results being twice as likely to reach publication than unfavorable results (OR=2.04; 95%CI: 1.62; 2.57). This association held across all tracking methods. Result significance was reported in a smaller sample of cohorts and was a significant predictor of publication across all tracking methods (OR=2.07; 95%CI: 1.52; 2.81). Industry funded studies, as a group, were 19% less likely to publish (OR=0.81; 95%CI: 0.67; 0.99). This trend was reversed in those cohorts that tracked from abstract presentation at a conference to publication, with industry funded studies approximately 57% more likely to publish (OR=1.57; 95%CI: 1.00; 2.49) than those funded through other channels. Studies that were single-center or phase 1/2 were also significantly associated with 32% (OR=0.68; 95%CI: 0.55; 0.84) and 34% (OR=0.66; 95%CI: 0.51; 0.86) lower probabilities of publication, respectively. Country of origin and study design were not significantly associated with the probability of publication. In the case of study design, the result seemed to be strongly effected by one large outlying study,[32] which tended in the opposite direction of many other cohorts. These same analyses were performed using fixed effects model without any notable differences in results.

Table 2: Meta-Analysis Results (Odds Ratio, 95%CI) by Method of Study Tracking

	Ethics Comm.	Abstract	Clinical Trial	Regulatory Sub.	Funding	Total
Result Favorability						
Odds Ratio (95% CI)[1]	3.05 (1.74; 5.37)	1.55 (1.21; 1.98)	11.67 (2.81; 48.51)	7.01 (2.71; 18.10)	2.63 (1.71; 4.03)	2.04 (1.62; 2.57)
I^2 Statistic	37.5%, NS	77.3%, p<0.05	Not Calculable	75.1%, p<0.05	0.0%, NS	78.5%, p<0.05
Result Significance						
Odds Ratio (95% CI)	4.49 (2.32; 8.70)	1.37 (1.04; 1.81)	Not Calculable	3.43 (2.31; 5.09)	4.56 (1.76; 11.82)	2.07 (1.52; 2.81)
I^2 Statistic	76.1%, p<0.05	66.5%, p<0.05	Not Calculable	Not Calculable	0.0%, NS	81.4%, p<0.05
Industry Funding						
Odds Ratio (95% CI)	0.78 (0.53; 1.17)	1.57 (1.00; 2.49)	0.59 (0.42; 0.82)	0.63 (0.29; 1.38)	2.19 (0.24; 19.99)	0.81 (0.67; 0.99)
I^2 Statistic	72.0%, p<0.05	73.7%, p<0.05	87.5%, p<0.05	49.7%, NS	Not Calculable	81.1%, p<0.05
Multicenter Status						
Odds Ratio (95% CI)	0.66 (0.49; 0.88)	0.65 (0.49; 0.86)	Not Calculable	2.02 (0.84; 4.88)	0.40 (0.11; 1.47)	0.68 (0.55; 0.84)
I^2 Statistic	49.2%, NS	77.4%, p<0.05	Not Calculable	Not Calculable	71.7%, p<0.05	71.7%, p<0.05
Study Phase						
Odds Ratio (95% CI)	0.74 (0.52; 1.05)	Not Calculable	0.60 (0.47; 0.78)	0.91 (0.83; 0.99)	Not Calculable	0.66 (0.51; 0.86)
I^2 Statistic	84.1%, p<0.05	Not Calculable	88.0%, p<0.05	57.9%, NS	Not Calculable	97.6%, p<0.05
RCT Status w/ Outlier						
Odds Ratio (95% CI)	1.55 (0.98; 2.46)	1.57 (1.28; 1.92)	0.88 (0.26; 2.97)	1.89 (1.22; 2.92)	1.54 (0.48; 4.94)	1.51 (0.79; 2.88)
I^2 Statistic	80.5%, p<0.05	22.9%, NS	99.0%, p<0.05	0.0%, NS	0.0%, NS	98.7%, p<0.05
RCT Status w/o Outlier						
Odds Ratio (95% CI)	1.55 (0.98; 2.46)	1.57 (1.28; 1.92)	1.27 (1.05; 1.53)	1.89 (1.22; 2.92)	1.54 (0.48; 4.94)	1.52 (1.30; 1.76)
I^2 Statistic	80.5%, p<0.05	22.9%, NS	0.0%, NS	0.0%, NS	0.0%, NS	43.8%, NS
North American Origin						
Odds Ratio (95% CI)	Not Calculable	0.91 (0.72; 1.16)	1.10 (0.61; 1.96)	Not Calculable	Not Calculable	0.94 (0.76; 1.17)
I^2 Statistic	Not Calculable	72.1%, p<0.05	76.3%, p<0.05	Not Calculable	Not Calculable	71.6%, p<0.05

[1]Random effect meta-analysis performed using DerSimonian and Laird method

Heterogeneity, as measured by the I^2 statistic, was between 70-80% for most study characteristics evaluated, suggesting significant heterogeneity. Our analysis for study design did have a higher than normal I^2 statistic reaffirming the suspicion of an outlying value. When this large outlying value was removed, the effect of study design became significant with studies with a randomized and controlled design 50% more likely to publish (OR=1.52; 95%CI: 1.30; 1.76). Additionally, removing this outlier reduced the heterogeneity as measured via the I^2 statistic from 98.7% to 43.8%.

2.3.3 *Effect Modification*

As this was an exploratory analysis, we systematically tested all 42 possible effect modifications of pairs of study characteristics via a random effects model. While the time to publication varied between methods of tracking (Table 1: Cohort Characteristics, by Method of Study Tracking), in a meta-regression model, the follow-up time did not significantly modify the effect of any of the other seven study characteristics on the odds of publication (Table 3: Results of Exploratory Analysis by Pairs of Study Characteristics (Odds Ratio, 95%CI)). Notably, the only statistically significant effect modification found was between favorable results and industry funding (OR=6.72; 95%CI: 1.28; 35.23).

Table 3: Results of Exploratory Analysis by Pairs of Study Characteristics (Odds Ratio, 95%CI)

Predictor Variable	**Effect Modifier**							
	Time	***Favorability***	***Significance***	***Industry Funding***	***Single Center***	***Study Phase***	***RCT Status***	***Country of Origin***
Favorable	1.01(0.81;1.26)		2.48(0.02;256.54)	6.72(1.28;35.23)*	1.77(0.31;10.04)	0.79(0.04;16.41)	1.32(0.64;2.75)	1.22(0.29;5.02)
Significant	1.13(0.88;1.44)	14.50(0.78;269.55)		2.09(0.29;15.18)	4.07(0.21;79.14)	Insufficient Obs.	0.45(0.16;1.25)	1.98(0.90;4.35)
Industry Funded	1.06(0.97;1.17)	16.95(0.60;482.68)	0.60(0.00;130.35)		2.35(0.32;17.10)	3.11(0.64;15.05)	0.42(0.13;1.42)	0.55(0.06;5.40)
Single Center	0.92(0.74;1.15)	1.08(0.04;30.38)	0.01(0.00;1847.05)	0.62(0.06;6.27)		Insufficient Obs.	0.76(0.18;3.14)	10.85(0.92;127.34)
Phase 3/4	1.07(0.93;1.24)	2.50(0.03;190.78)	Insufficient Obs.	3.87(0.36;41.66)	Insufficient Obs.		1.62(0.17;15.86)	Insufficient Obs.
RCT	1.14(0.99;1.31)	0.96(0.32;2.88)	0.37(0.02;8.26)	1.53(0.30;7.90)	0.89(0.24;3.27)	6.48(0.38;109.95)		1.39(0.41;4.71)
North American	0.98(0.82;1.16)	1.48(0.19;11.66)	0.30(0.03;2.93)	1.98(0.46;8.46)	0.59(0.05;7.63)	Insufficient Obs.	0.80(0.39;1.64)	

*p<0.05, CI = confidence interval; RCT = randomized controlled trial

2.4 DISCUSSION:

Our systematic review identified 85 manuscripts that tracked a cohort of studies to publication. Favorable results, statistical significance and multicenter status were all significantly associated with a higher probability of publication. Conversely, industry funding was associated with a lower probability of publication. Subgroup analysis by method of study tracking found largely the same results. One notable exception was that the probability of publication for studies presented as abstracts was significantly higher if the studies were industry funded. In an additional exploratory analysis for effect modification via meta-regression, we found the probability of publication for favorable results was significantly influenced by funding status. This suggests that industry funded studies may be strongly associated with differential publishing based on the study's result favorability. Yet, this result must be viewed as exploratory and interpreted with caution as, with 42 tests for interaction terms, it is possible that this significant result is due to chance. The result should be confirmed in future investigations.

Oher investigators have conducted reviews that evaluate the influence of study-level characteristics on the probability of publication.[16,22] Most recently, Song et al. found that both significance and favorability were strongly associated with the likelihood of publication.[22] While this study was rigorous, it did not evaluate factors beyond favorability and significance and only considered 48 cohorts. In contrast, our manuscript, which updates this previous review, evaluates several additional study characteristics that may influence publication, conducted a meta-regression to better understand the interaction of these characteristics, and included a much more comprehensive list of 85 cohorts of studies. Hopewell's review,[16] while rigorous, only analyzes the effect of statistical significance and result direction and does not stratify the analysis by method of study tracking.

Our analysis presents the most comprehensive study to date of the factors that influence a study's likelihood of publication. While previous analyses have considered one or two study-level predictors of publication we have considered seven possible study-level characteristics, thus presenting a more complete picture of what may be influencing publication. Additionally, this is the only review to assess for effect modification of these study characteristics. Finally, as method of study tracking has been shown to influence the likelihood of publication, we have conducted subgroup analyses to evaluate this effect on all of our characteristics. We believe this study provides an important addition to research on factors influencing the likelihood of publication. Our results are consistent with those of others.[16,17,22,33]

Although we took every possible step toward comprehensiveness and transparency, our study does have some notable limitations. First, we defined publication as a binary outcome of either fully published in a peer-reviewed journal or not. While this is the gold standard for dissemination in healthcare and science, it may miss the fact that some studies may only be disseminated via white paper or conference abstract. The use of 'grey literature' in reviews has been an area of active investigation in recent years.[34] As systematic review and evaluation of the clinical literature are the cornerstones of evidence-based medicine, we believe our definition of publication most closely reflects evidence based decision making. Further, our review focuses only on those studies that have been completed and does not consider the effect of studies that are stopped early for failure to enroll adequate numbers of patients. Importantly, as we have simultaneously tested for the effect of seven study characteristics within five methods of study tracking, our results, especially for our exploratory analyses, are limited in how strongly they can be interpreted, due to the possibility of statistical artifacts inherent in multiple comparisons.

Publication bias represents a critical threat to evidence-based medicine and systematically modifies our perception of the safety and efficacy of pharmaceuticals. A better understanding of the phenomenon enables us to better critically evaluate the studies we see published in the literature, and to apply these published findings in the context of treatment of patients and policy decisions. With a better understanding of the phenomenon of publication bias, what remains is an assessment of the tools for its mitigation. What is still unclear is which policy measures effectively mitigate this phenomenon. For example, the Food and Drug Administration Amendments Act (FDAAA) of 2007 requires trials of FDA approved medications to post their results to the ClinicalTrials.gov database within one year of study completion.[35] Despite this mandate, currently only 22% of trials meeting these criteria have associated results in the database within one year of trial completion.[36] Further development and evaluation of policy incentives are needed to address this growing problem.

Chapter 3. ADJUSTMENT OF PUBLICATION BIAS VIA A CUMULATIVE META-ANALYTIC FRAMEWORK

3.1 INTRODUCTION:

Evidence based medicine (EBM) is “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”[37] and one of the most powerful concepts in modern healthcare. The process of EBM naturally involves three steps: generation, synthesis and practice.[38] The first step in this process, the generation of evidence that informs all future practice is a monumental enterprise. It is estimated that global expenditures on medical research exceed $200B annually.[1] The ultimate product coming from all of this investment is the complete and timely publication of evidence in peer-reviewed journals. This results in an extraordinarily large number of publications. Recent bibliometric analysis has suggested that global scientific output as measured by number of publications grows at a rate of 8-9% annually[3] meaning that the number of scientific publications more than doubles every ten years. In healthcare alone, the National Library of Medicine’s bibliographic database, MEDLINE, adds over 800,000 new citations every year.[4]

This productivity creates an unmanageable amount of information for healthcare practitioners to incorporate into the care of patients. It is ultimately the second step of EBM, the synthesis of this large volume of information via systematic reviews and meta-analyses, that translates the results of clinical research into actionable information for health care practitioners. Publication bias represents a threat to the effectiveness of these methods of evidence synthesis and undermines one of the core tenets of EBM—

that systematic review of published evidence can create an accurate estimate of the known safety and efficacy of an intervention. In fact, many studies go unpublished and those studies that do go unpublished are often systematically different from those that are published.[15-17] This phenomenon is extensive in medicine: nearly half of studies monitored by Institutional Review Boards go unpublished after data collection is completed[7-13] and almost 60% of trials submitted to the US Food and Drug Administration (FDA) for approval of new treatments are never published in a peer-reviewed journal.[14] Not only does publication bias hamper the process of evidence synthesis but it can also introduce bias in the synthesis of these results used to inform clinical decisions. This bias can arise for several reasons. For example, we know that publication is strongly correlated with the study treatment's effect size, direction and significance,[15-17] as well as sponsorship.[19]

The need for access to the full results of medical research is such that the National Academy of Medicine recently completed a report entitled "Sharing Clinical Trial Data". This report framed the problem of publication bias in clear terms: "Clinical trials are essential to determining the safety and efficacy of new health treatments, but limited data sharing prevents maximum utilization of knowledge gained. In short, the current system fails to provide an adequate return on the investments of trial participants, investigators, and sponsors."[18] Despite the clear understanding that publication bias exists and limits access to a large portion of completed studies there is limited evidence of the impact of this bias on evidence synthesis, clinical decision making and patient outcomes. In particular, it is not clear if having all completed studies vs. only those published would have influenced clinical decision-making through time, that is, would healthcare providers have made different decisions if all the evidence for the risks and benefits of a treatment were available shortly after it was produced?

In the case of publication bias, cumulative meta-analysis (CMA) can be used to evaluate evidence accumulation by comparing a summary measures' level of significance over time for a comprehensive data set versus a published only data set. Under a scenario where all studies were available there would presumably be less uncertainty about the summary measure and the CMA would reach a significant finding earlier or with fewer studies completed than if there was only a partially reported set of studies. It is during this window of time that there is a potential for publication bias to have a real and measurable impact on patients and the healthcare system. While the effect of publication bias on real-world decision making has been shown at a single time point[39] it has not yet been evaluated through time to determine what potential effect this could have on clinical decisions in the window of time during which the evidence existed but was not available.

Our objectives were to: 1) determine if there was a difference in time to clinically meaningful evidence for a notable historical case of publication bias, rosiglitazone for patients with diabetes, using the methods of cumulative meta-analysis, and 2) evaluate if available methods of adjustment for publication bias could be useful in arriving at clinically meaningful evidence sooner under our CMA framework. For our purposes, we defined clinically meaningful evidence via a measure we are naming the clinically meaningful decision (CMD) threshold. The CMD threshold was defined as the level of evidence (as measured via treatment effect size of a healthcare outcome) at which either stated or revealed preferences[40] of healthcare providers would change their prescription patterns. This incorporates both the absolute measure of minimal clinically important difference[41,42] and uncertainty around this absolute value and will vary from analysis to analysis based on outcome, treatment and empirically defined prescriber preferences.

Our process to achieve this objective was three-fold. First, we determined if there was a systematic difference in summary estimate via traditional meta-analysis between what was available in the published-only data set for rosiglitazone and what was available to the manufacturer in the comprehensive data set. Second, we measured how the time to our CMD threshold would be effected by having access to a comprehensive data set rather than only published data using a cumulative meta-analytic framework. Finally, we evaluated whether currently available methods for adjustment of publication bias in traditional meta-analysis when used under a CMA framework would affect the time to our CMD threshold.

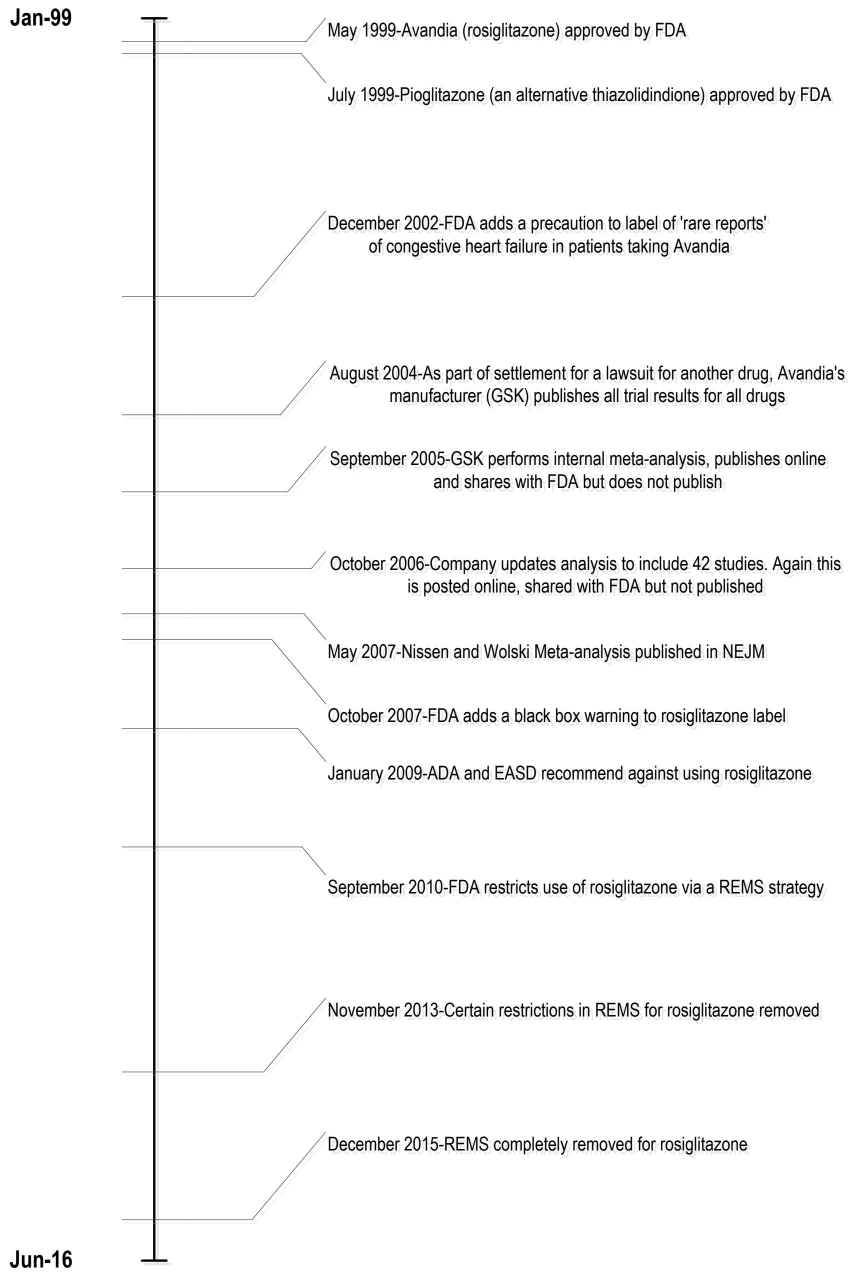
3.2 MATERIALS AND METHODS:

The central method for this project was cumulative meta-analysis (CMA). CMA is a version of meta-analysis that performs serial pooling of the evidence through time to evaluate how a pooled estimate for treatment effect evolves over time.[43] In practice this can identify the time at which the body of evidence reached a certain level of clinical relevance and statistical significance. For example, when does the confidence interval for the risk of a drug's serious adverse event exclude the null.

While CMA can provide a visual representation of how the evidence accumulates in both published-only and comprehensive data sets, the question remains whether available methods for statistical adjustment can be used to predict the comprehensive set of studies from the published set using available methods for adjustment. The most commonly used method for adjustment for publication bias, the trim and fill, uses the funnel plot to identify the asymmetric studies around the presumed mean from larger studies and then reflect these studies on the opposite side of the plot to create a symmetrical appearance.[44] Additionally numerous regression based methods are available that incorporate known characteristics of the studies that are available to impute the likely missing studies. Examples of weighted regression techniques for adjusting for publication bias include Harbord,[45] Peters,[46] and Conditional Harbord.[47]

The case study used for this analysis was rosiglitazone (trade name, Avandia™), an insulin sensitizer that works by sensitizing fat cells to make them more responsive to insulin. The drug was first approved in 1999 on the basis of the laboratory measure of blood sugar control via glycated hemoglobin (HbA1c) levels without sufficient numbers of patients to detect differences in clinical events such as heart attacks (Figure 3: Timeline for Rosiglitazone). Avandia ultimately rose to sales of more than $3B in 2006 before a meta-analysis by Nissen and Wolski showed that it was associated with a higher rate of myocardial infarction and death from cardiovascular causes (odds ratios of 1.43 and 1.64 respectively).[48] This is particularly troubling considering that over 50% of people with diabetes die from cardiovascular causes.[49] The Nissen meta-analysis included 42 qualifying studies, of which 26 were previously unpublished. Following the release of this information, sales for rosiglitazone dropped significantly although the drug was never pulled from the market.[50,51] While a risk mitigation strategy was implemented for rosiglitazone, this was ultimately lifted in 2015 after the results of the RECORD trial failed to show a risk of myocardial infarction associated with the drug.[52]

We included the studies from the meta-analysis performed by Nisssen and Wolski.[48] Responding to calls to increase transparency following a suspected risk of cardiovascular events GlaxoSmithKline, the manufacturer of rosiglitazone, created an online database of all studies for the agent that they had sponsored. Nissen and Wolski used this resource to conduct their meta-analysis. While we cannot guarantee this is complete, it does represent the most comprehensive list available and includes both published and unpublished studies. Additionally, if there were intentional publication bias occurring it would be performed by the manufacturer and captured in this database. For our analysis, we have as much as possible mirrored the analysis by Nissen and Wolski to replicate their analysis which caused a profound shift in prescription patterns[30,31] and subsequently have used myocardial infarctions (MI) as our outcome of interest.



FDA=Food and Drug Administration, GSK=GlaxoSmithKline, ADA=American Diabetes Association, EASD=European Association for the Study of Diabetes, NEJM=New England Journal of Medicine, REMS=Risk Evaluation and Mitigation Strategy

Figure 3: Timeline for Rosiglitazone

3.2.1 *Traditional Meta-Analysis*

As a first step, we conducted traditional meta-analyses with both the published-only and comprehensive data sets. This analysis was designed to mirror the analysis by Nissen and Wolski[53] in order to validate our results. To calculate the odds ratio of MI effect size, we used each arm's sample size as the denominator and performed no adjustment for arms with zero events. This effect was pooled across studies via the Peto method.[54] Use of the Peto method was appropriate given the outcome of MI is relatively rare occurring in less than 1% of patients and arms of the trials were relatively balanced in size.[55,56] Furthermore, Peto has the advantage of not needing zero-cell adjustment[56,57] and providing a direct comparison to the analysis of Nissen and Wolski[53] that resulted in a market shift. For any trial with more than two arms, such as a trial comparing control to multiple doses of interventional drug, we combined intervention arms. Additionally, as there was significant variability in the duration of trials we conducted a sensitivity analysis pooling with a person-year, rather than population denominator for effect.

3.2.2 *Assessment of Heterogeneity and Publication Bias*

To quantify the extent of heterogeneity in our analysis, we calculated the I^2 statistic[58] for each of the models evaluated. Additionally, to qualitatively assess publication bias or potential systematic missingness we performed a funnel plot analysis for all of our models. The funnel plot is a graph that displays studies included on the two axes of effect size and variance.[59] Publication bias is then evaluated visually by looking for the characteristic asymmetrical pattern and missingness in the quadrant of the plot representing small sample sizes and effects.[60] For our analysis as we had both published and comprehensive sets of studies and evaluated the patterns of these plots side by side to see if the unpublished studies were within the generally predicted location or more dispersed.

3.2.3 *Cumulative Meta-Analysis*

Our analysis is based upon comparing the decisions made through time with a published-only data set to what would have been possible with a comprehensive data set. The key method for performing this analysis is cumulative meta-analysis (CMA). For uniformity, we have applied all of the same methods from our traditional meta-analysis under a cumulative meta-analytic framework. We defined the clinically meaningful decision (CMD) threshold as the date at which the confidence interval for the odds ratio of rosiglitazone's risk of MI excluded the null. We chose this threshold as it resembled the level of evidence presented in the Nissen and Wolski analysis[53] that resulted in a distinct shift in prescriber patterns. A claims based analysis of prescriptions for diabetes medications showed that following the publication there was a dramatic reduction in the number of rosiglitazone prescriptions. [30,31] This gives us validation that the level of evidence presented by Nissen and Wolski was clinically meaningful and enough to shift decision making. Underlying this analysis is the assumption that had this same level of evidence been available sooner it would have produced a similar response among prescribers.

Using this method, we can estimate the time interval during which decision-making may have been affected by systematically biased information. To concisely capture the results of these analyses, we have recorded for each CMA the date at which the odds ratio for MI crossed our predefined CMD threshold for both comprehensive and published-only data sets.

3.2.4 *Methods of Adjustment Applied via Cumulative Meta-Analysis*

The next and final step of our analysis was to determine if any of the currently available methods for adjustment for publication bias when applied to a cumulative meta-analytic framework might alter (and hopefully shorten) any identified difference between the time to evidence crossing a clinically-meaningful decision threshold. To evaluate this, we used three of the most commonly used methods for publication bias adjustment, Harbord's regression, Peter's regression and the Trim and Fill. More detail on these methods and how they adjust for missingness can be found in our technical appendix.

3.2.5 *Measurements of Performance*

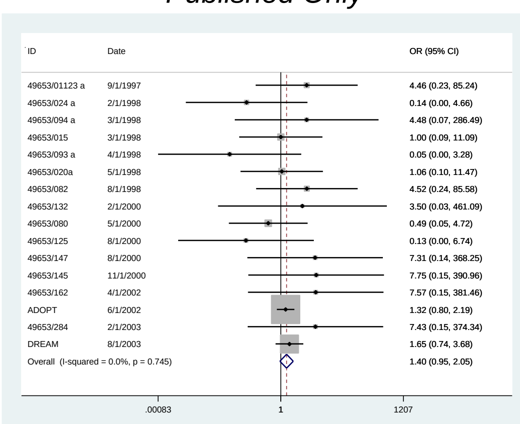
To measure the relative performance of each method of adjustment in a cumulative meta-analytic framework we considered how closely the adjusted data set matched the timing of effect estimates for the comprehensive data set crossing our predefined CMD threshold. For example, in a hypothetical example if a cumulative meta-analysis for the effect of Drug A on Outcome B using a comprehensive set of studies, published studies with adjustment, or only the published set of studies crossed the predefined CMD threshold in months one, four, and twelve respectively then that method for adjustment would receive a score of 8 months since it identified the meaningful effect 8 months sooner than would have been possible with no adjustment.

3.3 RESULTS:

3.3.1 *Traditional Meta-Analyses*

Our meta-analysis of odds ratio of myocardial infarction in rosiglitazone with population denominators showed little difference in our published and comprehensive data sets with estimates of 1.40 (95% CI: 0.95; 2.05) and 1.42 (95% CI: 1.03; 1.97) respectively (Figure 4: Meta-Analysis of MI events in Rosiglitazone Trials). Our results were not affected by the use of a person-year denominator (See Appendix). For all of our models, the I^2 statistic was 0% suggesting extremely low levels of heterogeneity.[58] Finally, visual comparison of the funnel plots for published versus all evidence did not suggest the characteristic pattern of missingness associated with publication bias. This pattern was similar across both population and person-year denominators (Appendix).

Published Only



All Trials

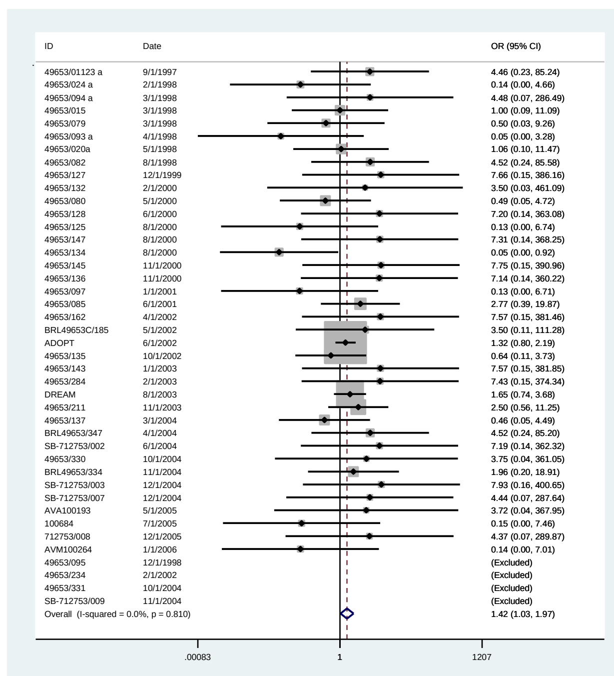


Figure 4: Meta-Analysis of MI events in Rosiglitazone Trials

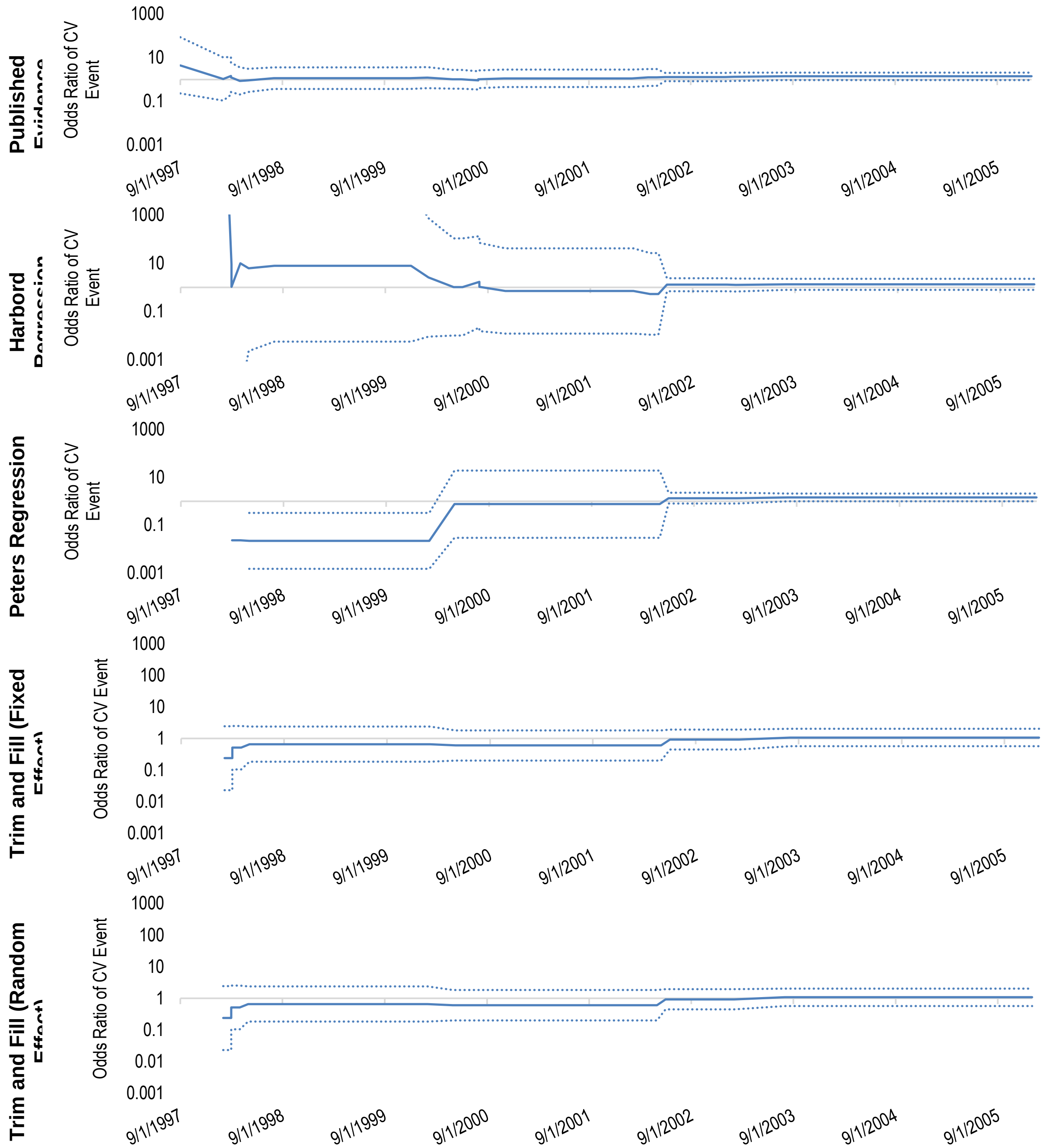
3.3.2 *Cumulative Meta-Analyses and Time to Clinically Meaningful Decision Threshold*

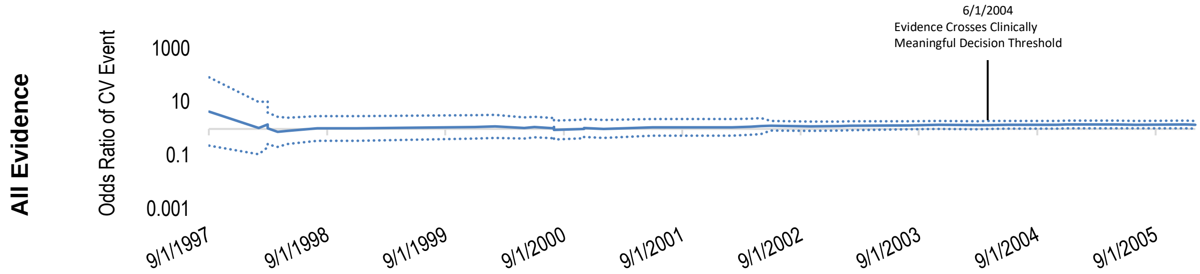
Our cumulative meta-analysis for both comprehensive and published-only data sets showed a rather large differential in time to crossing our pre-defined threshold. In fact, the evidence for MI risk would have never reached statistical significance using solely published data (Figure 5: Cumulative Meta-Analysis for Published-Only, Comprehensive and Adjusted Data Sets, Additional information in Appendix). Having access to all studies gives a clinically meaningful result a full 36 months sooner. Under the published-only scenario, the available evidence only showed a significant effect after the full analysis by Nissen and Wolski. Had all the studies been accessible and published, this same level of evidence would have been reached in June 2004 (See Appendix).

3.3.3 *Performance of Adjustment Methods via a Cumulative Framework*

Following our cumulative meta-analysis of published-only and cumulative data sets, we performed four adjustment methods in a cumulative framework to assess the degree to which each available method of adjustment corrected summary estimate in the published-only data set toward the comprehensive estimate. This process was only conducted for our primary statistical model, Peto method of pooling odds ratio and population denominator.

None of our methods for adjustment shortened the time differential to our CMD threshold (Figure 3). In terms of adjustment at the time of the final study, the Peter's regression (OR=1.44 95%CI: 0.99; 2.10) appeared to perform better than the Harbord (OR=1.34 95%CI: 0.79; 2.29) which slightly underestimated the effect although both were reasonably close to the effect estimate for all studies (OR=1.42 95%CI: 1.03; 1.97). Under the Trim and Fill using either a fixed or random effects model gave the same effect which was a notable underestimate of the true effect. Again, all methods showed the characteristic narrowing of confidence interval for a cumulative meta-analysis although none had a significant effect.





Each panel displays a cumulative analysis for a data set. The solid line represents the point estimate for odds ratio of myocardial infarction. Dotted line is 95% confidence interval. Statistical model used is the Peto method with population denominator. Middle four panels represent adjusted estimate using different methods for estimating comprehensive estimate from the published-only data set.

Figure 5: Cumulative Meta-Analysis for Published-Only, Comprehensive and Adjusted Data Sets

3.4 DISCUSSION:

Publication bias is a pervasive problem in healthcare that limits the accurate synthesis of clinical trials. While the release of previously unpublished trials has been found to influence clinical decisions, the impact of this evidence over time has not yet been evaluated. Our objective was to determine if access to a comprehensive data set would reduce time to a clinically meaningful decision threshold, a significant risk of MI, relative to a published only data set and if any currently available methods for adjustment could shorten this differential. Previous analyses have evaluated these adjustment methods in simulated[61] and real[39] data sets but none have tested them in the context of cumulative meta-analysis which is more useful in quantifying the potential impact of unpublished evidence on clinical practice.

Ultimately, we found a 36-month differential between when summary evidence for the risk of MI for rosiglitazone crossed our pre-defined CMD threshold in the published-only vs. comprehensive data sets. Known methods of adjustment for publication bias in traditional meta-analysis were not able to shorten this 36-month differential. Specifically, we found that these adjustment methods while somewhat helpful at indicating an adjusted point estimate widely expand the confidence interval and do not appear to be as useful in adjustment under a CMA framework.

The difference in timing between when evidence of an effect could have been found from a comprehensive set of studies and when it was available for decision-makers is potentially meaningful and impactful. It is during this window of time that patients are receiving a treatment with less than complete evidence for risk or benefit that could influence their decision if they had known about it. Unfortunately, none of the methods of adjustment for publication bias shortened this time frame. This suggests, albeit from a single yet high profile case study, that adjustment methods may be insufficient to address publication bias if it is suspected or established. In fact, the only way to shorten the time to more informed clinical decision making is complete and timely publication of all evidence.

Our analysis has several notable limitations. First we used a historical example so therefore did not perform a comprehensive simulation to assess the performance of these methods under alternative forms of publication bias. For example, all of the methods that we used adjusted for result size and significance but would not correct for any bias due solely to factors such as sponsorship. Additionally, while we have evaluated our case retrospectively with the full benefit of hindsight, this same method may be less generalizable when performed prospectively as a form of sequential testing. As has been shown in the monitoring of clinical trials, sequential testing of a data set through time with a static threshold for decision-making has the potential to lead to a higher number of false positive results.[62] This suggests caution should be taken in applying these methods prospective cases.

Cumulative meta-analysis is a helpful tool to evaluate the evolution of evidence over time. Using a known case of publication bias it can be seen how publication bias, whether intentional or not, creates two unique evidence streams. In our case study, having access to the comprehensive data set allowed a much earlier determination of risk of MI. The case that we chose is somewhat unique in that we had both a published and unpublished set of studies and the public had a chance to react to the release of unpublished work giving us a validated and meaningful threshold of clinical significance. While we evaluated whether methods of adjustment for publication bias might be useful in cases where the unpublished studies were not released, we did not find any of them to provide a useful adjunct to decision making. Ultimately, in the absence of improved methods for serial adjustment for publication bias, it is imperative that we continue advocating for complete and timely publication of all clinical studies.

Chapter 4. FRAMEWORK FOR ASSESSING THE IMPACT OF UNPUBLISHED RESEARCH (FAIR FRAMEWORK): A PROPOSED FRAMEWORK WITH DEMONSTRATION IN TWO NOTABLE CASES

4.1 INTRODUCTION:

Global expenditures on medical research have been estimated to exceed $200B annually.[1] In the US alone over $100B is spent on medical research representing roughly 5% of annual healthcare spending.[2] Recently, claims have been made that this system is unacceptably inefficient, with some groups estimating as much as 85% of this research is wasted.[5] A key component in this inefficiency is the incomplete dissemination or selective reporting of research, especially for clinical trials.[6] An economically efficient system would provide a return on this extensive investment in research in the form of clear and well conducted trials that are accessible to the scientific community at large. Failure to publish or disseminate trial results limits the impact of these studies on individuals who could possibly use them to make informed choices for patients or to plan future research. Limited publication is pervasive in medicine; almost half of studies monitored by Institutional Review Boards (IRBs) remain unpublished even after the study is completed and results are available,[7-13] and nearly 60% of trials received by the US Food and Drug Administration (FDA) for approval of new treatments are never published in a peer-reviewed journal.[14] Not only does incomplete or selective reporting hamper the process of evidence synthesis but it also introduces bias in the synthesis of these results to inform decisions.

We, along with other researchers, have shown that the likelihood of publication is strongly correlated with study sponsorship[19], direction and magnitude of treatment effect, and statistical significance.[15-17] Ultimately, this creates a systematically biased sample to inform practice guidelines and healthcare provider practice. The urgency of the issue is highlighted by the fact that the National Academy of Medicine has recently completed a report entitled “Sharing Clinical Trial Data”. In direct language, this report describes the phenomenon of publication bias in economic terms: “Clinical trials are essential to determining the safety and efficacy of new health treatments, but limited data sharing prevents maximum utilization of knowledge gained. In short, the current system fails to provide an adequate return on the investments of trial participants, investigators, and sponsors.”[18] Further, return on investment can be defined more broadly than in financial terms as either health improvement or greater certainty in which subsequent trials should be funded.

Publication bias creates the potential for clinical and economic impact through impacts on healthcare decision making, but this has not yet been demonstrated rigorously in known examples. While previous investigations have revealed population harm from treating patients with a medication that is later determined harmful,[63,64] this is not necessarily equivalent to harm occurring from systematically withheld evidence. Ultimately, the decision to adopt, reject, or collect more evidence for a given treatment is complex and relies on evaluations of evidence regarding the risks, benefits, and costs of new treatments along with a number of other factors. The specific criteria used to inform these decisions may vary depending on the situation but can include clinical efficacy, potential harm, costs as well as the risk-benefit profile of competing treatments.

Currently, health consequences can be compared via traditional meta-analysis or serially through time via cumulative meta-analysis. This approach is limited however as it does not quantify the trade-offs between different health consequences, i.e. survival gains vs. adverse event risks. To overcome this limitation and synthesize multiple health consequences a modeling approach can be used. The methods of decision analyses can be used to synthesize available data (e.g. clinical event rates from trials, lifetime disease trajectory, costs, quality of life estimates, etc.) to determine what the optimal course of action is for a given medical decision with currently available evidence. This modeling approach also quantifies the uncertainty in the model results.

Value of Information (VOI) analysis is an extension of decision analysis and utilizes this estimate of uncertainty to compare the clinical and economic impact of treatment decisions made with currently available evidence versus those that could be made after additional research is conducted. If the value of collecting additional information is greater the cost to produce it, then it may be worth pursuing. If the value is less than the cost to produce, then the decision to adopt or reject should be made now with current information.

In the context of publication bias, the results from a VOI analysis performed on a published-only versus comprehensive set of studies at the same point in time might therefore lead to different adoption decisions because the available evidence and the attendant uncertainty will be different. These methods have been extended to estimate a net economic return of previously conducted research.[65] However, neither cumulative meta-analysis nor VOI analysis have been applied to evaluating investment in efforts to identify studies that went unpublished and estimation of the potential clinical and economic consequences thereof. This study attempts to address these shortcomings in the field. The objective of our study was to develop a framework for identifying and quantifying clinical and economic impact from publication bias and applying that framework to known cases.

4.2 MATERIALS AND METHODS:

To accomplish our objective we built a framework for how unpublished evidence might modify decision making. We subsequently evaluated the performance of this framework using two well-known cases of publication bias. Dissemination occurs along a spectrum, with publication in an accessible peer-reviewed journal on one end and no external reporting on the other. As such, publication bias and selective reporting occur in a variety of ways.[23] At one end of the spectrum, disclosure to IRBs, data monitoring committees and regulatory authorities can be thought to represent the minimal level of reporting for clinical trials. The next level toward broad dissemination could include presentation at a conference. While this may reach a contemporary group of targeted peers it is often inaccessible after the fact and unavailable to those conducting the systematic reviews that ultimately inform policy decisions and treatment guidelines. Many systematic reviews will also exclude abstracts from their search either implicitly by not searching conference proceedings, or explicitly by requiring fully published manuscripts for included studies. Thus, an appropriate standard for defining full dissemination should be either publication in a peer-reviewed journal or result reporting in a publicly accessible database such as Clinicaltrials.gov.[66] For the purposes of this study, we have defined publication as a binary outcome of report in a peer-reviewed journal, as this represents the gold standard for dissemination of clinical trial results and is the means by which most meta-analysts and guideline groups will identify their units of study for inclusion in a systematic literature review. Therefore, we define publication bias as a pattern in cohorts of studies where the results of those studies that are published are systematically different from the results of those studies that remain unpublished. This definition not only requires missingness but a systematic nature to the missingness.

4.2.1 *Development of a Framework for Assessing the Impact of Unpublished Research*

We developed a set of ordered questions that would help create a better understanding of the impact of publication bias on decision-making and ultimately health outcomes and costs. We then applied this draft framework to our two case studies to evaluate framework performance. Shortcomings in our framework were addressed iteratively with modifications to the original framing of an item or the addition of a new item.

The framework was designed for retrospective cases. From the retrospective view, all evidence is available including both published and unpublished data, thereby allowing comparison of the outcomes of both bodies of evidence after full disclosure. In addition, in cases where unpublished research has been disseminated, allowing access to both published and unpublished data sets, the real-world response to the unpublished evidence can be evaluated. In effect, this gives revealed preferences[40] for how consumers responded to new evidence.

4.2.2 *Assessment of the Framework in Notable Cases of Publication Bias*

To demonstrate the application of our framework, we used two historical case studies, rofecoxib and rosiglitazone. Rofecoxib (trade name, Vioxx®) is a nonsteroidal anti-inflammatory drug approved in 1999 for treatment of acute pain from osteoarthritis and rheumatoid arthritis as well as dysmenorrhea. Rofecoxib targets cyclooxygenase-2 (COX-2), an enzyme involved in pain and the inflammation response.[67] Rofecoxib was extremely popular at its market peak, rising to greater than 100 million prescriptions and $2.5 billion in sales globally in what year.[68] After the results of two trials VIGOR[69] and APPROVe[70] trials indicated a heightened risk for cardiovascular events, the manufacturer voluntarily withdrew rofecoxib from the market. In a government report from regulators at the FDA, it was later estimated, that over the period which it was marketed may have resulted in 88,000 to 140,000 excess cardiovascular events in US alone.[71]

Our second case was rosiglitazone (trade name, Avandia®) which is an insulin sensitizer that sensitizes fat cells thereby making them more responsive to insulin. [67] Rosiglitazone was approved in 1999 on the basis of the surrogate endpoint of glycated hemoglobin (HbA1c) rather than the ultimate clinical endpoint of clinical events such as myocardial infarctions (MI) or deaths. Ultimately these clinical endpoints are the most important as over half of diabetic patients die from cardiovascular causes.[49] In fact, the trials for rosiglitazone never had a sufficiently sized sample of patients to detect these salient differences. At its peak, rosiglitazone had sales of greater than $3B in 2006 before a meta-analysis indicated that it was associated with a higher rate of MI and death from cardiovascular causes (odds ratios of 1.43 and 1.64, respectively).[48] The meta-analysis identified 42 studies, only 16 of which were published. After publication of this meta-analysis, sales for rosiglitazone fell dramatically, although the drug was never withdrawn from the market.[50,51] A risk mitigation strategy was ultimately launched for rosiglitazone but was removed in 2015 after the results of the RECORD trial showed no risk of MI associated with the drug.[52]

4.3 RESULTS:

4.3.1 *Framework for Assessing the Impact of unpublished Research (FAIR)*

Our framework is centered on two questions: did bias effect decision-making and was there an impact of this bias on cost and outcomes. This approach assumes that quantitative pooling is appropriate and that there is evidence for publication bias. From these questions, there are a number of subordinate minor questions that can be used to help the analyst evaluate how to answer the overall question. The set of these questions comprises our Framework for Assessing the Impact of unpublished Research (Table 4: Framework for Assessing the Impact of unpublished Research (FAIR Framework)). Each of the categories of questions is considered, in turn, below.

Table 4: Framework for Assessing the Impact of unpublished Research (FAIR Framework)

FACTOR	DESCRIPTION
	Did bias effect decision making?
Meaningful Outcome	A meaningful outcome is one about which evidence is likely to have a substantial impact on clinical decision making. When the outcome being considered is not the primary endpoint of the trial, caution should be taken in using this as the basis of publication.
Decision Threshold	Once the outcome has been decided, a threshold must be set for the effect size and significance of the outcome of interest that would result in a different decision.
Clear Decision	In order to identify the impact of publication bias, an assessment should be made as to how much crossing the decision threshold would change the clinical decision making. In order to quantify this impact, it is necessary to characterize what the different decision(s) would be. This impact may be determined either by the revealed preference of how the market responded to the actual disclosure of information or using stated preference methods.[40]
	Was there an impact of the bias on cost and outcomes?
Differential Timing	The impact of publication bias can be thought of as disrupting the incremental accumulation of evidence via a cumulative meta-analysis. If the cumulative meta-analysis of the meaningful outcome using all evidence crosses the threshold of significance earlier than would have occurred solely with published studies, then this difference in time can translate into a difference

	in outcomes and costs. If there is no difference in the time at which the weight of evidence crosses this threshold, there is no need to conduct any further analyses.[72]
Event modeling	To quantify the impact of unpublished information in the situation where there was differential timing, a decision model may be created comparing two scenarios, 'published studies only' and 'comprehensive set of studies. For both of these scenarios, the structure of the tree is exactly the same. In the 'published' scenario, the decisions do not change over time to reflect what actually happened. In the 'all' evidence scenario we model a shift in decision making based on differential timing and market response.
Treatment and Event Cost	The modelling of the clinical impacts should be drawn from the best available and most current information, not just what was available at the time, to reflect the true impact. For example, in the case where a drug was found to have an adverse event via a disclosure of a large release of previously unpublished data or a large and definitive trial, the rate of events used in the model must reflect our best current understanding of the event rate. For drug cost, the estimate of difference in drug cost should be based on the expected market shifts and the costs estimates at that time.

Before the framework can be applied, it is necessary to verify that quantitative pooling is appropriate and that there is in fact publication bias. Determining whether a set of evidence is appropriate for meta-analysis is the focus of numerous textbooks[73,74] and so we assume the analyst using this framework has some degree of familiarity with the methods of systematic reviews and meta-analysis. After determining that the evidence is suitable to quantitatively pool and analyze, the next step is to determine whether there is evidence of publication bias. There are numerous methods available including visual inspection of a funnel plot,[59] Egger's regression[75] as well as Trim and Fill.[76]

4.3.2 *Did bias affect decision making*

Following a positive determination that bias was present in the published evidence, the next step is to estimate its effect on decision making. This requires the evaluation of three elements. First, was there apparent publication bias on a meaningful outcome? Next, did the evidence cross a relevant clinical threshold for this outcome (e.g. statistical significance or a minimally important difference)? Finally, after crossing this threshold was there an attributable and measurable change in decisions? We will consider each of these, in turn.

First, the definition of meaningful outcome focuses on clinical relevance rather statistical properties and is considered in the context of the treatment decision. For example, an increased probability of nausea for a new treatment for an aggressive form of cancer, compared to an alternative therapy, may be an acceptable risk if the trade-off is increased survival; and the difference less meaningful. On the other hand, if there is an increased probability of major cardiovascular events with a newly marketed headache medication when several suitable alternatives are available, this difference would be very meaningful, as a debilitating cardiovascular event could be avoided when a number of available alternative treatments exist. The availability of additional data in the latter example would likely have a larger influence on clinician decision-making.

Second, there is a need to identify the magnitude of treatment effect that would be persuasive to clinicians. Using the second example above, the magnitude of effect for treatment of headache would need to be very large before it would outweigh the risk of an adverse cardiovascular event. For our purposes, we have used examples where there is historical evidence that a certain magnitude of effect and amount of uncertainty resulted in a shift in prescribing. In economics, this is defined as ‘revealed preference’ where consumers have demonstrated in how certain information affects their choice. Where this historical information is not available, ‘stated methods’ such as discrete choice experiments could also be to elicit what the predicted response would be to certain clinical effect. Third, is to determine if there is a measurable change in treatment decisions that can be linked to the clinical threshold. The nature of the decision and the availability of suitable alternatives determine whether the unpublished evidence may have had an effect. If no change can be identified in the rate of use of a treatment, then this criterion for a clear decision was not met.

4.3.3 *Was there an impact of the bias on costs and outcomes*

The final step is to determine the degree of impact on patient outcomes and healthcare costs. To start, it is necessary to compare the cumulative meta-analyses for the two evidence streams: comprehensive and published-only. For each of these streams it will be necessary to translate the accumulation of evidence into a date at which the pre-determined outcome of interest crossed its associated threshold. The difference in time to the pre-determined clinical threshold between these two evidence streams represents the primary window for which the unpublished information could have resulted in clinical and economic impact. If, however, these two streams of evidence crossed their threshold at the same time, the withheld evidence could not, by definition, have had any impact.

For the time-period during which patients and/or healthcare providers would have made different treatment decisions had they had access to a comprehensive set of studies, the clinical and economic impact can be estimated. The method for estimating this impact is a decision model that compares two scenarios. The first scenario represents the historical case where decision-making occurred with only published studies. This is compared to a scenario where a comprehensive set of studies is available, leading to a shift in the mix of treatments used for these same patients. By modeling the expected clinical outcomes and costs for each scenario, we can then estimate the incremental difference.

4.3.4 *Rofecoxib Case Study*

For rofecoxib we had access to studies from a number of different systematic reviews (See Appendix).[77-81] Most notably, Ross et al.[81] pulled data on the safety of rofecoxib versus placebo from judicial proceedings that included all trials that the manufacturer, Merck, was aware of. These reviews were all cross-referenced for the sake of completeness (See Appendix). There was some controversy at the time that rofecoxib's perceived CV risk was in fact due to a cardioprotective effect for naproxen, another analgesic used in many of the trials. While this turned out to not be true we still conducted analyses both with and without non-placebo controls to determine if this made any difference to our conclusions. Additionally, as the trials had highly variable time to follow-up we conducted analyses with both person-year and population denominators. For each of these two dimensions, type of control arm (active control or placebo) and denominator (population or person year), we conducted Mantel-Haenszel[82,83] (fixed effect), DerSimonian-Laird[84] (random effect) and Peto[54] (inverse variance) as well as adjusting with and without zero cells. This created 30 possible meta-analyses. For all of these analyses, I^2 was very low suggesting acceptable levels of heterogeneity. Our comparison of the means for the published versus unpublished data sets via Students T-test showed significant differences but this was not shown on a funnel plot via Egger's regression. However, this reflects that there is evidence for publication bias.

Our threshold for clinical decision-making for rofecoxib was cardiovascular thrombotic events odds ratio greater than 1. Rofecoxib was associated with a rare but significant adverse event of cardiovascular thrombotic events (myocardial infarction, thrombotic stroke or CV Death). Revealed preferences demonstrate that this is a meaningful outcome sufficient to change treatment decisions in providers. This was the level of evidence that prompted a recall of rofecoxib by the US Food and Drug Administration. There are a number of suitable alternatives to rofecoxib including celecoxib, naproxen and ibuprofen that depending on dose can provide comparable levels of pain relief with relatively few side effects. In fact it has been shown that this was, in fact, the case with former rofecoxib patients switching treatment to a wide variety of analgesics following the withdrawal of rofecoxib from the market.[85]. While the published and unpublished data sets did show noticeable difference overall at the end, none of our statistical models showed an earlier conclusion being reached via cumulative meta-analysis for the comprehensive data set rather than the published-only data set. Our cumulative meta-analysis for all studies compared to only published studies suggests that there was no difference in the time that level of evidence for our outcome of interest crossed our threshold for decision making (See Appendix). In fact, under several models, evidence became significant faster under just the published evidence. Ultimately while the published and unpublished data sets appear to show some level of bias in publishing and the complete set of information was enough to have the medication withdrawn from the market, the added evidence from the unpublished studies did not allow for a conclusion to be reached any sooner. As there was not differential timing of the availability of information, no differential number of events can be modelled for our published studies and all studies scenario.

4.3.5 *Rosiglitazone*

For rosiglitazone, we utilized data from the Nissen and Wolski meta-analysis that evaluated the risk of MI and CV death.[53] After concerns were raised about the cardiovascular safety of rosiglitazone, the manufacturer disseminated all trial results for both published and unpublished trials to a publicly accessible database. These trials were meta-analyzed by Nissen and Wolski who evaluated the risk of myocardial infarction and cardiovascular death.[53] Nissen and Wolski screened 116 trials of which 35 were ultimately included. Only 9 of these 35 trials were previously published in a peer-reviewed journal (See Appendix). The inclusion criteria for this analysis was trials phase 2 or later with a randomized comparator, greater than 24 weeks of exposure to treatment, and a similar level of exposure in treatment and control groups. This data set includes all trials of which the manufacturer was aware, that occurred prior to 2007 when the shift in prescription patterns occurred. The I^2 statistic[58] for all statistical models evaluated was 0% suggesting low levels of heterogeneity.[58]

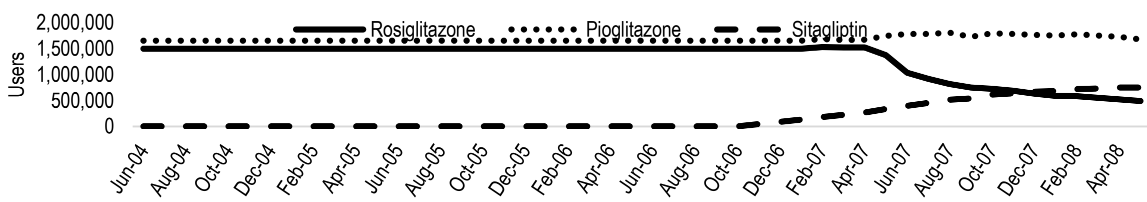
To assess the difference between the odds ratio for published and unpublished we performed a two-sample z-test with two-sided alpha of 0.05 (See Appendix). This analysis showed no statistically significant differences between published and unpublished data sets for any model evaluated. Additionally, Visual inspection of the funnel plots for all models considered does not suggest any pattern of publication bias (See Appendix). Despite this lack of difference in effect between data sets, we continued with our analysis to determine if the missing studies while not directionally different could have provided greater certainty and therefore have led to a differential time to decision. For this purpose, we used the Peto[54] (inverse variance) method of pooling for the outcome of myocardial infarction (See Appendix). This was the same model used by Nissen and Woslki, MI risk with population denominators, unadjusted for zeros with Peto method for pooling. We also conducted a comprehensive analysis to identify how model choice effected results. For the event rate we used the person-year or population denominators.

Following the publication of the Nissen and Wolski analysis there was an immediate and significant change in prescription patterns for rosiglitazone.[86,87] This change in prescription pattern indicates that the endpoint of myocardial infarction had powerful influence for prescribers. While rosiglitazone was not removed from the market following the publication of the Nissen and Wolski analysis, the number of prescription dropped dramatically. Alongside this drop in rosiglitazone prescriptions, there was a nearly proportional rise in prescriptions for pioglitazone, another drug in the thiazolidinediones class, as well as sitagliptin, a dipeptidyl peptidase-4 inhibitor. This suggests that the decision resulting from the evidence presented by Nissen and Wolski was to shift prescriptions form rosiglitazone to other available non-insulin medications. Using the same model as Nissen and Wolski, we conducted a cumulative meta-analysis using all evidence, as well as just published evidence. This resulted in a 36-month difference in the time to reach the clinical threshold for decision-making (See Appendix). This result was highly sensitive to the model that was used, as only the Peto models for MI showed any time difference.

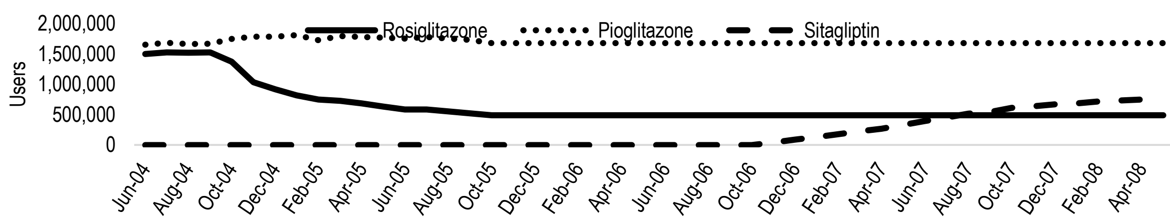
While a risk mitigation strategy was implemented for rosiglitazone, this was ultimately lifted in 2015 after the results of the RECORD trial failed to show a risk of myocardial infarction associated with the drug.[52] The implicit conclusion is that while rosiglitazone appeared to show a risk of cardiovascular events, this risk was negated by a subsequent larger study. This confirms our analysis as well with the observation that only the Peto based meta-analytic model showed a significant risk.

To calculate the economic impact from this case we use a minimal modeling approach, not to provide an exact estimate but to demonstrate the key concepts of the method. For the relative use of rosiglitazone as well as two alternatives, pioglitazone and sitagliptin, we drew from an analysis conducted in a commercially-insured plan in the US that tracked prescriptions before and after the publication by Nissen and Wolski.[87] While this analysis started in January 2007, we make the simplifying assumption that the number of users was constant between January 2004 until the start of their analysis (Figure 6: Economic Loss from Unpublished Evidence for Rosiglitazone, Panel A). While this analysis was focused on the shift in claims per million members, the authors also reported an absolute number of 5,117 rosiglitazone users per million members at the start of their study period, which we have extrapolated to the US population using census data. To generate a hypothetical scenario for a change with comprehensive evidence, we apply the same shift in prescribing 36 months earlier when the same evidence level that caused a market shift was present in the comprehensive evidence set (Figure 6: Economic Loss from Unpublished Evidence for Rosiglitazone, Panel B). We did not assume any changes to sitagliptin as this was approved in October 2006. From these two scenarios we calculated the difference in number treated by drug (Figure 6: Economic Loss from Unpublished Evidence for Rosiglitazone, Panel C). This represents the patients who theoretically would have been treated differently during this period had the evidence been published. To calculate drug cost, we multiplied the number treated by historical costs for each of drugs (Figure 6: Economic Loss from Unpublished Evidence for Rosiglitazone, Panel D).[88] While other analyses have attempted to calculate clinical effects,[64] in light of the new evidence that led the FDA to lift all prescribing restrictions on rosiglitazone we are limiting our analysis to only drug expense and are making the simplifying assumption that no clinical harm ensued to patients using rosiglitazone during this time period. This analysis ultimately showed $3.8B in unnecessary drug spending from providers prescribing a medication that they otherwise wouldn't have prescribed, given complete evidence.

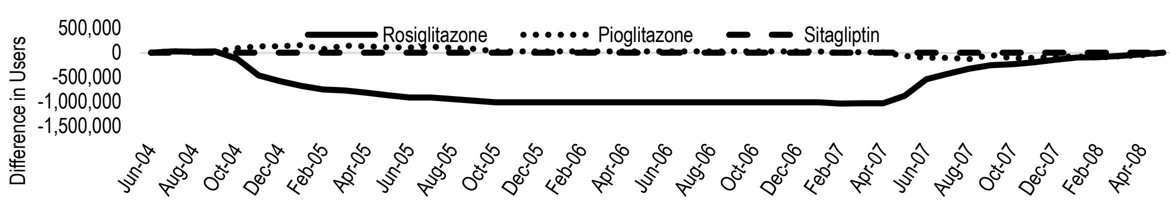
Panel A: Rosiglitazone Users under Publish-Only Evidence Scenario



Panel B: Rosiglitazone Users under Comprehensive Evidence Scenario



Panel C: Difference in Number of Users



Panel D: Difference in Drug Costs

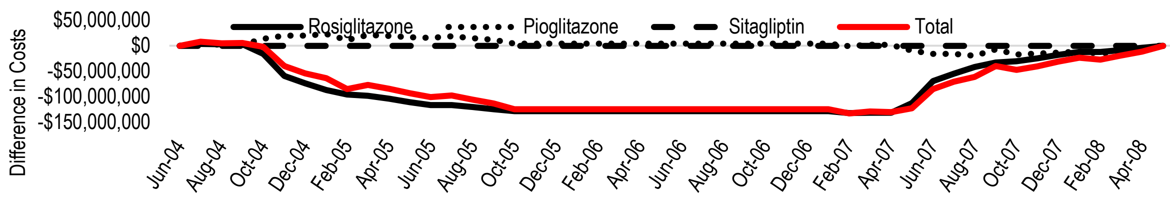


Figure 6: Economic Loss from Unpublished Evidence for Rosiglitazone

4.4 DISCUSSION:

We developed and implemented a framework to assess the impact of systematically unpublished results on clinical outcomes and healthcare cost. We subsequently applied this framework to two well-known examples: rofecoxib and rosiglitazone. For rofecoxib, while there was no immediately evident pattern of publication bias via funnel plot, the published and unpublished data sets did result in statistically different effect sizes for many of the models that we considered. This difference in effect size for the data sets did not represent any differential in time to our decision threshold. Without this difference in timing it is not possible to assign any impact to systematically withheld information. Ultimately, this means that while rofecoxib does appear to have a significant effect on cardiovascular endpoints, the evidence for this association does not appear to have affected the time to a clinically meaningful decision.

For rosiglitazone, a very different pattern emerged. While cumulative meta-analysis under the model used by Nissen and Wolski did reveal results that crossed our decision threshold 36 months sooner if all evidence had been available, the differences between published and unpublished data sets via traditional meta-analysis was not readily apparent. This suggests that by the time a traditional meta-analysis would have been performed, the published and unpublished data sets had largely converged on their pooled effect size. Instead, the unpublished evidence allowed decreasing uncertainty from the larger sample size, which would have allowed for an earlier determination of risk. Arguably, this highlights the added value of performing a cumulative meta-analysis as a means of identifying potential publication bias. Additionally, we conducted a minimal modeling exercise to show that this difference in time to reaching a clinically meaningful decision threshold let to approximately $3.8B in additional drug spend. In other words, had the comprehensive set of studies been made available immediately, and prescribers responded the same way to this level of evidence if it were released over time, they would have made different prescribing decisions resulting in $3.8B less expense on drugs. This difference in price was driven primarily by patients being treated with cheaper alternatives. Given that the RECORD trial showed no risk of myocardial infarction associated with rosiglitazone we have assumed that there were no difference in clinical effects.[52]

While other researchers have considered the value of information gained from future studies,[89,90] the economic return on particularly informative studies that have already been completed,[91] or the clinical impact from the use of a medication that we later find out to be harmful[63,64] none have yet created a framework for quantifying the impact of systematically withheld evidence. Broadly speaking, in contrast to previously conducted analyses, our work does not attempt to quantify the positive impact of planned or completed research that is assumed to be communicated and incorporated into decision-making. Instead, our analysis creates a framework for quantifying the clinical and economic impact from research that never had a chance to be incorporated into decision-making. In this way, rather than evaluating economic return, we have proposed a first step to quantifying the economic loss of a key component in the inefficiency of clinical research.

While this analysis represents the first attempt to define the factors that might influence economic impact from publication bias, there are some limitations. First, in both of our case studies, the endpoint we are evaluating is an adverse event for which even small risks may be unacceptable, given other treatment options available to patients. While not impossible, the same process would have been much more complicated had each endpoint considered not had such a clearly defined threshold. For example, if a case study were selected with an efficacy endpoint, much more effort would need to be devoted to rigorously defining the minimal clinically important differences (MCID). Additionally, in our analysis we intentionally chose cases wherein there was both a robust set published and unpublished data, and for which the result of a sudden release of previously unpublished evidence resulted in a shift in prescribing patterns. This was necessary to evaluate the validity of our framework, but is rather unique and arguably limits the generalizability of our assessment.

Publication bias represents a tremendous waste and inefficiency in the process of the conduct of clinical research. Nearly 60% of all studies reviewed by the FDA are never published as a full manuscript in a peer-reviewed journal[14] and half of studies approved and monitored by an ethics committee or IRB for which results are available, remain unpublished. [7-13] It is impossible for trials to provide a societal return on a funder's investment when the results are not disseminated for the benefit of other researchers or decision-makers. Quantifying the exact impact of this unpublished evidence, even in the clearest scenarios, can be complicated and assumption driven.

We have attempted to address this issue by creating a framework to quantify the impact of systematically withheld evidence in two notable case studies. While in the case of rosiglitazone we did find that the same level of evidence that caused a market shift had been available sooner, this result is limited by the fact that the conclusion of evidence crossing our threshold for decision-making was highly dependent on the choice of statistical model for pooling evidence. Ultimately, this leads us to be cautious about any approaches that claim to quantify the impact of previously unpublished research.

While our study did not identify a clinical impact for publication bias in the two cases considered, for rosiglitazone we found an inefficiency in prescribing patterns that may have resulted in an additional $3.8B in drug spending. Additionally, our analysis highlights the difficulties in attributing effect to work that goes unpublished. That being said, we believe the frame of combining cumulative meta-analysis with value of information analysis has the potential to better define the impact of studies that go unpublished as delaying the time to a clinically-meaningful decision threshold.

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APPENDIX

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Appendix Table 1: Search Terms

Data Source	Search terms	Limits
Cochrane Methodology Register	“publication bias”	None
Cochrane Database of Systematic Reviews	“publication bias”	None
Medline via PubMed	“publication bias”	English Language
Medline via PubMed	“publication bias”	English Language Systematic Review or Meta-Analysis (An ancestry method will be applied to identify studies from this search)
MedLine via MeSH	"Publication Bias"[Mesh]	English Language 1994 and after[1]
EmBase	“publication bias”	English Language Not in MedLine
CINAHL Plus	“publication bias”	English Language

[1] This MeSH term added to database in 1994

Appendix Table 2: Example 2x2 Table for Stern and Simes 1997[9]

	Significant	**Not Significant**	**Total**
Published	99	27	126
Not Published	47	45	92
Total	146	72	218

Appendix Table 3: Studies Published Within each Cohort by Characteristics

Name	t	All Studies	Results Favor.	Unfavor.	Significance p<0.05	p>0.05	Funding Source Ind	Non-Ind	No. of Centers Single	Multicenter	Study Phase 1/2	3/4	Design RCT	Other	Country US/NA	Other	Sample Size	Small	Large
Conference Abstract Method of Tracking																			
Bellefeuille et al. '92[92]	5	103/197	48/65	10/31								20/31				103/197			
Landry 1996[93]	5	44/168	24/114	20/54															
Callaham et al. 1998[94]	5	113/227	77/153	36/74															
Evers 2000[95]	3	85/151			43/69	41/82							85/151				31	40/75	46/76
Kiroff 2000[96]	5	174/298	98/139	76/159															
Eloubeidi et al. 2001[97]	4	113/351	36/98	77/353					94/374	19/77			14/41	99/410	81/350	32/101			
Klassen et al. 2002[98]	8	255/422	162/235	93/187															
Timmer et al. 2002[99]	6	392/836			86/177	94/213	102/154	93/128							71/147	112/243			
Bhandari et al. 2002[100]	5	159/465													148/412	11/53			
Krzyzanowska et al. '03[101]	5	133/510	35/183	98/327	42/223	92/287	13/74	120/436	18/67	115/443			133/510				500	39/124	97/386
Hashkes & Uziel 2003[102]	4	56/126	54/112	2/14															
Ospina et al. 2006[103]	5	194/383	80/154	4/7	84/161	110/222			165/322	29/61			194/383		169/339	25/44			
Zamakhshary 2006[104]	2	118/183			105/151	13/32									90/143	28/40			
Harris et al. 2006[105]	6	62/200	45/132	17/68	12/24	50/176							1/3	61/197	21/55	41/145			
Peng et al. 2006[106]	5	237/473	189/337	13/26									55/84	182/389					
Glick et al. 2006[107]	4.5	607/1147			208/397	95/234	45/66	562/1081	387/776	220/371			39/64	568/1083	398/804	209/343			
Sanossian et al. 2006[108]	5	219/353	136/220	83/133			26/37	193/316	142/227	77/126					153/251	86/126	200	127/205	93/148
Harris et al. 2007[109]	5	175/318	123/203	53/115	68/99	6/11							11/18	165/300	153/283	23/35			
Smith et al. 2007[110]	2	740/1683	521/1481	86/202					487/1147	253/536			78/163	662/1520	461/1052	279/629	500	436/1024	281/559
Ha et al. 2008[111]	4.5	301/1097	288/982	13/115													50	202/745	99/352
Vecchi et al 2009[112]	4	359/581	120/161	239/420									284/455	75/126					
Kho & Brouwers 2009[113]	5	45/86	41/79	4/7			16/20	29/66					7/8	38/78	23/44	22/42			
Saeed et al. 2010[114]	5	43/141	20/53	23/88					33/119	10/22									
Kottachchi et al. 2010[115]	5	64/82	53/58	11/24			37/38	26/43							18/20	46/62			
Paulson et al. 2011[116]	5	217/501	164/327	11/33					153/381	58/101			141/294	76/207			40	65/145	73/141
Sinno et al. 2011[117]	5	78/138	57/103	21/35	38/55	40/83									53/104	25/34			
Harel et al. 2011[118]	5	127/300	104/211	12/29			23/46	104/254	72/182	55/118			11/18	116/282	50/137	77/163			
Polyzos et al. 2011[119]	5	89/155	44/65	45/89	49/83	40/72	56/94	33/61	7/129	19/26			89/155		5/14	84/141	250	68/113	12/18
Yoon et al 2012[120]	2	183/614							175/592	8/22			15/34	168/580					
Okike et al. 2012[121]	5	696/918	365/488	139/181			102/116	504/666							374/459	322/459	100	446/598	198/246

Salami et al. 2013[122]	5	114/184	86/123	28/61	46/66	5/10			70/121	44/63					110/170	4/13			
Cohen et al. 2013[123]	5	309/378	281/343	28/35					157/205	152/173			24/26	285/352					
Izadpanah et al 2014[124]	6	73/128	57/98	19/30	34/57	41/71									6/13	72/115			
Livas et al. 2014[125]	6	308/590			201/340	81/145													
Menditto et al. 2015[126]	5	43/298							4/17				5/8	29/177			100	16/212	27/86
Wilson et al. 2015[127]	5	97/250	87/209	10/41															
Regulatory Submission Method of Tracking																			
Melander et al. 2003[128]	8	25/42	19/21	6/21															
Bardy 1998[129]	7	68/188	52/111	16/77															
Rawal & Deane 2014[130]	2	784/882									400/465	368/401							
Rawal & Deane 2015[131]	2	312/340									191/213	119/124							
Khan et al. 2014[132]	2	85/143	64/74	31/53			65/101	36/42	30/38	65/100	48/78	39/51	85/143						
Braend et al. 2016[133]	5	135/191					130/184	5/7			6/14	100/105							
Urrutia et al. 2016[134]	10	168/303					126/226	42/72											
Lee et al. 2008[14]	5	394/909			285/432	52/144	394/909			394/909		394/909	329/602	38/98			135	120/443	273/440
Turner et al. 2008[135]	3	45/62	37/38	8/24															
Turner et al. 2012[136]	5	20/24	15/16	5/8															
Roest et al. 2015[137]	2	48/57	40/41	9/16															
Rising et al. 2008[138]	5.5	128/164	90/114	38/50									127/163	1/1					

t=Time to define publication, RCT=Randomized Controlled Trial, US-=United States, NA=North America, Favor=Favorable, Unfavor=Unfavorable

Appendix Table 4: Studies Published Within each Cohort by Characteristics Continued

Name	t	All Studies	Results		Significance		Funding Source		No. of Centers		Study Phase		Design		Country		Sample		
			Favor.	*Unfavor.*	*p<0.05*	*p>0.05*	*Ind*	*Non-Ind*	*Single*	*Multicenter*	*1/2*	*3/4*	*RCT*	*Other*	*US/NA*	*Other*	*Size*	*Small*	*Large*
Funder Records Method of Tracking																			
Dickersin & Min '92[139]	7	184/198	121/124	63/74	121/124	63/74		184/198	109/120	75/78			119/126	59/64	184/198		100	76/84	102/107
Ioannidis 1997[140]	5	36/66	15/27	11/39															
Misakian & Bero 1998[141]	10	39/50			24/28	15/22	7/8	32/42					3/3	36/47			500	18/20	21/30
Cronin 2004[142]	6	49/70	26/34	23/36															
Gordon et al. 2013[143]	4	183/244	74/98	77/134				183/244					183/244				1000	135/195	47/49
Ethics Committee Method of Tracking																			
Easterbrook et al. '91 [12]	3	207/285			93/154	45/131													
Dickersin et al. 1992[13]	5	390/514			259/314	131/200	27/42	362/470	258/359	122/144			136/168	254/346	309/514		100	208/275	170/226
Stern and Simes 1997[9]	4	126/218			99/146	27/72					45/70	51/97	46/88	50/79			100	100/180	82/134
Cooper et al. 1997[144]	8	55/117			53/72	2/45													
Decullier et al. 2005[11]	6	190/501					131/407	59/94	89/291	101/210			90/232	100/269			150	138/389	48/106
Decullier et al 2006[145]	5	32/47	26/37	6/10			9/10	13/18											
Turer et al. 2007[146]	7	110/197					83/152	27/45			58/105	52/92					500	78/143	24/43
Hall et al. 2007[147]	10	84/190					60/130	24/60			9/40	59/103	55/90	29/100		84/190			
von Elm et al. 2008[148]	8	233/451					182/366	51/85	51/105	182/346			233/451			233/451			
Blumle et al. 2008[7]	7	109/225					56/119	18/36	41/83	68/142			54/103	9/21		109/225	120	59/109	47/106
Decullier et al. 2009[149]	8	107/151	97/196	10/62							18/83	89/175							
Sune et al. 2013[150]	5	380/785	180/212	128/186			341/697	39/88			76/184	304/601	315/590	65/195			500	227/520	153/246
Decullier et al. 2014[151]	8	53/73			51/67	2/6													
Begum et al. 2015[152]	3	37/116					3/24	24/92	16/53	21/63							100	23/69	14/47
Kirkham et al. 2016[153]	5	167/308					119/198	20/40	28/65	139/243									
Clinical Trial Registration Method of Tracking																			
Ross et al. 2009[154]	2	311/677					144/357	224/442					124/221	16/27	148/339	87/192	160	120/282	131/283
Ramsey 2009[155]	1	357/2028					36/614	321/1414			272/1655	78/320	96/490	261/1538					
Bourgeois et al. 2010[156]	2	362/546					271/407	91/139											
Xuemei et al. 2010[157]	1	152/443					16/67	136/376					105/316	23/81		152/443			

Gandhi et al. 2011[158]	1	15/33			9/19	6/14									
Prenner et al. 2011[159]	2	35/64			21/40	14/24	15/36	20/28							
Shamliyan 2011[160]	2	28/166			18/132	10/34	2/43	23/94	26/145	2/21					
Smith et al. 2012[161]	2	25/101			3/40	20/81									
Ross et al. 2012[162]	2.5	266/636				266/636	92/198	50/89	221/451	10/19	241/524	25/45	100	149/334	133/278
Shamliyan 2012[163]	2	214/738			82/341	37/90	46/177	118/392	158/494	56/244					
Vawdrey et al. 2013[164]	3	47/62	35/38	12/24											
Jones et al. 2013[165]	4	414/585			318/468	137/168	43/81	330/452							
Guo et al. 2013[166]	10	11/35			5/25	6/10	5/26	6/9							
Riveros et al. 2013[167]	1	202/297			182/267	20/30		202/297			152/209	50/88			
Thorn et al. 2013[168]	3	43/100			36/81	3/7							120	6/30	37/70
Shamliyan et al. 2014[32]	3	12,938/137,607			4,810/51,567	8,128/86,040	3,261/47,044	5,617/37,339	9,399/71,535	33,382/62,293					
Son et al. 2016[169]	1	62/161			44/118	18/43	4/17	25/45							

t=Time to define publication, RCT=Randomized Controlled Trial, US-=United States, NA=North America, Favor=Favorable, Unfavor=Unfavorable

Appendix Table 5: Rosiglitazone Evidence

Manufacturer Study ID	Completion Date	Indication	ROS Dose	Arm	Age	%Male	Duration	**Cardiovascular Thrombotic Events Number** *Rosiglitazone Arm(s)* *Total*	*MI*	*CV Death*	*Control Arm* *Total*	*MI*	*CV Death*
					PUBLISHED EVIDENCE								
			8mg	ROS	60.7	66.9							
49653/011[170 a]	09/97	T2D	4mg	ROS	59.6	64.5	24wk	357	2	1	176	0	0
				PBO	58.8	65.8							
			8mg	ROS	60.9	57.6							
49653/020[a]	05/98	T2D	4mg	ROS	60.4	68.2	52wk	391	2	0	207	1	0
				GLY	60.1	70.4							
			4mg QD	ROS	57.5	58.6							
			2mg BID	ROS	56.8	59.1							
49653/024[a]	02/98	T2D	8mg QD	ROS	58.9	65.7	26wk	774	1	0	185	1	0
			4mgBID	ROS	56.5	59.9							
				PBO	57.7	68.8							
			8mg	ROS+MET	57.8	60.0							
49653/093[a]	04/98	T2D poorly controlled on MET	8mg	ROS	58.8	53.7	26wk	213	0	0	109	1	0
				MET	59.5	67.0							
			8mg	ROS+MET	58.3	68.2							
49653/094[a]	03/98	T2D poorly controlled on MET	4mg	ROS+MET	57.5	62.1	26wk	232	1	1	116	0	0
				MET	58.8	74.3							
49653/284	02/03	T2D	4/8mg	ROS+MET	55.5	51.1	24wk	382	1	0	384	0	0
				MET	55.6	51.0							
			4mg	ROS+SUL	60.6	53.2							
49653/015	03/98	T2D	2mg	ROS+SUL	61.0	62.8	24wk	395	2	2	198	1	0
				SUL	61.9	57.3							
49653/080	05/00	T2D	8mg	ROS	55.1	75.0	156wk	104	1	0	99	2	0
				GLY	56.1	70.1							
			8mg	ROS+INS	57.7	54.3							
49653/082	08/98	T2D poorly controlled by insulin	4mg	ROS+INS	57.1	56.6	26wk	212	2	1	107	0	0
				INS	55.6	55.8							
49653/125	08/00	T2D	4mg	ROS+SUL	54.6	45.7	26wk	175	0	0	173	1	0
				SUL	57.3	42.4							
49653/145	11/00	T2D	8mg	ROS+SUL	61.1	57.3	26wk	231	1	1	242	0	0
				SUL	61.9	62.7							
49653/147	08/00	Indo-Asian T2D	8mg	ROS+SUL	54.3	20.2	26wk	89	1	0	88	0	0
				SUL	54.1	25.3							
49653/162	04/02	T2D	8mg	ROS+GLY	60.0	55.1	26wk	168	1	1	172	0	0
				GLY	59.9	61.8							
			4mg	ROS+SUL	58.9	47.6							
49653/132	02/00	Chinese T2D	8mg	ROS+SUL	59.0	41.4	24wk	442	1	1	112	0	0
				SUL	58.8	45.7							
DREAM	08/03	Poor glucose tolerance	4/8mg	ROS	54.6	41.7	156wk	2635	15	12	2634	9	10
				PBO	54.8	39.9							
			4mg	ROS	56.3	55.7							
ADOPT	06/02	New T2D		MET	57.9	59.4	208wk	1465	27	2	2895	41	5
				GLY	56.4	58.0							
					UNPUBLISHED EVIDENCE								
100684	07/05	Korean T2D	4/8mg	ROS+GLY	55.2	53.5	52wk	43	0	0	47	1	0
				GLY	54.5	45.6							
49653/143	01/03	T2D poorly controlled on GLY	8mg	ROS+GLY	52	45.3	24wk	121	1	0	124	0	0
				GLY	53	48.3							
49653/211	11/03	T2D w/CHF	4mg	ROS+UC	64.3	84.3	52wk	110	5	3	114	2	2
				UC	63.9	79.0							
			8mg	ROS+MET	54.6	63.2							
712753/008	12/05	T2D poorly controlled on MET	4mg	ROS+MET	56.0	65.2	48wk	284	1	0	135	0	0
				MET	56.9	53.4							

[a]Included in original approval package , T2D=Type 2 diabetes, ROS=rosiglitazone, MET=Metformin, GLY=glyburide, SUL=sulfonylureas, CHF=chronic heart failure, wk=week, MI=myocardial infarction, CV=cardiovascular, INS=insulin, PBO=placebo, UC=usual care, QD=once daily, BID=twice daily, mg=milligrams

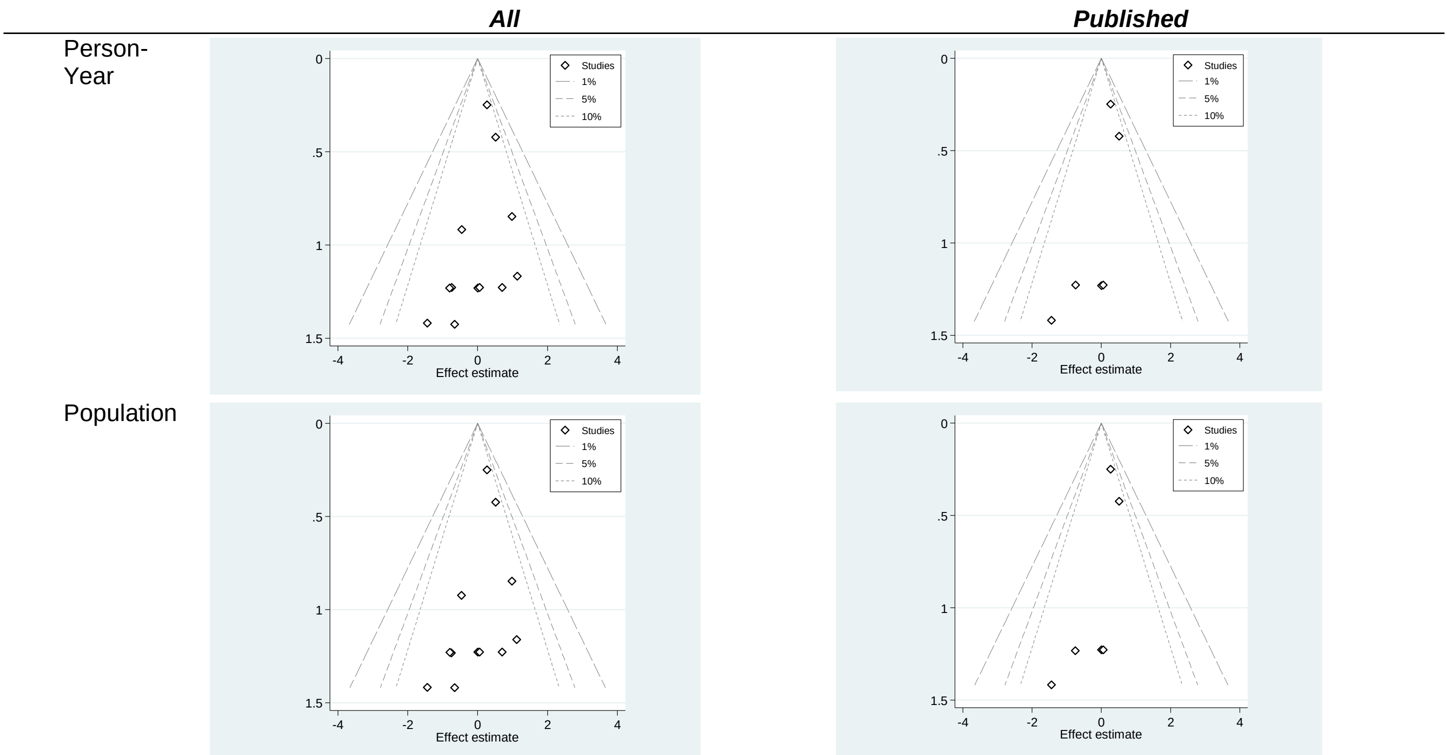
Appendix Table 6: Rosiglitazone Evidence[81] Continued

Manufacturer Study ID	Completion Date	Indication	ROS Dose	Intervention	Age[1]	%Male[1]	Duration	Cardiovascular Thrombotic Events Number					
								Rosiglitazone Arm(s)			*Control Arm*		
								Total	*MI*	*CV Death*	*Total*	*MI*	*CV Death*
				UNPUBLISHED EVIDENCE									
49653/079	03/98	T2D poorly controlled on GLY	4mg 4mg	ROS ROS+GLY GLY	59.1 57.7 58.5	63.6 69.4 66.7	26wk	203	1	1	106	1	1
49653/085	06/01	T2D	4/8mg	ROS+INS INS	61.3 61.5	54.0 46.8	26wk	138	3	1	139	1	0
49653/095	12/98	T2D poorly controlled on insulin	8mg 4mg	ROS+INS ROS+INS INS	57.4 57.8 58.9	58.9 63.9 45.3	26wk	196	0	1	96	0	0
49653/097	01/01	T2D	8mg	ROS GLY	55.8 56.0	72.1 70.8	156wk	122	0	0	120	1	0
49653/127	12/99	T2D poorly controlled on GLY	8mg	ROS+GLY GLY	60.0 59.4	51.0 66.0	26wk	56	1	0	58	0	0
49653/128	06/00	T2D on concurrent SU	4mg	ROS PBO	58.3 57.7	51.3 42.1	28wk	39	1	0	38	0	0
49653/134	08/00	T2D on GLY and MET	8mg 4mg	ROS+GLY+MET ROS+GLY+MET GLY+MET	55.5 55.6 55.8	62.0 58.0 61.0	28wk	561	0	1	276	2	0
49653/135	10/02	Elderly T2D	4/8mg	ROS+GLP GLP	68.7 68.2	74.1 71.2	104wk	116	2	2	111	3	1
49653/136	11/00	T2D with CRF on SU or INS	4/8mg	ROS+SU+INS SU+INS	61.1 61.9	57.3 62.7	26wk	148	1	2	143	0	0
49653/234	02/02	T2D	8mg 4mg	ROS+GLM ROS+GLM GLM	62.9 60.5 65.0	44.0 57.0 60.0	26wk	116	0	0	61	0	0
49653/330	10/04	Chronic Psoriasis	8mg 4mg 2mg	ROS ROS ROS PBO	44.3 44.8 45.0 44.5	65.0 66.0 63.0 63.0	52wk	1172	1	1	377	0	0
49653/331	10/04	Chronic Psoriasis	4mg 2mg	ROS ROS PBO	44.9 45.2 46.4	64.1 62.0 58.3	52wk	706	0	1	325	0	0
49653/137	03/04	T2D	>2mg	ROS+MET GLY+MET	60.0 58.8	63.4 68.9	32wk	204	1	0	185	2	1
SB-712753/002	06/04	T2D poorly controlled	4/8mg	ROS+MET MET	58.1 57.6	58.3 56.8	24wk	288	1	1	280	0	0
SB-712753/003	12/04	Mild T2D	4/8mg	ROS+MET MET	58.9 59.0	54.7 55.5	32wk	254	1	0	272	0	0
SB-712753/007	12/04	T2D previously treated	2/8mg 4/8mg	ROS+MET ROS MET	50.1 51.5 50.6	57.4 56.5 58.5	32wk	314	1	0	154	0	0
SB-712753/009	11/04	T2D on insulin	8mg	ROS,MET+INS INS	57.2 56.9	51.8 53.1	24wk	162	0	0	160	0	0
AVA100193	05/05	Mild to Moderate Alzheimer's Disease	2mg 4mg 8mg	ROS ROS ROS PBO	71.0 70.0 71.0 72.0	44.1 43.8 34.1 36.9	24wk	394	1	1	124	0	0
AVM100264	01/06	T2D with high BMI poorly controlled on MET	4/8mg	ROS+MET MET+SUL	58.5 59.3	52.7 52.5	52wk	294	0	2	302	1	1
BRL49653C/185	05/02	T2D	4mg 4mg	ROS+MET ROS MET UC	58.0 59.0 60.0 57.0	65.2 60.2 56.4 60.9	32wk	563	2	0	142	0	0
BRL49653/334	11/04	T2D	4/8mg	ROS PBO	67.7 67.3	44.8 47.7	52wk	278	2	0	279	1	1
BRL49653/347	04/04	T2D poorly controlled on INS	4mg 2/4mg	ROS+INS ROS+INS INS	52.6 52.7 53.8	48.1 60.0 46.2	24wk	418	2	0	212	0	0

[a]Included in original approval package , T2D=Type 2 diabetes, ROS=rosiglitazone, MET=Metformin, GLY=glyburide, SUL=sulfonylureas, CHF=chronic heart failure, wk=week, MI=myocardial infarction, CV=cardiovascular, INS=insulin, PBO=placebo, UC=usual care, QD=once daily, BID=twice daily, mg=milligrams

Appendix Table 7: Meta-Analysis Rosiglitazone

	Published Trials	Unpublished Trials	All Trials
Person Year Denominator	1.40 (0.95; 2.05)	1.49 (0.80; 2.76)	1.42 (1.03; 1.97)
Population Denominator	1.40 (0.95; 2.05)	1.49 (0.80; 2.76)	1.42 (1.03; 1.97)



Appendix Figure 1: Rosiglitazone Contour Enhanced Funnel Plots

Appendix Table 8: Rosiglitazone Cumulative Meta-Analysis

	Odds Ratio of Myocardial Infarction					
Date	***Published Only***	***Harbord***	***Peter***	***Meta-Trim (Fixed)***	***Meta-Trim (Random)***	***All Evidence***
9/1/1997	4.46 (0.23; 85.24)					4.46 (0.23; 85.24)
2/1/1998	1.06 (0.11; 10.18)			0.24 (0.02; 2.45)	0.24 (0.02; 2.45)	1.06 (0.11; 10.18)
3/1/1998	1.48 (0.20; 10.75)			0.24 (0.02; 2.45)	0.24 (0.02; 2.45)	1.48 (0.20; 10.75)
3/1/1998	1.26 (0.27; 5.83)	1.06 (0.00; 217,643,726.12)		0.51 (0.10; 2.52)	0.51 (0.10; 2.52)	1.26 (0.27; 5.83)
3/1/1998	1.26 (0.27; 5.83)	1.06 (0.00; 217,643,726.12)		0.51 (0.10; 2.52)	0.51 (0.10; 2.52)	1.03 (0.27; 4.01)
4/1/1998	0.86 (0.21; 3.62)	9.89 (0.00; 3,370,629.23)		0.51 (0.10; 2.52)	0.51 (0.10; 2.52)	0.77 (0.21; 2.81)
5/1/1998	0.91 (0.27; 3.11)	6.23 (0.00; 16,902.60)	0.02 (0.00; 0.32)	0.66 (0.18; 2.39)	0.66 (0.18; 2.39)	0.83 (0.27; 2.58)
8/1/1998	1.16 (0.37; 3.59)	7.86 (0.01; 11,110.73)	0.02 (0.00; 0.32)	0.66 (0.18; 2.39)	0.66 (0.18; 2.39)	1.03 (0.36; 2.98)
12/1/1998	1.16 (0.37; 3.59)	7.86 (0.01; 11,110.73)	0.02 (0.00; 0.32)	0.66 (0.18; 2.39)	0.66 (0.18; 2.39)	1.03 (0.36; 2.98)
12/1/1999	1.16 (0.37; 3.59)	7.86 (0.01; 11,110.73)	0.02 (0.00; 0.32)	0.66 (0.18; 2.39)	0.66 (0.18; 2.39)	1.19 (0.43; 3.29)
2/1/2000	1.22 (0.41; 3.69)	2.57 (0.01; 734.90)	0.02 (0.00; 0.32)	0.66 (0.18; 2.39)	0.66 (0.18; 2.39)	1.24 (0.46; 3.37)
5/1/2000	1.03 (0.38; 2.77)	1.03 (0.01; 106.45)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.07 (0.43; 2.66)
6/1/2000	1.03 (0.38; 2.77)	1.03 (0.01; 106.45)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.18 (0.48; 2.87)
8/1/2000	0.91 (0.35; 2.37)	1.70 (0.02; 132.59)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.06 (0.44; 2.52)
8/1/2000	1.02 (0.40; 2.60)	1.04 (0.02; 71.23)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.16 (0.50; 2.70)
8/1/2000	1.02 (0.40; 2.60)	1.04 (0.02; 71.23)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	0.91 (0.40; 2.05)
11/1/2000	1.14 (0.46; 2.83)	0.72 (0.01; 41.78)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	0.99 (0.45; 2.20)
11/1/2000	1.14 (0.46; 2.83)	0.72 (0.01; 41.78)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.07 (0.49; 2.35)
1/1/2001	1.14 (0.46; 2.83)	0.72 (0.01; 41.78)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	0.99 (0.46; 2.13)
6/1/2001	1.14 (0.46; 2.83)	0.72 (0.01; 41.78)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.13 (0.56; 2.32)
2/1/2002	1.14 (0.46; 2.83)	0.72 (0.01; 41.78)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.13 (0.56; 2.32)
4/1/2002	1.25 (0.52; 3.04)	0.53 (0.01; 26.48)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.21 (0.60; 2.43)
5/1/2002	1.25 (0.52; 3.04)	0.53 (0.01; 26.48)	0.75 (0.03; 18.94)	0.61 (0.20; 1.83)	0.61 (0.20; 1.83)	1.26 (0.63; 2.50)
6/1/2002	1.30 (0.84; 2.03)	1.29 (0.69; 2.41)	1.34 (0.80; 2.23)	0.93 (0.45; 1.94)	0.93 (0.45; 1.94)	1.30 (0.86; 1.95)
10/1/2002	1.30 (0.84; 2.03)	1.29 (0.69; 2.41)	1.34 (0.80; 2.23)	0.93 (0.45; 1.94)	0.93 (0.45; 1.94)	1.25 (0.84; 1.86)
1/1/2003	1.30 (0.84; 2.03)	1.29 (0.69; 2.41)	1.34 (0.80; 2.23)	0.93 (0.45; 1.94)	0.93 (0.45; 1.94)	1.28 (0.86; 1.89)
2/1/2003	1.33 (0.86; 2.06)	1.25 (0.68; 2.32)	1.34 (0.80; 2.23)	0.93 (0.45; 1.94)	0.93 (0.45; 1.94)	1.30 (0.88; 1.93)
8/1/2003	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.36 (0.96; 1.94)
11/1/2003	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.40 (1.00; 1.98)
3/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.37 (0.98; 1.93)
4/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.39 (0.99; 1.95)
6/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.41 (1.01; 1.97)
10/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.42 (1.01; 1.98)
10/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.42 (1.01; 1.98)

11/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.42 (1.01; 1.98)
11/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.43 (1.02; 1.99)
12/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.44 (1.04; 2.01)
12/1/2004	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.45 (1.05; 2.02)
5/1/2005	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.46 (1.05; 2.03)
7/1/2005	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.44 (1.04; 2.00)
12/1/2005	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.45 (1.04; 2.01)
1/1/2006	1.40 (0.95; 2.06)	1.34 (0.79; 2.29)	1.44 (0.99; 2.10)	1.08 (0.57; 2.03)	1.08 (0.57; 2.03)	1.42 (1.03; 1.97)
Date Significant						6/1/2004

TECHNICAL APPENDIX

There are a number of regression models that test for the presence of publication bias by measuring the association between study effects size (T_i) and some measure of its precision. When such an association is present it is suggestive that there may be a pattern of publication bias. This regression line is then evaluated for the scenario where within-study standard error is zero thereby predicting the result of a study with infinite sample size and thereby presumably estimating the underlying true global effect size (θ).[61] One of the most commonly used methods for doing this is the Egger regression. The Egger method was developed to better understand the discordance between meta-analyses and later published large trials that contradicted the results of the meta-analysis.[171] The plot of study level z_i against $prec_i$ that this regression corresponds to the Galbraith radial plot.[172] In the absence of any publication bias this method would predict the linear regression would travel through the origin on the radial plot ($\beta_0 = 0$). The slope of this regression indicates the direction and size of the global treatment effect (θ). This test has shown erratic performance and a high false positive rate with binary event data,[173-175] and so we have chosen not to use this method in our analysis. Instead the only regression-based methods we have utilized are the Harbord and Peter's regression.

The Harbord regression was developed to evaluate small study effects which is a broader term for the phenomenon of larger effect sizes in smaller trials that encompasses publication bias as well as other issues around trial quality and sample selection. The model is based on the component scores of the score test, the Z_i or efficient score and the score variance V_i. In practice, the Harbord regression is a test of non-zero slope in a linear regression of (Z_i/V_i) against $1/\sqrt{V_i}$ with weights of V_i.[45] The regression form of this model is expressed as ($Z_i/V_i = \beta_0 + {}^{\beta_1}\!/\!_{\sqrt{V_i}} + \omega_i$) where $\omega_i \sim$

$N(0, \sigma^2/_{V_i} \times \phi)$.[61] The validation of this test suggests that it significantly reduces the number of false positive results generated by Egger Test methods. The intercept for Harbord test provides the estimate of effect size adjusted for publication bias and small study effects.

The Peters regression uses an ordinary least squares regression that does not require structural dependence between effect size and variance. For a binary outcome, this takes the functional form:

$$E[\hat{\theta}_i] = \alpha + \frac{\beta}{a_i+b_i+c_i+d_i} + \varepsilon_i \text{ weighted by } \left(\frac{1}{a_i+b_i} + \frac{1}{c_i+d_i}\right)^{-1} \text{ where } \varepsilon_i \sim N(0, se_i^2 \times \phi)$$

with $a_i$and b_i representing those with the outcome of interest in the treatment and control groups respectively and $c_i$and d_i representing those without the outcome of interest in the treatment of interest and control arms of the i^{th}study.[61] Similar to Harbord above, this method reduces type 1 error but has the added advantage of breaking the structural dependence of effect size and variance in the regression form.[46]

Finally, we utilized the non-parametric Trim and Fill method to assess its performance in our cases. The 'Trim and Fill' method quantifies the asymmetry present in this plot in order to estimate how the overall effect size would change if studies were added to improve symmetry. The main intent of this procedure in practice is a sensitivity analysis of how responsive the results of a meta-analysis are to unpublished information. The main assumption of this method is that those studies with the most extreme lower-left effect sizes go unpublished. For the set of studies under consideration we first define (n) as the number of observed studies around the same clinical question. For this set of studies, there is an assumed global effect size (θ) that each study attempts to measure. Each study (i) produces an effect size (T_i) that approximates (θ) with a study-level variance of (v_i). As well as the (n) studies that were observed, the method assumes there were (k_0) unreported studies such that the true number of completed studies is defined as ($N = n + k_0$). There are three proposed estimators for (k_0) (equations 1a-c):

1a) $L_0 = \frac{4S_{rank} - n(n+1)}{2n-1}$, where S_{rank} is the Wilcoxon statistic

1b) $R_0 = \gamma - 1$, where γ is the length of the rightmost run of ranks ≥1 for $(T_i - \theta)$

1c) $Q_0 = n - (1/2) - \sqrt{2n^2 - 4S_{rank} + 1/4}$

The method works by in the following discrete and iterative steps:

a) The global effect size $(\hat{\theta}_n)$ is calculated using either a fixed or random effect model

b) This estimate $(\hat{\theta}_1)$ is used to calculate (S_{rank}) and thereby (k_0)

c) (k_0) number of studies are 'trimmed' from the right-hand side of the plot

d) A new adjusted global effect size $(\hat{\theta}_{n+1})$ is calculated using either a fixed or random effect model. Usually the value of $(\hat{\theta}_{n+1})$ will be to the left of $(\hat{\theta}_n)$ on the funnel plot

e) Steps b-d are repeated until the estimate for $(\hat{\theta})$ stabilizes, this usually happens in 2-3 iterations

f) All trimmed studies are then reflected around this final $(\hat{\theta})$ with the distance from this adjusted mean determined by their original (T_i)

g) Finally the $(\hat{\theta}_{adjusted})$ is recalculated including the reflected (k_0) studies on both sides of the final $(\hat{\theta})$ calculated in step f

In practice, various combinations of fixed and random effects models can be used for the trim and filling (steps a-f) and the final $(\hat{\theta})$ estimation (step g). Combined with the different potential estimators for k_0 (L_0, R_0, Q_0) this means that there are 12 potential ways to adjust via trim and fill methods. The relative performance of these three different methods is the subject of some debate among methodologists. For our purposes we chose the native adjustment methods within our Stata software package (L_0) to conduct only two analyses with either a fixed or random effect estimator for both trimming and filling.

Appendix Table 5: Rofecoxib Study Availability

ID	Study	Konstam et al 2001[77]	Reicin et al. 2002[78]	Weir et al. 2003[79]	Juni et al. 2004[80]	Ross et al. 2009[81]	Current Study
			PUBLISHED EVIDENCE				
R010	Ehrich et al.[176]				X	X	X
R029	Ehrich et al.[177]	X	X	X	X	X	X
R033	Saag et al.[178]	X	X	X	X	X	X
R035	Cannon et al.[179]	X	X	X	X		X
R040	Day et al.[180]	X	X	X	X	X	X
R044	Laine et al.[181]	X	X	X	X	X	X
R045	Hawkey et al.[182]	X	X	X	X	X	X
R058	Truitt et al.[183]	X	X	X	X	X	X
R085	Kivitz et al.[184]	X		X	X	X	X
R088	Bombardier et al.[69]	X		X			X
R090	Weaver et al.[185]	X		X	X	X	X
R102	Lisse et al.[186]	X		X	X		X
R112	Smugar et al.[187]					X	X
R116	Smugar et al.[187]					X	X
R136	Laine et al.[188]					X	X
R219	Birbara et al.[189]					X	X
R220	Birbara et al.[189]					X	X
R068	Schitzner et al.[190]	X		X	X	X	X
R097	Geusens et al.[191]	X		X	X	X	X
R098	Hawkey et al.[192]	X		X	X	X	X
R103	Hawkey et al.[192]	X		X	X	X	X
R078	Thal et al.[193]	X		X		X	X
R091	Reines et al.[194]	X		X		X	X
R118	Nickel et al.[195]					X	X
R120	Katz et al.[196]	X		X	X	X	X
R121	Katz et al.[196]	X		X	X	X	X
R122	Bresalier/Baron[197,198]					X	X
			UNPUBLISHED EVIDENCE				
R029 Ext.	Extension of Ehrich et al.[177]				X		X
R034	Saag et al Abstract	X	X	X	X		X
R083		X		X		X	X
R017						X	X
R096		X		X	X	X	X
R096 Ext.	Extension of R096				X		X
R097 Ext.	Extension of Geusens et al.[191]				X		X
R126				X		X	X
R125						X	X
R129						X	X

Appendix Table 6: Rofecoxib Evidence

										Cardiovascular Thrombotic Events					
										Rofecoxib			Control		
ID	**Reference**	**Date**	**Indication**	**(n)**	**Age**	**%Male**	**Duration**	**Doses**	**Control**	*events*	*PYR*	*Total*	*events*	*PYR*	*Total*
							PUBLISHED EVIDENCE								
R010	Ehrich et al.[176]	2/8/96	OA	219	63.5	29	6wks	25/125mg	Placebo	2	16	147	0	7	72
R029	Ehrich et al.[177]	2/5/97	OA	523	62.4	29	6wks	12.5/25/50mg	Placebo	3	46	378	0	16	145
R033	Saag et al.[178]	11/18/97	OA	515	61.0	25	6wks	12.5/25mg	Placebo	1	66	446	1	9	69
R035	Cannon et al.[179]	1/1/1998	OA	784	64.0	33	52wks	12.5/25mg	Diclofenac	3	516	516	3	268	268
R040	Day et al.[180]	1/1/98	OA	560	63.4	19	6wks	12.5/25mg	Placebo	2	72	486	0	11	74
R044	Laine et al.[181]	2/18/98	OA	558	61.5	32	24wks	25/50mg	Placebo	3	154	381	0	52	177
R045	Hawkey et al.[182]	2/18/98	OA	582	61.6	25	24wks	25/50mg	Placebo	3	157	388	3	61	194
R058	Truitt et al.[183]	4/1/98	OA	226	83.3	37	6wks	12.5/25mg	Placebo	1	21	174	0	6	52
R085	Kivitz et al.[184]	3/3/99	OA	632	63.8	33	6wks	12.5mg	Placebo	1	61	424	0	28	208
R088	Bombardier et al.[69]	1/1/2000	RA	8076	58.0	20	52wks	50mg	Naproxen	35	4047	4047	18	4029	4029
R090	Weaver et al.[185]	5/17/99	OA	586	62.3	31	6wks	12.5mg	Placebo	5	56	390	0	27	196
R102	Lisse et al.[186]	1/1/2003	OA	5586	63.0	29	12wks	25mg	Naproxen	7	646	2799	7	643	2787
R112	Smugar et al.[187]	9/8/00	OA	1065	61.4	32	6wks	12.5/25mg	Placebo	0	104	915	0	15	150
R116	Smugar et al.[187]	6/22/00	OA	622	62.0	33	6wks	25mg	Placebo	1	54	471	0	15	151
R136	Laine et al.[188]	2/5/02	OA	1215	61.0	26	12wks	25mg	Placebo	1	95	399	1	201	816
R219	Birbara et al.[189]	11/28/03	OA	238	59.8	29	6wks	12.5mg	Placebo	0	18	157	1	8	76
R220	Birbara et al.[189]	11/24/03	OA	244	60.9	35	6wks	12.5mg	Placebo	0	18	159	0	8	85
R068	Schitzner et al.[190]	9/10/98	RA	500	55.2	23	8wks	25/50mg	Placebo	1	49	332	0	24	168
R097	Geusens et al.[191]	6/6/00	RA	911	53.3	17	12wks	25/50mg	Placebo	0	137	612	0	62	299
R098	Hawkey et al.[192]	7/6/00	RA	440	51.5	16	12wks	50mg	Placebo	0	11	45	1	12	48
R103										0	44	174	0	45	173
R078	Thal et al.[193]	4/23/03	AD	1451	75.0	67	208wks	25mg	Placebo	78	1148	723	59	1374	728
R091	Reines et al.[194]	11/30/00	AD	692	75.3	47	52wks	25mg	Placebo	23	273	346	20	189	346
R118	Nickel et al.[195]	7/26/00	CNP	160	45.9	100	6wks	25/50mg	Placebo	0	15	102	0	8	58
R120	Katz et al.[196]	6/27/00	LBP	690	53.4	38	4wks	25/50mg	Placebo	1	28	252	0	14	128
R121										0	23	210	0	11	100
R122	Bresalier/Baron[197,198]	9/30/04	CA	2586	59.4	62	156wks	25mg	Placebo	64	3429	1287	42	3598	1299
							UNPUBLISHED EVIDENCE								
R029 Ext.	Extension of Ehrich et al.[177]	8/5/97	OA	438			26wks	12.5/25/50mg	Diclofenac	1	174	348	1	45	90
R034	Saag et al Abstract	6/1/97	OA	693	62	80	52wks	12.5/25mg	Diclofenac	2	463	463	2	230	230
R083		2/9/00	OA	198	63.1	54	64wks	25mg	Placebo	0	21	98	1	21	100
R017		5/21/97	RA	137	54.1	23	6wks	125/175mg	Placebo	1	8	69	0	7	68
R096		7/21/00	RA	760	56.4	26	12wks	12.5/25mg	Placebo	5	97	459	0	58	301
R096 Ext.	Extension of R096	7/21/00	RA	673			40wks	25/50mg	Naproxen	7	345	449	0	172	224
R097 Ext.	Extension of Geusens et al.[191]	11/6/00	RA	893			40wks	25/50mg	Naproxen	6	496	645	1	191	248
R126		5/30/01	AD	756	75.3	50	52wks	25mg	Placebo	12	193	380	11	100	376
R125		6/29/01	MP	172	39.8	16	12wks	25mg	Placebo	0	23	89	0	22	83
R129		5/14/02	FAP	17	40.2	29	24wks	25mg	Placebo	0	3	8	0	4	9

Table 7: Meta-Analysis Results Rofecoxib (Odds Ratio, 95%CI)

	Published Trials	Unpublished Trials	All Trials	
Person Year Denominator Unadjusted All Drugs				
Fixed Effect[1]	1.42 (1.16; 1.74)	1.04 (0.58; 1.85)	1.37 (1.13; 1.67)	P<0.05
Random Effect[2]	1.41 (1.15; 1.73)	0.95 (0.41; 2.21)	1.33 (1.08; 1.62)	
Peto Method	1.47 (1.20; 1.81)	1.07 (0.58; 1.95)	1.43 (1.17; 1.73)	P<0.05
I^2 Statistic[3]	0.0%, NS	19.9%, NS	0.8%, NS	
Person Year Denominator Adjusted All Drugs				
Fixed Effect[1]	1.46 (1.18; 1.79)	1.06 (0.58; 1.93)	1.41 (1.16; 1.71)	P<0.05
Random Effect[2]	1.42 (1.15; 1.76)	0.67 (0.34; 1.34)	1.34 (1.09; 1.63)	P<0.05
Peto Method	1.46 (1.19; 1.79)	1.06 (0.58; 1.92)	1.41 (1.16; 1.71)	P<0.05
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS	
Person Year Denominator Unadjusted Placebo Controls				
Fixed Effect[1]	1.40 (1.12; 1.76)	0.82 (0.40; 1.68)	1.34 (1.08; 1.66)	
Random Effect[2]	1.39 (1.10; 1.74)	0.90 (0.26; 3.06)	1.31 (1.05; 1.63)	
Peto Method	1.46 (1.16; 1.84)	0.82 (0.38; 1.77)	1.40 (1.12; 1.74)	
I^2 Statistic[3]	0.0%, NS	23.2%, NS	0.0%, NS	
Person Year Denominator Adjusted Placebo Controls				
Fixed Effect[1]	1.44 (1.15; 1.81)	0.82 (0.39; 1.72)	1.37 (1.10; 1.71)	P<0.05
Random Effect[2]	1.40 (1.11; 1.77)	0.59 (0.26; 1.36)	1.32 (1.05; 1.65)	P<0.05
Peto Method	1.44 (1.15; 1.81)	0.81 (0.38; 1.74)	1.38 (1.11; 1.71)	P<0.05
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS	
Population Denominator Unadjusted All Drugs				
Fixed Effect[1]	1.40 (1.14; 1.71)	1.43 (0.79; 2.56)	1.40 (1.15; 1.70)	
Random Effect[2]	1.38 (1.12; 1.70)	1.19 (0.63; 2.24)	1.36 (1.12; 1.66)	
Peto Method	1.44 (1.17; 1.77)	1.47 (0.83; 2.63)	1.44 (1.19; 1.75)	
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS	
Population Denominator Adjusted All Drugs				
Fixed Effect[1]	1.44 (1.15; 1.81)	0.82 (0.39; 1.72)	1.37 (1.10; 1.71)	P<0.05
Random Effect[2]	1.40 (1.11; 1.77)	0.59 (0.26; 1.36)	1.32 (1.05; 1.65)	P<0.05
Peto Method	1.44 (1.15; 1.81)	0.81 (0.38; 1.74)	1.38 (1.11; 1.71)	P<0.05
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS	
Population Denominator Unadjusted Placebo Controls				

Fixed Effect[1]	1.37 (1.09; 1.72)	1.35 (0.66; 2.75)	1.37 (1.10; 1.70)	
Random Effect[2]	1.35 (1.07; 1.70)	1.22 (0.57; 2.59)	1.34 (1.08; 1.67)	
Peto Method	1.42 (1.13; 1.79)	1.40 (0.67; 2.89)	1.42 (1.14; 1.77)	
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS	
Person Year Denominator Adjusted Placebo Controls				
Fixed Effect[1]	1.44 (1.15; 1.81)	0.82 (0.39; 1.72)	1.37 (1.10; 1.71)	P<0.05
Random Effect[2]	1.40 (1.11; 1.77)	0.59 (0.26; 1.36)	1.32 (1.05; 1.65)	P<0.05
Peto Method	1.44 (1.15; 1.81)	0.81 (0.38; 1.74)	1.38 (1.11; 1.71)	P<0.05
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS	

[1]Fixed effect meta-analysis performed via Mantel-Hanszel model, [2]Random effect meta-analysis performed via DerSimonian and Laird model, [3] *I^2 is reported for* Mantel-Hanszel model, p-value is the result of a two-sided t-test

Appendix Table 8: Rofecoxib Cumulative Meta-Analysis

	Zero Unadjusted			Zero Adjusted		
	All	***Published***	***Difference***	***All***	***Published***	***Difference***
			All Comparison			
Person-Year Denominator						
Fixed Effect	09/30/2004	04/23/2003	-17 months	09/30/2004	04/23/2003	-17 months
Random Effect	NS	NS	0 months	09/30/2004	04/23/2003	-17 months
Peto	04/23/2003	04/23/2003	0 months	04/23/2003	04/23/2003	0 months
Population Denominator						
Fixed Effect	09/30/2004	04/23/2003	-17 months	04/23/2003	04/23/2003	0 months
Random Effect	09/30/2004	09/30/2004	0 months	04/23/2003	04/23/2003	0 months
Peto	01/01/2000	01/01/2000	0 months	06/22/2000	01/01/2000	-6 months
			Only Comparison to Placebo			
Person-Year Denominator						
Fixed Effect	09/30/2004	09/30/2004	0 months	09/30/2004	09/30/2004	0 months
Random Effect	NS	NS	0 months	09/30/2004	09/30/2004	0 months
Peto	04/23/2003	04/23/2003	0 months	09/30/2004	04/23/2003	-17 months
Population Denominator						
Fixed Effect	09/30/2004	09/30/2004	0 months	09/30/2004	09/30/2004	0 months
Random Effect	09/30/2004	09/30/2004	0 months	09/30/2004	09/30/2004	0 months
Peto	04/23/2003	04/23/2003	0 months	04/23/2003	04/23/2003	0 months

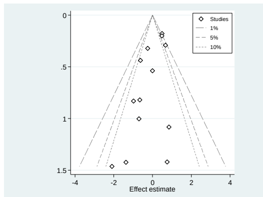
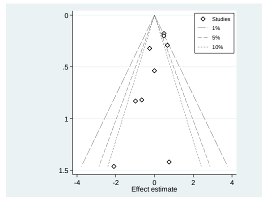
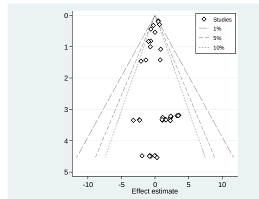
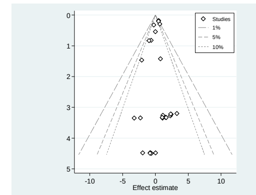
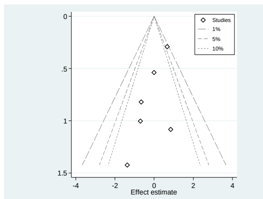
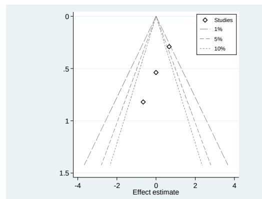
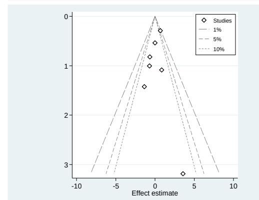
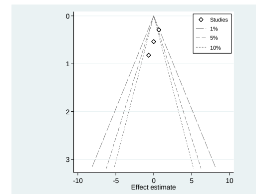
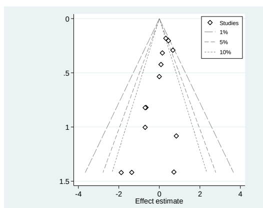
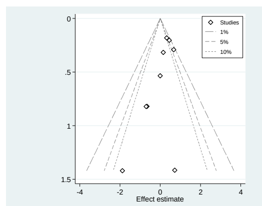
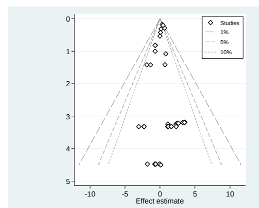
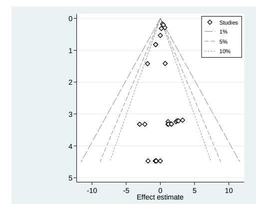
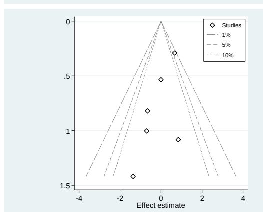
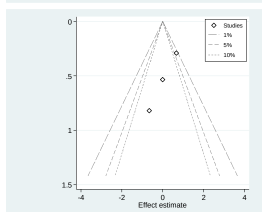
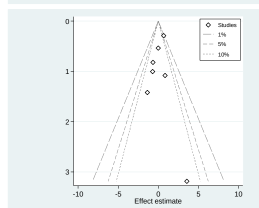
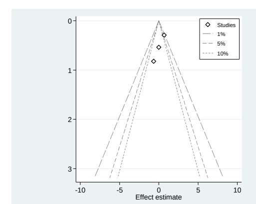
	Zero Unadjusted		**Zero Adjusted**	
	All	***Published***	***All***	***Published***
Person-Year				
All Drugs				
Placebo Controlled				
Population				
All Drugs				
Placebo Controlled				

Figure 7: Rofecoxib Contour-Enhanced Funnel Plots

Table 9: Meta-Analysis Results Rosiglitazone

	Published Trials	Unpublished Trials	All Trials
	Myocardial Infarction		
Person Year Denominator Adjusted			
Fixed Effect[1]	1.36 (0.94; 1.99)	1.38 (0.75; 2.55)	1.37 (0.99; 1.89)
Random Effect[2]	1.32 (0.89; 1.95)	1.41 (0.66; 2.99)	1.34 (0.95; 1.89)
Peto Method	1.37 (0.94; 2.01)	1.37 (0.75; 2.50)	1.37 (0.99; 1.89)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
Person Year Denominator Unadjusted			
Fixed Effect[1]	1.31 (0.91; 1.88)	1.21 (0.71; 2.05)	1.27 (0.94; 1.72)
Random Effect[2]	1.30 (0.90; 1.88)	1.23 (0.69; 2.21)	1.28 (0.94; 1.75)
Peto Method	1.40 (0.95; 2.05)	1.49 (0.80; 2.76)	1.42 (1.03; 1.97)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
Population Denominator Adjusted			
Fixed Effect[1]	1.37 (0.94; 2.00)	1.38 (0.75; 2.55)	1.37 (0.99; 1.89)
Random Effect[2]	1.32 (0.89; 1.96)	1.41 (0.66; 2.99)	1.34 (0.95; 1.90)
Peto Method	1.37 (0.94; 2.01)	1.37 (0.75; 2.50)	1.37 (1.00; 1.90)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
Population Denominator Unadjusted			
Fixed Effect[1]	1.31 (0.91; 1.88)	1.20 (0.71; 2.05)	1.27 (0.94; 1.72)
Random Effect[2]	1.30 (0.90; 1.89)	1.23 (0.69; 2.21)	1.28 (0.94; 1.75)
Peto Method	1.40 (0.95; 2.05)	1.49 (0.80; 2.76)	1.42 (1.03; 1.97)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
	Cardiovascular Death		
Person Year Denominator Adjusted			
Fixed Effect[1]	1.39 (0.72; 2.70)	1.63 (0.72; 3.67)	1.49 (0.89; 2.48)
Random Effect[2]	1.24 (0.62; 2.49)	1.50 (0.60; 3.78)	1.33 (0.76; 2.32)
Peto Method	1.37 (0.72; 2.61)	1.60 (0.74; 3.45)	1.46 (0.89; 2.39)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
Person Year Denominator Unadjusted			
Fixed Effect[1]	1.29 (0.70; 2.41)	1.39 (0.68; 2.83)	1.33 (0.83; 2.13)
Random Effect[2]	1.27 (0.67; 2.39)	1.37 (0.64; 2.91)	1.31 (0.81; 2.13)
Peto Method	1.49 (0.77; 2.89)	1.89 (0.83; 4.30)	1.64 (0.98; 2.74)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
Population Denominator Adjusted			
Fixed Effect[1]	1.39 (0.72; 2.70)	1.63 (0.72; 3.67)	1.49 (0.89; 2.48)
Random Effect[2]	1.24 (0.62; 2.50)	1.50 (0.60; 3.78)	1.33 (0.76; 2.32)
Peto Method	1.38 (0.72; 2.62)	1.60 (0.74; 3.45)	1.46 (0.89; 2.40)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS
Population Denominator Unadjusted			
Fixed Effect[1]	1.29 (0.69; 2.41)	1.38 (0.68; 2.82)	1.33 (0.83; 2.13)
Random Effect[2]	1.27 (0.67; 2.39)	1.37 (0.64; 2.90)	1.31 (0.80; 2.13)
Peto Method	1.49 (0.77; 2.89)	1.89 (0.83; 4.30)	1.64 (0.98; 2.74)
I^2 Statistic[3]	0.0%, NS	0.0%, NS	0.0%, NS

[1]Fixed effect meta-analysis performed via Mantel-Hanszel model, [2]Random effect meta-analysis performed via DerSimonian and Laird model, [3] *I^2 is reported for* Mantel-Hanszel model

Zero Unadjusted — *All* | *Published*

Zero Adjusted — *All* | *Published*

Myocardial Infarction

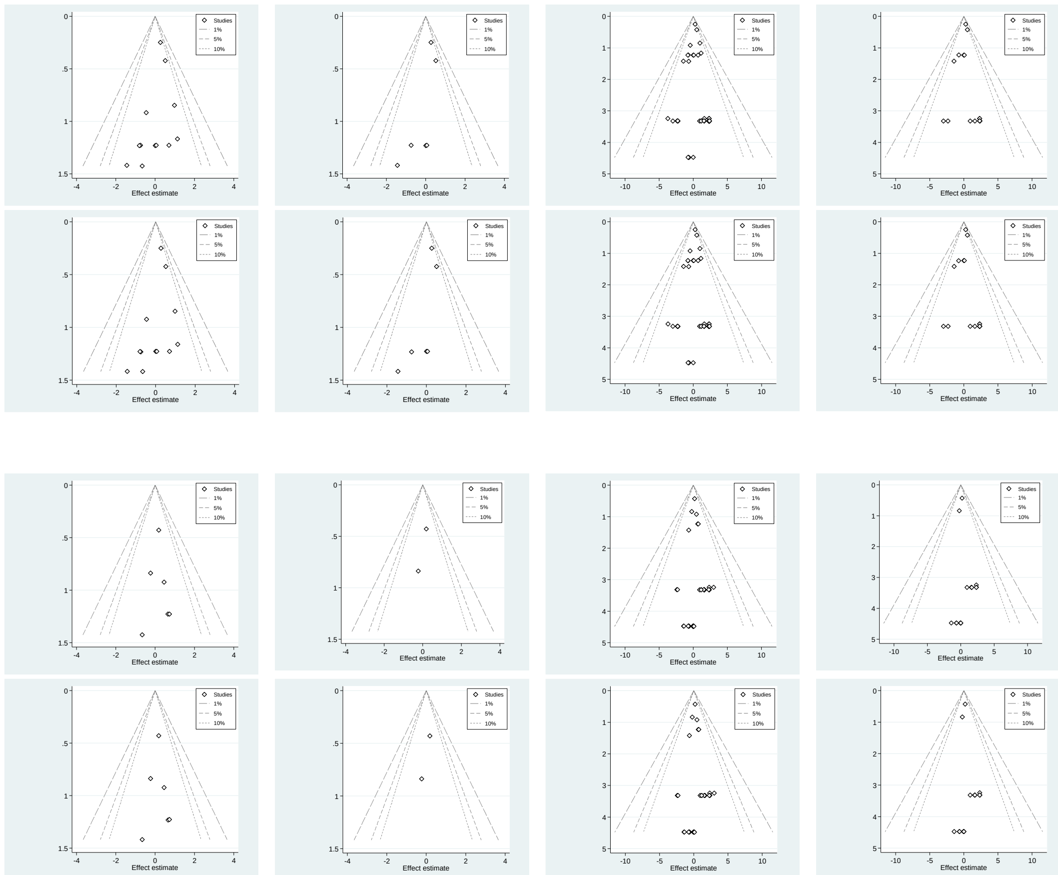
Person-Year

Population

All CV Events

Person-Year

Population



Appendix Figure 8: Rosiglitazone Contour Enhanced Funnel Plots

Appendix Table 10: Rosiglitazone Cumulative Meta-Analysis

	Zero Unadjusted			Zero Adjusted		
	All	***Published***	***Difference***	***All***	***Published***	***Difference***
		Myocardial Infarction				
Person-Year Denominator						
Fixed Effect	06/14/2007	06/14/2007	0 months	06/14/2007	06/14/2007	0 months
Random Effect	06/14/2007	06/14/2007	0 months	06/14/2007	06/14/2007	0 months
Peto	06/01/2004	06/14/2007	36 months	12/01/2004	06/14/2007	30 months
Population Denominator						
Fixed Effect	06/14/2007	06/14/2007	0 months	06/14/2007	06/14/2007	0 months
Random Effect	06/14/2007	06/14/2007	0 months	06/14/2007	06/14/2007	0 months
Peto	06/01/2004	06/14/2007	36 months	12/01/2004	06/14/2007	30 months
		Cardiovascular Death				
Person-Year Denominator						
Fixed Effect	NS	NS	0 months	NS	NS	0 months
Random Effect	NS	NS	0 months	NS	NS	0 months
Peto	NS	NS	0 months	NS	NS	0 months
Population Denominator						
Fixed Effect	NS	NS	0 months	NS	NS	0 months
Random Effect	NS	NS	0 months	NS	NS	0 months
Peto	NS	NS	0 months	NS	NS	0 months

VITA

William Canestaro is a health economist and meta-epidemiologist living in Seattle, WA. William received his undergraduate degree in medical sociology from Dartmouth College in Hanover, NH a degree that he petitioned the college to create. Following a year serving as a volunteer for Hurricane Katrina relief in the Gulf Coast, will completed his master's degree at Oxford University in Medical Anthropology. Before coming to the University of Washington, William worked in a number of entrepreneurial ventures in the Boston area.