Impact of study outcome on submission and acceptance metrics for peer-reviewed medical journals: a 6-year retrospective review of all completed GlaxoSmithKline human drug research studies

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TITLE PAGE:

Impact of study outcome on submission and acceptance metrics for peer-reviewed medical journals: a 6-year retrospective review of all completed GlaxoSmithKline human drug research studies

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ABSTRACT

Objectives: To determine whether drug study outcome influenced submission or acceptance rates for publication in peer-reviewed journals.

Design: 6-year, retrospective review of publication status by study outcome for all human drug studies conducted by a single industry sponsor (GlaxoSmithKline) completing between Jan 1st 2009 and June 30th 2014 and therefore due for manuscript submission (per sponsor's policy) between 2010-2015. Manuscripts from studies completing after June 30th 2014 also were included if submitted between 2010-2015. Publication status, study completion date, manuscript submission date, number of submissions, journal decision(s), and publication date were recorded. Studies were classified while blinded to publication status as "Positive" (favourable outcome for study drug), "Negative" (unfavourable outcome for study drug), Mixed, or Noncomparative based on outcome of the primary outcome measure(s). "Negative" studies included safety studies where the primary outcome was achieved but was adverse for study drug. We hypothesized that studies with "Negative" outcomes would have similar submission rates but lower acceptance rates and require greater number of submissions to be published in peer-reviewed journals.

Setting: N/A

Participants: N/A

Interventions: N/A

Outcome measures: Descriptive statistics for: study phase, time from study completion to submission and publication, number and outcome (accepted/rejected) of publication submissions.

Results: 1064 studies were classified as: "Positive" (n=321), "Negative" (n=155), Mixed (n=52), or Noncomparative (n=536). 85% of studies were submitted for publication as full manuscripts and 71% were successfully published or accepted, with 9% still under journal review. 7% of studies were disclosed only as congress abstracts (not included in submission or publication rates). Submission rates by study outcome were "Positive" 79%, "Negative" 92%, Mixed 94%, Noncomparative 85%. Publication rates were "Positive" 66%, "Negative" 77%, Mixed 77%, Noncomparative 71%. Median time from study completion to submission was 537 days (interquartile range [IQR] 396-638 days) and from completion to publication was 823 days (IQR 650-1063 days) with similar times across study outcomes. First-time acceptance rates were "Positive" 56% and "Negative" 48%. >10% of studies across all categories required 3 or more submissions to achieve publication.

Conclusions: There was no evidence of submission or publication bias: publication rates were higher for studies with "Negative" outcomes compared with "Positive" outcomes despite lower first time acceptance rates. Analyses focusing solely on publication rates do not take into account unsuccessful efforts to publish. We encourage other sponsors and journal editors to share similar information in efforts to contribute to better understanding of issues and barriers to full transparency.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Large (n>1000) contemporaneous (2010-2015) cohort that includes both study and publication outcomes
- Data on submissions and number of attempts provide a more complete picture of sponsors' efforts to publish
- Data are from a single pharmaceutical sponsor, limiting generalizability

INTRODUCTION

Industry, and to a lesser extent academia, have been criticized for failing to submit clinical trial data for publication, especially when the data are perceived to be "negative", i.e. unfavourable to the drug under study, leading to publication bias. Despite a commitment by many industry sponsors to publish all research results, failure to publish regardless of outcome adversely impacts the credibility of all industry-sponsored research. (1, 2)

Transparent reporting of medical research irrespective of outcome fulfills an ethical obligation to trial patients, advances scientific understanding and may inform treatment decisions. Although public posting of summary results is now a legal requirement for many types of studies, publication in peer-reviewed journals is still considered the gold standard of disclosure as it provides critical context that aids interpretation. Literature surveys carried out since 2010 suggest that between 56-85% of study protocols registered on www.clinicaltrials.gov and other public sites were eventually published. (3-9) There was wide variance across and within sponsor categories (e.g. industry, academia, government) and by study outcomes (presence vs. absence of statistical significance) in both publication rates as well as time to publication with a general temporal trend toward increased disclosure rates. (3, 4, 6-12) Studies lacking statistically significant outcomes were less likely to be published and when published, took a longer time from study completion to publication. (10, 11)

Most surveys rely on information on public websites (e.g. www.clinicaltrials.gov) that lack the information necessary to take into account the effect of unsuccessful attempts to publish (i.e. journal rejection) on publication rates and time to publish. We therefore undertook an analysis of study and publication outcomes utilizing a cohort of all drug trials completed during the period from January 2009 to June 2014 from a single pharmaceutical sponsor, GlaxoSmithKline (GSK). Since 2009, GSK policy requires that all human research studies of its drug products (whether investigational or marketed) are submitted for journal publication within 18 months of study completion unless exempted. For this analysis, all studies completing during this period (including those not submitted or published) were classified by outcome as: "Positive" (i.e. favourable for the study drug)," Negative" (unfavourable for the study drug), Mixed, or Noncomparative; whether they were submitted (including number of attempts) and/or accepted for publication during this period; and the time from study completion to manuscript submission and (when applicable) publication. We hypothesized that there would be no difference in submission rates for "Positive" vs. "Negative" study outcomes (due to sponsor policy

requiring all studies to be submitted for publication), but that "Negative" studies would have lower acceptance rates and require a greater number of submissions to be published in peer-reviewed medical journals.

METHODS

A comprehensive list of all human drug research studies sponsored by GSK Pharmaceuticals that completed (last subject last visit, or completion of statistical analysis for observational studies) between January 1, 2009 and June 30, 2014 was compiled from the sponsor's clinical trial management system, from which other study characteristics (study type, phase, end date) were also extracted and cross-checked against www.clinialtrials.gov and www.gsk-clinicalstudyregister.com. January 1, 2009 was selected as the start as it was the date from which GSK policy required all human drug research studies to be submitted for publication within 18 months of study completion. June 30, 2014 was selected as the cutoff to ensure capture of the cohort of studies expected by this policy to have been submitted by December 31, 2015. In order to capture all manuscript submissions from 2010-2015, studies completing after June 30, 2014 were also included irrespective of outcome, if they had a manuscript submitted by December 31, 2015. Excluded were studies involving: vaccines; consumer products; no drug administration; a change in sponsor; termination prior to completion of significant patient enrollment (primary statistical analyses were not conducted); and studies submitted for publication outside of the period from 2010-2015 (see Supplemental Table 1 - CONSORT flowchart).

Using study results summaries posted to www.clinicaltrials.gov and/or www.gsk-clinicalstudyregister.com, study outcomes were classified into the following categories:

> "Positive": Significant difference ($p<0.05$ or non-overlapping 95% confidence intervals) on the protocol pre-specified primary outcome measure in favour of the experimental drug, OR for safety studies: a lack of adverse safety findings (e.g. QTc studies)/non-inferiority) OR all formulations tested were within bioequivalence/non-inferiority limits. A subcategory of "pure positive" studies was also tracked for those studies only meeting the first criterion listed above.
>
> "Negative": Lack of significant difference (as defined above) on protocol pre-specified primary outcome measure OR appearance of an adverse safety finding OR lack of bioequivalence. A subcategory of "pure negative" studies was also tracked for those studies meeting only the first criterion listed above.
>
> Mixed: Both statistically significant and non-significant results on studies with more than one protocol pre-specified primary endpoint
>
> Noncomparative: Studies that did not meet the above criteria, including those with only descriptive statistics, i.e. no preplanned formal comparisons or prospective identification of a primary endpoint (typically phase I and pharmacokinetic studies) OR studies that were terminated early without conducting the planned statistical analysis of the primary outcome

Only the outcomes of the primary endpoint were considered in classifying study outcomes. Secondary endpoints were not considered. Outcomes were assessed by an external party (Tata Consultancy Services Medical Writing Team) and verified by one of the authors (GE) while blinded to publication status. Concordance of initial assessments was >80% with discrepancies resolved by consensus discussion.

Publication status was determined from a snapshot review of information within the sponsor's publication tracking system as of Feb. 26, 2016, which provided the following information for studies included in this cohort: number of submissions, outcome of each submission, and dates of submission and publication (when available). Only submissions of full manuscripts to peer-reviewed journals were included in the main analysis. Posting of study outcomes to public registries such as www.clinicaltrials.gov or www.gsk-clinicalstudyregister.com did not qualify as submission for publication. Disclosure via congress abstracts was also tracked but not included in the main analysis. Studies were grouped into published (including those accepted but awaiting publication), those currently under journal review, and those not published (either rejected or not submitted). The number of submissions for each study was also recorded. Resubmission to the same journal was not counted as a separate submission, but resubmission to a separate journal within or outside of a given publisher's journal "family" was counted. Although more than one study could be combined into a single publication submission, for the purpose of this analysis each study was considered as a separate attempt to publish, given the interest in comparing study outcomes to publication status.

After separate compilation of study outcomes and publication status, the data were merged and descriptive statistics were generated for publication status and number of submission attempts. No other formal statistical comparisons were planned but Fisher's Exact Test was applied post hoc to proportion of submissions, acceptance and first-time acceptance for "Positive" vs. "Negative" studies.

Patient Involvement

All data from this analysis were drawn from previously conducted clinical trials. No new patients were recruited for this analysis, nor were patients involved in setting the research question or the outcome measures, design or implementation of the analysis. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the analysis to the original study participants or relevant patient communities.

RESULTS

The search identified 1003 studies that completed between January 1st 2009 and June 30th 2014 and were therefore expected to have a primary manuscript submitted within 18 months of study completion (i.e. by the end of 2015) and an additional 61 more recently completed studies that had a manuscript submitted by the end of 2015, making a total of 1064 studies in the cohort. These studies were then classified according to study outcome (Table 1). 45% of all studies and 50% of interventional studies could be classified as "Positive" or "Negative", including 69% of all Phase IIb and Phase III studies. In contrast, 65% of Phase I studies were classified as Noncomparative, and comprised nearly half of the

studies within this outcome category (see Supplemental Table 2 for additional information on Noncomparative study characteristics).

Table 2 summarizes publication status by study phase: 85% of all studies had been submitted for publication as full manuscripts. Seventy-one percent of studies had been accepted and/or published as full manuscripts with an additional 9% of studies submitted but still awaiting a journal decision. Of the 904 studies submitted for publication as full manuscripts, 133 studies were combined into a total of 65 submissions to increase their scientific interest. The remaining 771 studies were submitted as standalone publications. Full manuscript publication rates for phase II and III studies were highest (78-88%) whereas Phase I studies had the lowest publication rate (57%) although an additional 18% were disclosed via congress abstracts.

Of the 83 studies that were not submitted for publication in any form at the time of analysis cut off, 49 were bioequivalence studies that showed no differences between formulations (i.e. “Positive” studies); 24 did not address the safety or efficacy of a drug; 9 were terminated early such that the primary outcome measure was not analyzed; and 1 was excluded due to confounding by indication. 81 of these studies were in scope for, and had results posted to www.clinicaltrials.gov or www.gsk-clinicalstudyregister.com (for the full cohort of 1064 studies, 1041 had results posted).

Table 3 summarizes publication status by study outcome. Rates of publication were similar across all categories of study outcome: 66-77% of all categories were published as full manuscripts by the cutoff date with a further 5-8% disclosed as abstracts only. Submission rates were lower for “Positive” vs. ”Negative” studies (79 vs. 92%, Fisher’s Exact p = 0.0006) as were acceptance rates (66% vs. 77%, p = 0.019). Rates of non-publication were similar across all categories of study outcome, whether due to journal rejections (3-10%) or lack of manuscript submission during the analysis period (6-16%). Overall, the median time from study completion to submission was 537 days (interquartile range [IQR] 396-638 days) and from completion to publication was 823 days (IQR 650-1063 days). These times were broadly similar across study outcomes although for “Negative” studies, median times to submission and publication were respectively 31 and 102 days longer than for “Positive” studies.

Figure 1 summarizes acceptance rates for ”Positive” vs. ”Negative” studies. First-time acceptance rates were 56% for ”Positive” vs. 48% for ”Negative” studies (p=0.17), respectively. These rates were also similar when the same analysis was performed using the “pure positive” and “pure negative” categories described in Methods (50% vs. 49%). Approximately three quarters of studies were accepted after 1-2 submissions for both study outcome categories (78% for “Positive” vs. 73% for ”Negative” studies).

DISCUSSION

In this 6-year systematic review of more than 1000 studies from a single industry sponsor, publication submission rates were broadly similar across study types and outcomes. Over the study period, a greater proportion of “Negative” vs. “Positive” studies were submitted (92% vs. 79%) and accepted (77% vs. 66%) for journal publication, indicating a lack of bias against either submission or publication of “Negative” studies by sponsor and journals, respectively. Given the proximity of the analysis cutoff point to the end of the 6 year review period, journal decisions were still pending for 9% of manuscripts

submitted. An additional 7% of studies were disclosed via congress abstract only (not included in publication totals). In total, 83 studies (8%) had not been submitted for publication in any form at the time of analysis, of which 49 were "Positive" bioequivalence studies and 33 were Noncomparative studies. 98% of studies had results posted to one or more public registers, including 100% of studies subject to FDAAA requirements for posting on www.clinicaltrials.gov.

While the topic of industry bias in reporting results of negative studies had been recently and widely debated, to our knowledge no previous study has systematically addressed the issue of publication bias according to study outcome. (1, 6, 7, 10-13) In our cohort, overall publication rates were broadly in line with recent estimates based solely on data obtained from www.clinicaltrials.gov. (5-7) Median times to publication were also consistent with previously published figures. (6-9) When evaluating the impact of study outcome, first time acceptance rates for "Positive" studies were numerically, but not statistically higher than for "Negative" studies (56% vs. 48%). Median time from study completion to submission was 31 days longer for "Negative" vs. "Positive" studies and time to publication was 99 days longer, suggesting that greater effort and care (e.g. journal selection) are required for publication of "Negative" data. Even so, 10% of all studies and 13% of negative studies required 3 or more submissions to achieve journal publication. These data suggest that rates of publication discussed in the scientific literature may substantially underestimate the effort that sponsors make to publish their results, since they do not capture the number of submissions and journal rejection rates.

This analysis also demonstrates that "Negative" studies can and have been successfully published in the scientific literature and provides no evidence of a systematic bias against their acceptance by journals. 92% of studies in our cohort that had an unfavourable outcome for the drug under evaluation were submitted and 77% had been published by the analysis cutoff date. However, the fact that slightly more than half of studies included in this analysis could not be readily classified into "Positive" vs. "Negative" outcomes also suggests that such a dichotomous scheme represents an oversimplification of study outcomes, particularly when early phase studies are included. The current transparency debate and efforts may be better served by focusing on ensuring full publication of all studies, irrespective of outcome.

Although this study has a number of strengths including: a large, systematic cohort; inclusion of all studies (irrespective of phase or outcome); rigorous methodology; and metrics on submissions as well as final publication rates, it also has important limitations. Clarity in specifying endpoints and classification of study outcomes may be inexact and subject to debate. For applicable studies, we deliberately chose to classify studies as having a "Positive" or "Negative" outcome for the drug, rather than on the basis of statistical significance alone, because for some types of studies (e.g. QTc safety studies) lack of significance is a favourable outcome for the drug being tested. Conversely, statistically significant negative safety findings may preclude further development of an investigational drug. This study did not address selective outcome reporting for the 751 studies that were published, although a unified process for reporting endpoints in study summaries and reports is followed by the sponsor to ensure consistent reporting. Most importantly, the data reported here are from a single industry sponsor. Without further data from other research sponsors, it is not possible to determine whether these results generalize to other industry sponsors or to other types of sponsors (academia, government). Despite

this limitation, these data provide a clear signal that submission and publication bias against "Negative" studies may be less widespread than may have generally been assumed and should not deter efforts to publish them.

In summary, conducting and publishing analyses of submissions and successful publication according to study outcome are potentially important actions needed to assess and improve actual practice, and where appropriate, to correct misperceptions regarding publication bias that adversely impact the credibility of drug research. We encourage other sponsors and journal editors to share similar information in efforts to contribute to better understanding of issues and barriers to full transparency.

Acknowledgments, Competing Interests, Funding and all other required statements.

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The authors thank the many thousands of patients who participated in the clinical trials that comprised our data set. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. All four authors were employees and shareholders in GSK at the time this research was conducted. GSK sponsored the >1000 individual studies described in this analysis, paid the salaries of the four named authors and funded the services acknowledged above, but was not otherwise involved in the project conception or execution. The authors declare no other support, financial relationships, nor any other relationships or activities that could appear to have influenced the submitted work. GE conceived the project and its design, supervised the collection of data and its analysis, prepared the first draft of this manuscript, led its critical revisions and is the project's guarantor. BAM participated in the collection of data and its analysis and interpretation, and contributed critical revisions to the manuscript. BDC participated in the collection of data and its analysis and interpretation, and contributed critical revisions to the manuscript. JS contributed to data analysis and interpretation as well as critical revisions to the manuscript. All four authors assume accountability as individuals for the final manuscript and its contents. As lead author and guarantor, GE affirms that this manuscript is an honest, accurate and transparent account of the research being reported, that no important aspects have been omitted, and that any discrepancies from the study as planned have been explained. As a meta-analysis of previously completed (and registered) human research, the current analysis did not require study registration, ethics committee approval or informed consent (the latter were obtained for the individual studies contained in the analysis).

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Table 1 – Overall Study Outcome by Study Phase and Type

	ALL Studies	"Positive"		"Negative"		Mixed		Noncomparative	
	N	n	%	n	%	n	%	n	%
Phase I	**385**	87	23	37	10	11	3	250	65
Phase II/IIa	**121**	30	25	36	30	10	8	45	37
Phase IIb	**57**	20	35	21	37	3	5	13	23
Phase III/IIIa	**113**	57	50	14	12	6	5	36	32
Phase IIIb	**59**	30	51	16	27	2	3	11	19
Phase IV	**125**	46	37	19	15	9	7	51	41
Phase N/A	**204**	51	25	12	6	11	5	130	64
Interventional	**779**	246	32	140	18	31	4	362	46
Noninterventional [1]	**285**	75	26	15	5	21	7	174	61
TOTAL	**1064**	321	30	155	15	52	5	536	50

% based on proportion of study outcomes within a study phase/type

[1]Includes observational studies

Table 2 – Overall Publication status by Study Phase

	All Studies		Phase I		Phase II/IIA		Phase IIB		Phase III/IIIA		Phase IIIB		Phase IV		Phase NA	
	n	**%**	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Submitted: Published*	**751**	**71**	219	57	95	79	45	79	100	88	46	78	93	74	153	75
Pending	**100**	**9**	28	7	11	9	7	12	9	8	10	17	14	11	21	10
Rejected	**53**	**5**	9	2	9	7	2	4	1	1	2	3	10	8	20	10
Abstract	**77**	**7**	69	18	2	2	0	0	2	2	1	2	2	2	1	<1
Not submitted	**83**	**8**	60	16	4	3	3	5	1	1	0	0	6	5	9	4
TOTAL	**1064**		385		121		57		113		59		125		204	

% based on proportion of publication status within a given study phase

*includes 48 studies accepted but not yet published as of data cutoff date

Table 3 – Overall publication status for the full cohort and subcategories:

	ALL Studies		"Positive"		"Negative"		Mixed		Noncomparative	
	n	**%**	n	%	n	%	n	%	n	%
Submitted: Published[1]	**751**	**71**	212	66	119	77	40	77	380	71
Time to submission (IQR) days[2]	**537 (396-638)**		504 (343-601)		535 (408-612)		538 (366-640)		543 (427-674)	
Time to publication (IQR) days[3]	**823 (650-1063)**		774 (628-949)		876 (708-1203)		824 (694-1041)		833 (650-1103)	
Pending	**100**	**9**	32	10	13	8	4	8	51	10
Rejected	**53**	**5**	11	3	10	6	5	10	27	5
Abstract only	**77**	**7**	16	5	13	8	3	6	45	8
Not submitted	**83**	**8**	50	16	0	0	0	0	33	6
TOTAL	**1064**		321		155		52		536	

% based on proportion of study outcome with a given publication status

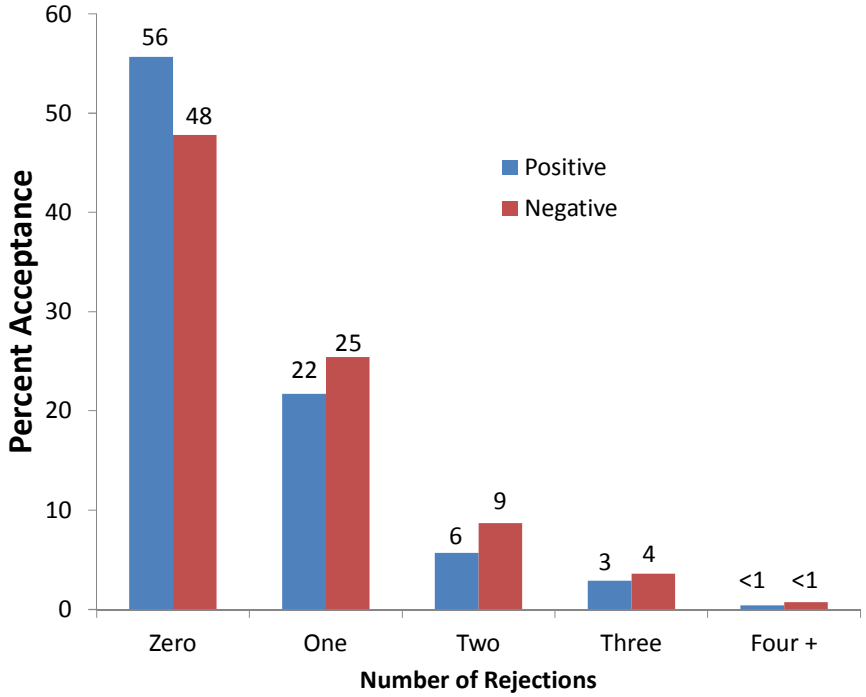
IQR = Interquartile range

[1]includes 48 studies accepted but not yet published as of data cutoff date

[2]based on n=867 studies with study end and subsequent submission dates

[3]based on n=670 studies with study end and subsequent publication dates

Figure 1 – Acceptance Rates for Positive vs. Negative Studies



% based on total number of studies with a journal decision

Appendix 1 – Summary Box

What is already known on this topic:

Literature surveys carried out since 2010 suggest that between 15-44% of studies registered on www.clinicaltrials.gov and other public sites had not been published in medical journals.

Studies lacking statistically significant outcomes were less likely to be published and when published, took a longer time from study completion to publication.

Failure of sponsors to publish all research results, regardless of outcome adversely impacts the credibility of medical research.

What this study adds:

Rates of publication previously discussed in the scientific literature may have substantially underestimated the effort that sponsors made to publish their results, since they did not capture sponsor submission and journal rejection rates.

Submission and publication bias against "Negative" studies may be less widespread than may have generally been assumed and should not deter efforts to publish them.

Greater sharing of submission and rejection metrics by sponsors and journals may contribute to better understanding of issues and barriers to full transparency.

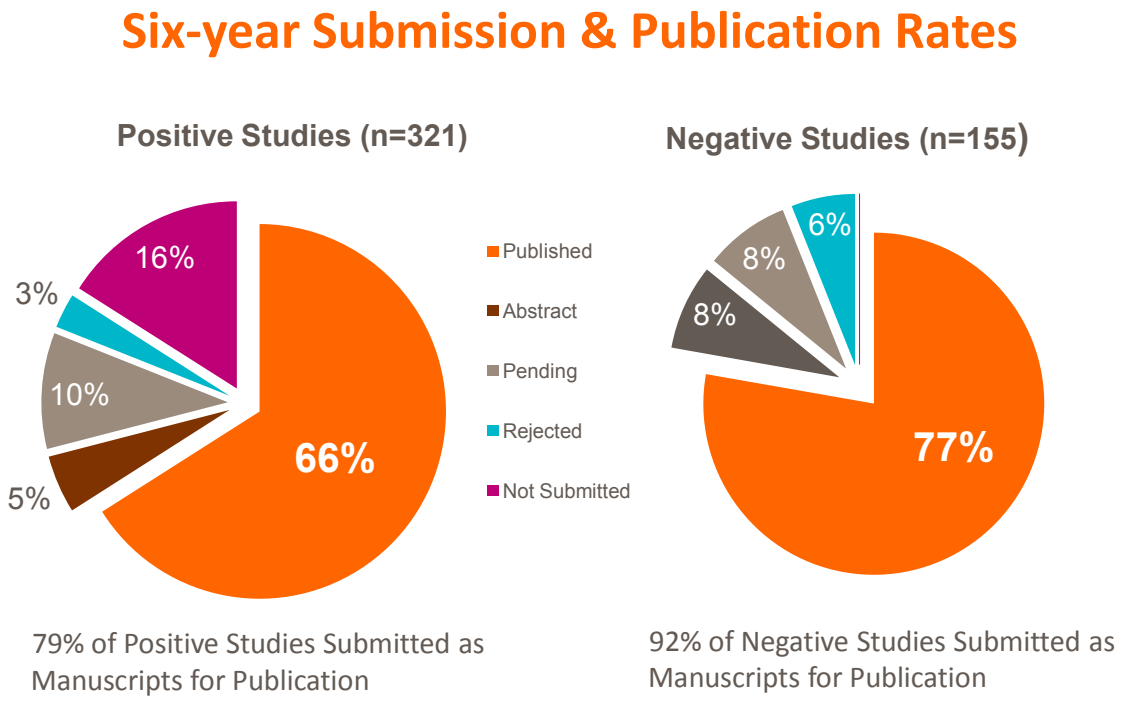
Print abstract

Impact of study outcome on submission and acceptance metrics for peer-reviewed medical journals: a 6-year retrospective review of all completed GlaxoSmithKline human drug research studies

Evoniuk G, et al. (BMJ paper linnXXXXX)

Industry, and to a lesser extent academia, have been criticized for failing to submit clinical trial data for publication, especially when the data are perceived to be “negative”, i.e. unfavourable to the drug under study, leading to publication bias. The objective of this study was to determine whether study outcome influenced manuscript submission by industry or acceptance rates by journals. This six-year review looked at publication status by study outcome for all drug studies in humans conducted by a single industry sponsor (GlaxoSmithKline) completed between Jan 1st 2009 and June 30th 2014 and thereby due for manuscript submission per the sponsor’s policy within 18 months of study completion (i.e., by December 31st 2015). Manuscripts from studies completing after June 30th 2014 were also included if they were submitted between 2010-2015. To avoid potential bias in assessing study outcome, studies were independently classified as “Positive” (favourable outcome for study drug), “Negative” (unfavourable outcome for study drug), Mixed, or Noncomparative based on outcome of the primary outcome measure(s). In total, 85% of studies were submitted for publication as full manuscripts and 71% were successfully published or accepted, with 9% still under journal review at the conclusion of the analysis. There was no evidence of submission or publication bias: submission and publication rates were higher for studies with “Negative” outcomes (92% submitted; 77% published) compared with ”Positive” outcomes (79% submitted; 66% published). Transparent reporting of results of medical research regardless of outcome fulfills an ethical obligation to trial patients, advances scientific understanding and may inform treatment decisions. Conducting and publishing analyses of submissions and publication are an important step to improve practice and correct misperceptions regarding publication bias that adversely impact the credibility of drug research.

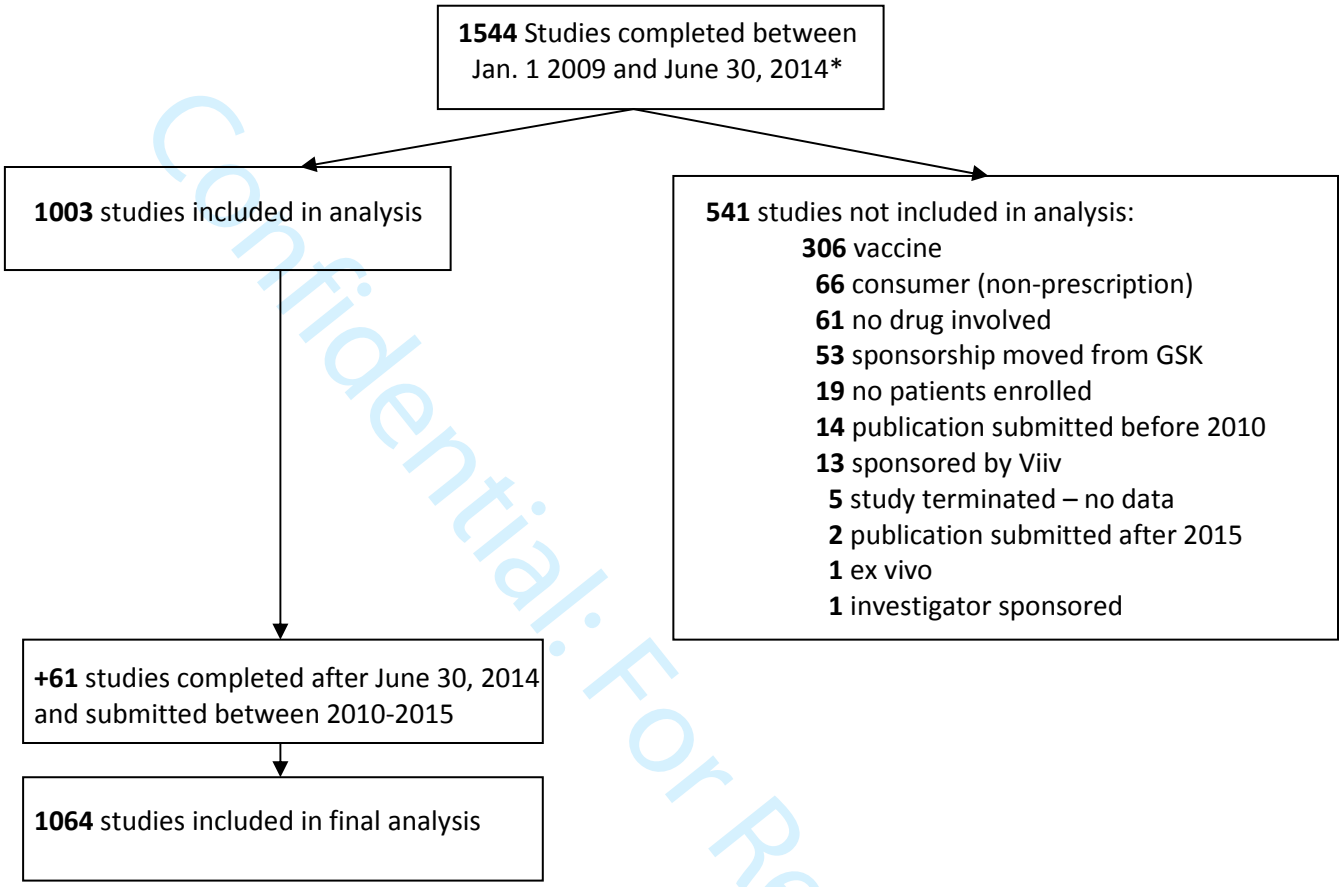
Suggested figure for publication abstract (or use figure 1 from manuscript)



- 83 studies had not been submitted for publication at the time of the analysis, including 49 "Positive" bioequivalence studies and 33 Noncomparative studies. However, all in-scope studies were posted on clinialtrials.gov or gsk-clinicalstudyregister.com as applicable (81 studies)
- 98% (1041 out of 1064) of studies in this cohort were disclosed in one or more public register - including 100% of studies meeting FDAAA requirements for posting on CT.gov. The remaining 23 (2%) did not meet the disclosure requirements for either CT.gov or the GSK clinical study register.

[1]

Supplemental Table 1 – Inclusion/Exclusion



*GSK policy mandates that all studies during this period would be submitted for publication between 2010-2015 (i.e., within 18 months of completion)

Supplemental Table 2 – Characteristics of Noncomparative Studies

TOTAL (n)	**536**
Phase I	**250**
Single or multiple ascending dose	83
Other pharmacokinetic (elderly, renal, etc.)	74
No control group	40
Formulation comparison	37
Drug-drug interaction	10
Methodology	2
Descriptive epidemiology	1
Pharmacogenetics	1
Safety/Tolerability	1
Phase II	**58**
No control group	24
Other pharmacokinetic (elderly, renal, etc.)	13
Safety/Tolerability	6
Open-label extension	5
Single or multiple ascending dose	4
Formulation comparison	2
Drug-drug interaction	2
Primary endpoint not evaluable	2
Phase III	**47**
No control group	21
Open-label extension	14
Primary Endpoint not defined or evaluated	6
Safety/Tolerability	4
Other pharmacokinetic (elderly, renal, etc.)	2
Phase IV/NA	**181**
Descriptive epidemiology	58
No control group	50
Open-label extension	45
Pharmacogenetic	10
Primary Endpoint not defined or evaluated	5
Instrument validation	5
Pregnancy registry	4
Safety/Tolerability	1
Pharmacokinetic	1
Formulation comparison	1
Drug-drug interaction	1

Supplemental File 1 – Listing of additions/deletions to database since original October submission

Changes to Database v2-9-17.xls

Supplemental File 2 – Listing of studies only submitted as congress abstracts

Studies Submitted Only as Congress Abs

Supplemental File 3 – Listing of studies not submitted for publication in any form

Studies Not Submitted in Any Forı

Supplemental File – Data Tool

BMJ Manuscript Data Tool_Final Version_Fe

Alternate Figures

BMJ manuscript alternate figures v2-1

Figure 1 (original) – Acceptance Rates for Positive vs. Negative Studies

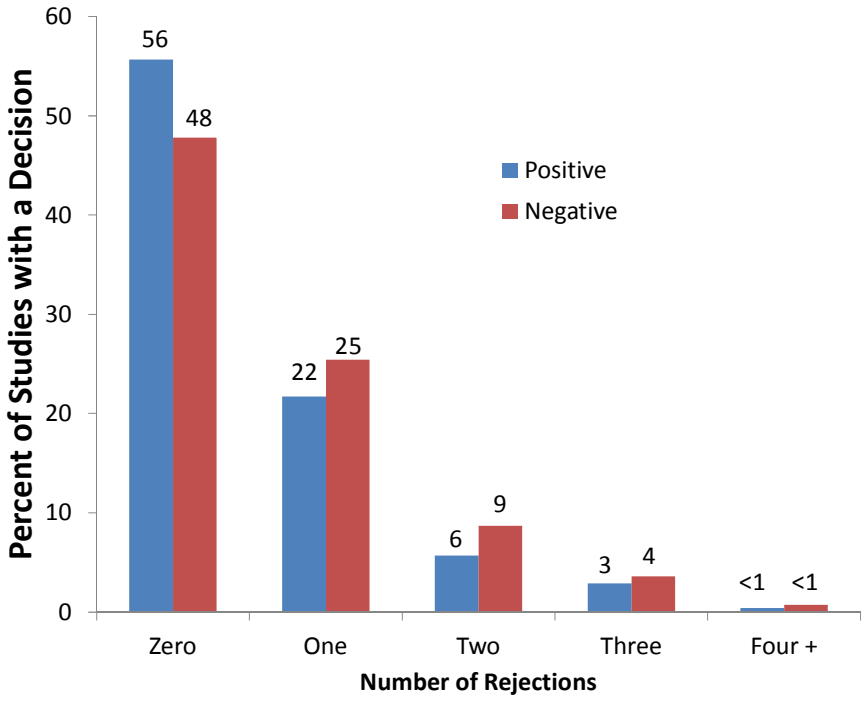


Figure 1Alt1 – Acceptance Rates by Study Outcome (includes all 4 groups)

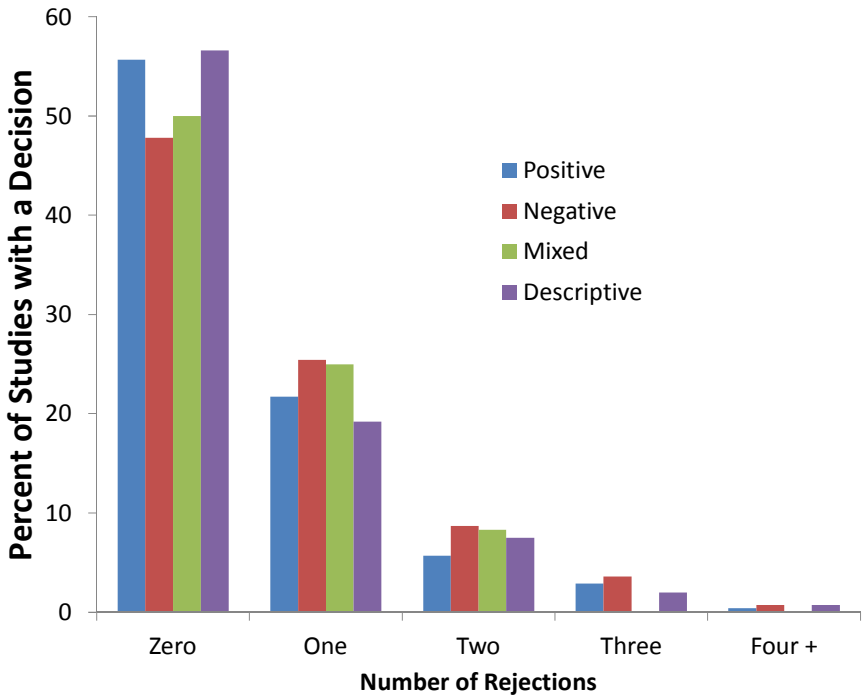


Figure 1alt – Acceptance Rates for Positive vs. Negative Studies (rates calculated separately at each step, rather than cumulatively)

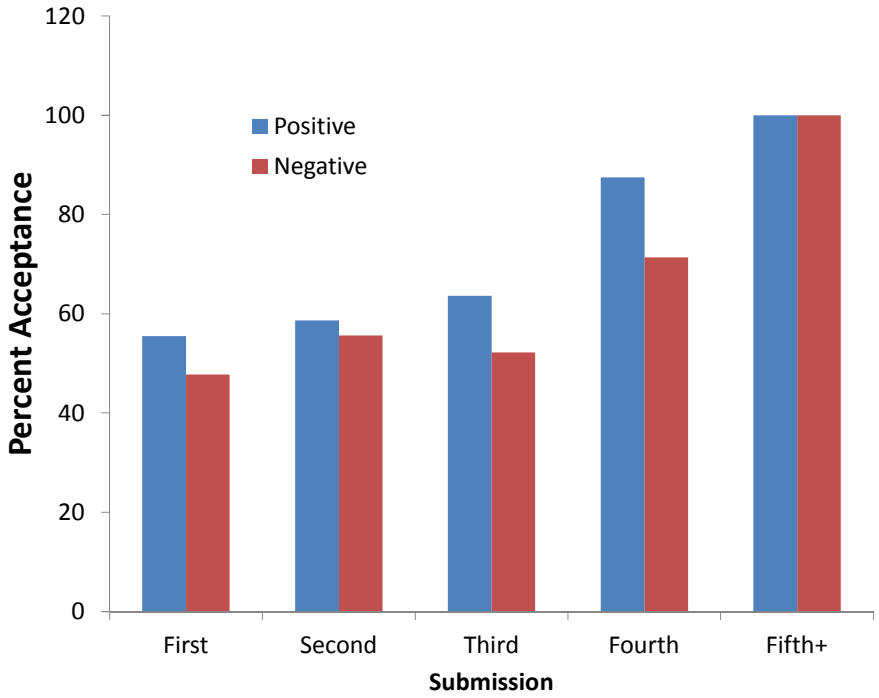
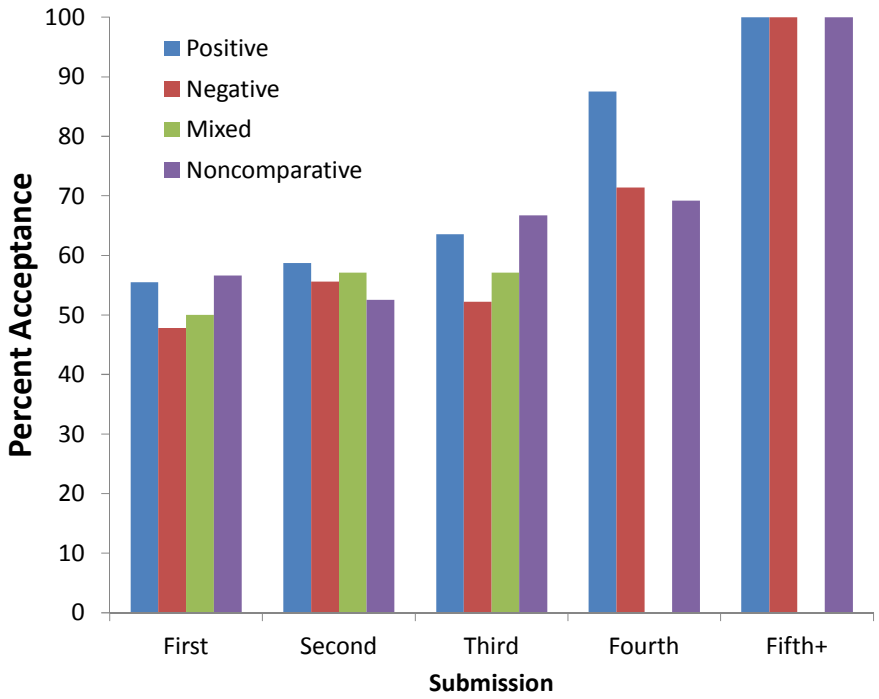


Figure 1alt – Acceptance Rates for All Groups (rates calculated separately at each step, rather than cumulatively)



TITLE PAGE:

Impact of study outcome on submission and acceptance metrics for peer-reviewed medical journals: a 6-year retrospective review of all completed GlaxoSmithKline human drug research studies

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KEYWORDS: Transparency, clinical trials, pharmaceutical industry, publication bias

WORD COUNT: 2498

ABSTRACT

Objectives: To determine whether drug study outcome influenced submission and/or acceptance rates for publication in peer-reviewed medical journals.

Design: A 6-year, retrospective review of publication status by study outcome for all human drug research studies conducted by a single industry sponsor (GlaxoSmithKline) that completed between Jan 1st 2009 and June 30th 2014 and were therefore due for manuscript submission (per the sponsor's policy) to peer-reviewed journals within 18 months of study completion, i.e., by December 31st 2015. In addition, manuscripts from studies completing after June 30th 2014 were included irrespective of outcome if submitted prior to December 31st 2015. All studies were assigned a publication status including (as applicable): study completion date, date of first primary manuscript submission, number of submissions, journal decision(s), and publication date. All studies were also classified while blinded to publication status as "Positive" (perceived as a favourable outcome for the drug under study), "Negative" (perceived as an unfavourable outcome for the drug under study), Mixed, or Noncomparative based on the presence and outcome of the primary outcome measure(s) for each study. "Negative" studies included safety studies where the primary outcome was achieved but was adverse for the drug under study. We hypothesized that studies with a "Negative" outcome would have similar submission rates but lower acceptance rates and require a greater number of submissions to be published in peer-reviewed medical journals.

Setting: N/A

Participants: N/A

Interventions: N/A

Outcome measures: For the total cohort and each of the 4 study outcomes, descriptive statistics for: study phase (n, %), time from study completion to submission and publication, number and outcome (accepted/rejected) of publication submissions.

Results: 1064 studies (Phase I-IV, interventional and non-interventional) had study outcomes classified as: "Positive" (n=321), "Negative" (n=155), Mixed (n=52), or Noncomparative (n=536). At the time of data cutoff, Feb 26th 2016, 85% of studies had been submitted for publication as full manuscripts and 71% had been successfully published or accepted, with an additional 9% still under journal review. An additional 7% of studies were disclosed as only congress abstracts and were not included in submission or publication rates. Submission rates by study outcome were "Positive" 79%, "Negative" 92%, Mixed 94%, and Noncomparative 85%; whilst publication rates at data cutoff were "Positive" 66%, "Negative" 77%, Mixed 77%, and Noncomparative 71%. Median time from study completion to submission was 537 days (interquartile range [IQR] 396-638 days) and from completion to publication was 823 days (IQR 650-1063 days) with similar times observed across study outcomes. First-time acceptance rates were "Positive" 56% and "Negative" 48%. Over 10% of studies across all categories required 3 or more submissions to achieve successful publication. 83 studies had not been submitted for publication at the time of the analysis, including 49 "Positive" bioequivalence studies and 33 Noncomparative studies.

98% (1041/1064) of studies had results posted to one or more public registers, including 100% of studies subject to FDAAA requirements for posting to www.clinicaltrials.gov.

Conclusions: There was no evidence of submission or publication bias over this 6 year period: 92% of "Negative" studies were submitted for publication by the cutoff date vs. 79% of "Positive" studies. Publication rates were slightly higher for studies with a "Negative" (i.e., unfavourable) outcome compared with a "Positive" outcome despite a slightly lower first time acceptance rate. Achieving greater transparency of human study outcomes via journal publication required multiple submissions for some studies. Analyses focusing solely on publication rates do not take into account unsuccessful efforts to publish. We encourage other sponsors and journal editors to share similar information in efforts to contribute to better understanding of issues and barriers to full transparency.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Large (n>1000) contemporaneous (2010-2015) cohort that includes both study and publication outcomes
- Data on submissions and number of attempts provide a more complete picture of sponsors' efforts to publish
- Data are from a single pharmaceutical sponsor, limiting generalizability

INTRODUCTION

Industry, and to a lesser extent academia, have been criticized for failing to submit clinical trial data for publication, especially when the data are perceived to be "negative", i.e. unfavourable to the drug under study, leading to publication bias. Despite a commitment by many industry sponsors to publish all research results, failure to publish regardless of outcome adversely impacts the credibility of all industry-sponsored research. (1, 2)

Transparent reporting of medical research irrespective of outcome fulfills an ethical obligation to trial patients, advances scientific understanding and may inform treatment decisions. Although public posting of summary results is now a legal requirement for many types of studies, publication in peer-reviewed journals is still considered the gold standard of disclosure as it provides critical context that aids interpretation. Literature surveys carried out since 2010 suggest that between 56-85% of study protocols registered on www.clinicaltrials.gov and other public sites were eventually published. (3-9) There was wide variance across and within sponsor categories (e.g. industry, academia, government) and by study outcomes (presence vs. absence of statistical significance) in both publication rates as well as time to publication with a general temporal trend toward increased disclosure rates. (3, 4, 6-12) Studies lacking statistically significant outcomes were less likely to be published and when published, took a longer time from study completion to publication. (10, 11)

Most surveys rely on information on public websites (e.g. www.clinicaltrials.gov) that lack the information necessary to take into account the effect of unsuccessful attempts to publish (i.e. journal rejection) on publication rates and time to publish. We therefore undertook an analysis of study and publication outcomes utilizing a cohort of all drug trials completed during the period from January 2009 to June 2014 from a single pharmaceutical sponsor, GlaxoSmithKline (GSK). Since 2009, GSK policy requires that all human research studies of its drug products (whether investigational or marketed) are submitted for journal publication within 18 months of study completion unless exempted. For this analysis, all studies completing during this period (including those not submitted or published) were classified by outcome as: "Positive" (i.e. favourable for the study drug)," Negative" (unfavourable for the study drug), Mixed, or Noncomparative; whether they were submitted (including number of attempts) and/or accepted for publication during this period; and the time from study completion to manuscript submission and (when applicable) publication. We hypothesized that there would be no difference in submission rates for "Positive" vs. "Negative" study outcomes (due to sponsor policy requiring all studies to be submitted for publication), but that "Negative" studies would have lower acceptance rates and require a greater number of submissions to be published in peer-reviewed medical journals.

METHODS

A comprehensive list of all human drug research studies sponsored by GSK Pharmaceuticals that completed (last subject last visit, or completion of statistical analysis for observational studies) between January 1, 2009 and June 30, 2014 was compiled from the sponsor's clinical trial management system, from which other study characteristics (study type, phase, end date) were also extracted and cross-checked against www.clinialtrials.gov and www.gsk-clinicalstudyregister.com. January 1, 2009 was selected as the start as it was the date from which GSK policy required all human drug research studies to be submitted for publication within 18 months of study completion. June 30, 2014 was selected as the cutoff to ensure capture of the cohort of studies expected by this policy to have been submitted by December 31, 2015. In order to capture all manuscript submissions from 2010-2015, studies completing after June 30, 2014 were also included irrespective of outcome, if they had a manuscript submitted by December 31, 2015. Excluded were studies involving: vaccines; consumer products; no drug administration; a change in sponsor; termination prior to completion of significant patient enrollment (primary statistical analyses were not conducted); and studies submitted for publication outside of the period from 2010-2015 (see Supplemental Table 1 - CONSORT flowchart).

Using study results summaries posted to www.clinicaltrials.gov and/or www.gsk-clinicalstudyregister.com, study outcomes were classified into the following categories:

> "Positive": Significant difference ($p<0.05$ or non-overlapping 95% confidence intervals) on the protocol pre-specified primary outcome measure in favour of the experimental drug, OR for safety studies: a lack of adverse safety findings (e.g. QTc studies)/non-inferiority) OR all formulations tested were within bioequivalence/non-inferiority limits. A subcategory of "pure positive" studies was also tracked for those studies only meeting the first criterion listed above.

"Negative": Lack of significant difference (as defined above) on protocol pre-specified primary outcome measure OR appearance of an adverse safety finding OR lack of bioequivalence. A subcategory of "pure negative" studies was also tracked for those studies meeting only the first criterion listed above.

Mixed: Both statistically significant and non-significant results on studies with more than one protocol pre-specified primary endpoint

Noncomparative: Studies that did not meet the above criteria, including those with only descriptive statistics, i.e. no preplanned formal comparisons or prospective identification of a primary endpoint (typically phase I and pharmacokinetic studies) OR studies that were terminated early without conducting the planned statistical analysis of the primary outcome

Only the outcomes of the primary endpoint were considered in classifying study outcomes. Secondary endpoints were not considered. Outcomes were assessed by an external party (Tata Consultancy Services Medical Writing Team) and verified by one of the authors (GE) while blinded to publication status. Concordance of initial assessments was >80% with discrepancies resolved by consensus discussion.

Publication status was determined from a snapshot review of information within the sponsor's publication tracking system as of Feb. 26, 2016, which provided the following information for studies included in this cohort: number of submissions, outcome of each submission, and dates of submission and publication (when available). Only submissions of full manuscripts to peer-reviewed journals were included in the main analysis. Posting of study outcomes to public registries such as www.clinicaltrials.gov or www.gsk-clinicalstudyregister.com did not qualify as submission for publication. Disclosure via congress abstracts was also tracked but not included in the main analysis. Studies were grouped into published (including those accepted but awaiting publication), those currently under journal review, and those not published (either rejected or not submitted). The number of submissions for each study was also recorded. Resubmission to the same journal was not counted as a separate submission, but resubmission to a separate journal within or outside of a given publisher's journal "family" was counted. Although more than one study could be combined into a single publication submission, for the purpose of this analysis each study was considered as a separate attempt to publish, given the interest in comparing study outcomes to publication status.

After separate compilation of study outcomes and publication status, the data were merged and descriptive statistics were generated for publication status and number of submission attempts. No other formal statistical comparisons were planned but Fisher's Exact Test was applied post hoc to proportion of submissions, acceptance and first-time acceptance for "Positive" vs. "Negative" studies. Patients were not involved in the design of this analysis.

RESULTS

The search identified 1003 studies that completed between January 1st 2009 and June 30th 2014 and were therefore expected to have a primary manuscript submitted within 18 months of study completion

(i.e. by the end of 2015) and an additional 61 more recently completed studies that had a manuscript submitted by the end of 2015, making a total of 1064 studies in the cohort. These studies were then classified according to study outcome (Table 1). 45% of all studies and 50% of interventional studies could be classified as "Positive" or "Negative", including 69% of all Phase IIb and Phase III studies. In contrast, 65% of Phase I studies were classified as Noncomparative, and comprised nearly half of the studies within this outcome category (see Supplemental Table 2 for additional information on Noncomparative study characteristics).

Table 1 – Overall Study Outcome by Study Phase and Type

	ALL Studies	"Positive"		"Negative"		Mixed		Noncomparative	
	N	n	%	n	%	n	%	n	%
Phase I	**385**	87	23	37	10	11	3	250	65
Phase II/IIa	**121**	30	25	36	30	10	8	45	37
Phase IIb	**57**	20	35	21	37	3	5	13	23
Phase III/IIIa	**113**	57	50	14	12	6	5	36	32
Phase IIIb	**59**	30	51	16	27	2	3	11	19
Phase IV	**125**	46	37	19	15	9	7	51	41
Phase N/A	**204**	51	25	12	6	11	5	130	64
Interventional	**779**	246	32	140	18	31	4	362	46
Noninterventional [1]	**285**	75	26	15	5	21	7	174	61
TOTAL	**1064**	321	30	155	15	52	5	536	50

% based on proportion of study outcomes within a study phase/type

[1]Includes observational studies

Table 2 summarizes publication status by study phase: 85% of all studies had been submitted for publication as full manuscripts. Seventy-one percent of studies had been accepted and/or published as full manuscripts with an additional 9% of studies submitted but still awaiting a journal decision. Of the 904 studies submitted for publication as full manuscripts, 133 studies were combined into a total of 65 submissions to increase their scientific interest. The remaining 771 studies were submitted as standalone publications. Full manuscript publication rates for phase II and III studies were highest (78-88%) whereas Phase I studies had the lowest publication rate (57%) although an additional 18% were disclosed via congress abstracts.

Of the 83 studies that were not submitted for publication in any form at the time of analysis cut off, 49 were bioequivalence studies that showed no differences between formulations (i.e. "Positive" studies); 24 did not address the safety or efficacy of a drug; 9 were terminated early such that the primary outcome measure was not analyzed; and 1 was excluded due to confounding by indication. 81 of these studies were in scope for, and had results posted to www.clinicaltrials.gov or www.gsk-clinicalstudyregister.com (for the full cohort of 1064 studies, 1041 had results posted).

Table 2 – Overall Publication status by Study Phase

	All Studies		Phase I		Phase II/IIA		Phase IIB		Phase III/IIIA		Phase IIIB		Phase IV		Phase NA	
	n	**%**	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Submitted: Published*	**751**	**71**	219	57	95	79	45	79	100	88	46	78	93	74	153	75
Pending	**100**	**9**	28	7	11	9	7	12	9	8	10	17	14	11	21	10
Rejected	**53**	**5**	9	2	9	7	2	4	1	1	2	3	10	8	20	10
Abstract	**77**	**7**	69	18	2	2	0	0	2	2	1	2	2	2	1	<1
Not submitted	**83**	**8**	60	16	4	3	3	5	1	1	0	0	6	5	9	4
TOTAL	**1064**		385		121		57		113		59		125		204	

% based on proportion of publication status within a given study phase

*includes 48 studies accepted but not yet published as of data cutoff date

Table 3 summarizes publication status by study outcome. Rates of publication were similar across all categories of study outcome: 66-77% of all categories were published as full manuscripts by the cutoff date with a further 5-8% disclosed as abstracts only. Submission rates were lower for “Positive” vs. ”Negative” studies (79 vs. 92%, Fisher’s Exact p = 0.0006) as were acceptance rates (66% vs. 77%, p = 0.019). Rates of non-publication were similar across all categories of study outcome, whether due to journal rejections (3-10%) or lack of manuscript submission during the analysis period (6-16%). Overall, the median time from study completion to submission was 537 days (interquartile range [IQR] 396-638 days) and from completion to publication was 823 days (IQR 650-1063 days). These times were broadly similar across study outcomes although for “Negative” studies, median times to submission and publication were respectively 31 and 102 days longer than for “Positive” studies.

Table 3 – Overall publication status for the full cohort and subcategories:

	ALL Studies		"Positive"		"Negative"		Mixed		Noncomparative	
	n	**%**	N	%	n	%	n	%	n	%
Submitted: Published[1]	**751**	**71**	212	66	119	77	40	77	380	71
Time to submission (IQR) days[2]	**537 (396-638)**		504 (343-601)		535 (408-612)		538 (366-640)		543 (427-674)	
Time to publication (IQR) days[3]	**823 (650-1063)**		774 (628-949)		876 (708-1203)		824 (694-1041)		833 (650-1103)	
Pending	**100**	**9**	32	10	13	8	4	8	51	10
Rejected	**53**	**5**	11	3	10	6	5	10	27	5
Abstract only	**77**	**7**	16	5	13	8	3	6	45	8
Not submitted	**83**	**8**	50	16	0	0	0	0	33	6
TOTAL	**1064**		321		155		52		536	

% based on proportion of study outcome with a given publication status

IQR = Interquartile range

[1]includes 48 studies accepted but not yet published as of data cutoff date

[2]based on n=867 studies with study end and subsequent submission dates

[3]based on n=670 studies with study end and subsequent publication dates

Figure 1 summarizes acceptance rates for "Positive" vs. "Negative" studies. First-time acceptance rates were 56% for "Positive" vs. 48% for "Negative" studies (p=0.17), respectively. These rates were also similar when the same analysis was performed using the "pure positive" and "pure negative" categories described in Methods (50% vs. 49%). Approximately three quarters of studies were accepted after 1-2 submissions for both study outcome categories (78% for "Positive" vs. 73% for "Negative" studies).

DISCUSSION

In this 6-year systematic review of more than 1000 studies from a single industry sponsor, publication submission rates were broadly similar across study types and outcomes. Over the study period, a greater proportion of "Negative" vs. "Positive" studies were submitted (92% vs. 79%) and accepted (77% vs. 66%) for journal publication, indicating a lack of bias against either submission or publication of "Negative" studies by sponsor and journals, respectively. Given the proximity of the analysis cutoff point to the end of the 6 year review period, journal decisions were still pending for 9% of manuscripts submitted. An additional 7% of studies were disclosed via congress abstract only (not included in publication totals). In total, 83 studies (8%) had not been submitted for publication in any form at the time of analysis, of which 49 were "Positive" bioequivalence studies and 33 were Noncomparative studies. 98% of studies had results posted to one or more public registers, including 100% of studies subject to FDAAA requirements for posting on www.clinicaltrials.gov.

While the topic of industry bias in reporting results of negative studies had been recently and widely debated, to our knowledge no previous study has systematically addressed the issue of publication bias according to study outcome. (1, 6, 7, 10-13) In our cohort, overall publication rates were broadly in line with recent estimates based solely on data obtained from www.clinicaltrials.gov. (5-7) Median times to publication were also consistent with previously published figures. (6-9) When evaluating the impact of study outcome, first time acceptance rates for "Positive" studies were numerically, but not statistically higher than for "Negative" studies (56% vs. 48%). Median time from study completion to submission was 31 days longer for "Negative" vs. "Positive" studies and time to publication was 99 days longer, suggesting that greater effort and care (e.g. journal selection) are required for publication of "Negative" data. Even so, 10% of all studies and 13% of negative studies required 3 or more submissions to achieve journal publication. These data suggest that rates of publication discussed in the scientific literature may substantially underestimate the effort that sponsors make to publish their results, since they do not capture the number of submissions and journal rejection rates.

This analysis also demonstrates that "Negative" studies can and have been successfully published in the scientific literature and provides no evidence of a systematic bias against their acceptance by journals. 92% of studies in our cohort that had an unfavourable outcome for the drug under evaluation were submitted and 77% had been published by the analysis cutoff date. However, the fact that slightly more than half of studies included in this analysis could not be readily classified into "Positive" vs. "Negative" outcomes also suggests that such a dichotomous scheme represents an oversimplification of study outcomes, particularly when early phase studies are included. The current transparency debate and efforts may be better served by focusing on ensuring full publication of all studies, irrespective of outcome.

Although this study has a number of strengths including: a large, systematic cohort; inclusion of all studies (irrespective of phase or outcome); rigorous methodology; and metrics on submissions as well as final publication rates, it also has important limitations. Clarity in specifying endpoints and classification of study outcomes may be inexact and subject to debate. For applicable studies, we deliberately chose to classify studies as having a "Positive" or "Negative" outcome for the drug, rather than on the basis of statistical significance alone, because for some types of studies (e.g. QTc safety studies) lack of significance is a favourable outcome for the drug being tested. Conversely, statistically significant negative safety findings may preclude further development of an investigational drug. This study did not address selective outcome reporting for the 751 studies that were published, although a unified process for reporting endpoints in study summaries and reports is followed by the sponsor to ensure consistent reporting. Most importantly, the data reported here are from a single industry sponsor. Without further data from other research sponsors, it is not possible to determine whether these results generalize to other industry sponsors or to other types of sponsors (academia, government). Despite this limitation, these data provide a clear signal that submission and publication bias against "Negative" studies may be less widespread than may have generally been assumed and should not deter efforts to publish them.

In summary, conducting and publishing analyses of submissions and successful publication according to study outcome are potentially important actions needed to assess and improve actual practice, and

where appropriate, to correct misperceptions regarding publication bias that adversely impact the credibility of drug research. We encourage other sponsors and journal editors to share similar information in efforts to contribute to better understanding of issues and barriers to full transparency.

Acknowledgments, Competing Interests, Funding and all other required statements.

The authors acknowledge the assistance of Tata Consultancy Services (TCS) Medical Writing Team in classifying study outcomes and WNS Global Services, Knowledge Centre for verification and formatting of publication data, both of which were paid for by GSK. TCS provided a variety of services to GSK but had neither direct involvement in the conduct of studies included in this cohort, nor any knowledge of their publication status. Data underlying these analyses are available as a supplemental data tool attached to this submission.

All authors have completed the ICMJE uniform disclosure form. All four authors were employees and shareholders in GSK at the time this research was conducted. GSK sponsored the >1000 individual studies described in this analysis, paid the salaries of the four named authors and funded the services acknowledged above, but was not otherwise involved in the project conception or execution. GE conceived the project and its design, supervised the collection of data and its analysis, prepared the first draft of this manuscript and led its critical revisions. BAM participated in the collection of data and its analysis and interpretation, and contributed critical revisions to the manuscript. BDC participated in the collection of data and its analysis and interpretation, and contributed critical revisions to the manuscript. JS contributed to data analysis and interpretation as well as critical revisions to the manuscript. All four authors assume accountability as individuals for the final manuscript and its contents. As lead author and guarantor, GE affirms that this manuscript is an honest, accurate and transparent account of the research being reported, that no important aspects have been omitted, and that any discrepancies from the study as planned have been explained. As a meta-analysis of previously completed (and registered) human research, the current analysis did not require study registration, ethics committee approval or informed consent (the latter were obtained for the individual studies contained in the analysis).

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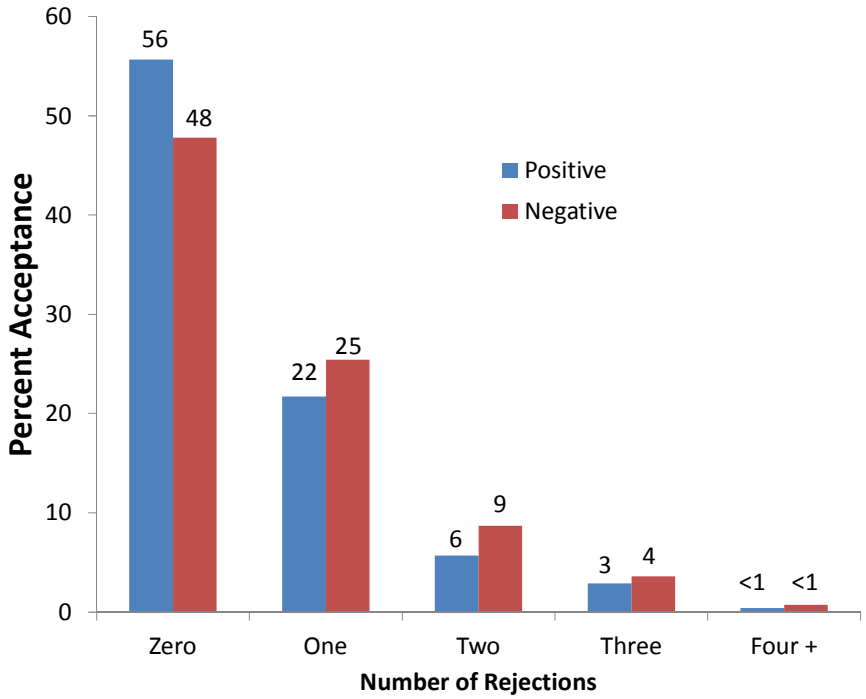
Figure 1 – Acceptance Rates for Positive vs. Negative Studies



% based on total number of studies with a journal decision