Are results from pharmaceutical-company-sponsored studies available to the public?

Rafael Dal-Ré, Alejandro Pedromingo, Manuel García-Losa, Juan Lahuerta, Rafael Ortega

Are results from a pharmaceutical company-sponsored studies available to the public?

Journal:	*European Journal of Clinical Pharmacology*
Manuscript ID:	EJCP-2010-0177.R2
Type of submission:	Original
Date Submitted by the Author:	02-Aug-2010
Complete List of Authors:	Dal-Ré, Rafael; Rey Juan Carlos University, Preventive Medicine Public Health and Medical Immunology and Microbiology Pedromingo, Alejandro; GlaxoSmithKline, Medical Department Garcia-Losa, Manuel; GlaxoSmithKline, Medical Department Lahuerta, Juan; GlaxoSmithKline, Medical Department Ortega, Rafael; GlaxoSmithKline, Medical Department

Are results from a pharmaceutical company-sponsored studies available to the public?

Rafael Dal-Ré MD, PhD, MPH (*), Alejandro Pedromingo L Sc (a), Manuel García-Losa MD, Juan Lahuerta MD, PhD, MHA, Rafael Ortega MD

Medical Department, GlaxoSmithKline SA, Tres Cantos, Madrid, Spain

(a) Biometry Department, GlaxoSmithKline SA, Tres Cantos, Madrid, Spain

(*) Corresponding author: Dr R Dal-Ré

Current address: Dr R Dal-Ré; Department of Preventive Medicine, Public Health and Medical Immunology and Microbiology, School of Health Sciences, Rey Juan Carlos University, Avda Atenas s/n; 28922 Alcorcón, Madrid, Spain

Phone: +34-91-488 8804; Fax: +34-91-488 8955 ; Email: rafael.dalre@urjc.es

Purpose

Only 53% and 63% of studies and clinical trials results presented at congresses are published.Company-sponsored trials' results are being posted on publicly accessible websites.We analyze the public availability (publication or posting on a website) rate, time to publication and factors predicting public availability of results of studies sponsored by a pharmaceutical company

Methods

Retrospective cohort study analyzing all studies conducted by GlaxoSmithKline in Spain between 2001-2006.Initiation and completion were defined as first subject/first visit and last subject/last visit (or their equivalents).Papers published up to March 31st,2009 were considered. Logistic regression models were used to identify factors predicting public availability of results.

Results

The cohort comprised 143 studies (94 clinical trials, of these,87 were included in international products' clinical development plans). Public availability rate was 80%(114/143) for all studies and 78%(73/94) for clinical trials; publication rates were 68% and 61%, respectively. The median time to publication for all studies and trials was 27.3 and 28.4 months, respectively. 'Study associated to a cancelled project' was the only significant factor associated to lower publication rate for all studies (OR:0.069; 95%CI 0.02-024;p<0.001) and trials (OR:0.075;95%CI 0.016-0.343;p=0.001) and a lower public availability rate (OR:0.052;95%CI 0.007-0.382;p=0.004) for trials' results. Therapy area,sample size,positive trial results,duration of experimental phase and being a clinical trial,did not predict publication or public availability.

Conclusions

80% of studies included in this analysis are publicly available. Website posting increases clinical trial results' public availability rate from 61% to 78%.Cancellation of projects is the single factor negatively influencing publication and public availability rates.

Key words: clinical trials, results, disclosure, sponsor, pharmaceutical company

Publication bias is well recognized [1] with important implications. One of them is that researchers have no access to all the data regarding the intervention of interest. The conclusions of their analyses are therefore bound to be biased but may nevertheless still influence treatment guidelines and decisions. Since it has been shown that positive studies are more likely to be published than negative or inconclusive ones [1-13], reviews tend to overestimate the effects of the intervention. Publication of results could be influenced by investigators, sponsors, journal editors and regulations [14]. Many papers have addressed the publication rate and time to publication of studies and factors influencing these. Most of them are based on abstracts presented at scientific congresses [6,7,12,15-18,24], studies approved by Research Ethics Committees (REC; or Institutional Review Boards in the US) [2-4,8,13, 19-22], studies funded by public agencies [5], or clinical trials submitted to Regulatory Agencies [10,11,23]. To our knowledge, none of them, however, has so far used internal data from a pharmaceutical company.

Indeed, controversy persists about how the industry, as compared to other sponsors, can affect the publication rate of study results. Some authors have found that industry-sponsored studies tend to be less likely published than those funded or sponsored by non-commercial organisations [2,3,22]. This however has not been confirmed by others [15,20,24] Several other factors seem to influence this, with the type of studies under review (e.g. Phase 1 and 2 trials are less likely to be published [2,13,25]) being a critical one. Finally, its worth mentioning a recent report comprising phase 2-4 trials registered in Clinicaltrials.gov showed that industry-sponsored trials (44%) were lees likely to be published than non-industry/non-government-sponsored ones (56%), but there was no difference when compared with government-sponsored trials (40%) [26]

Following a public debate on the publication of trial results, GlaxoSmithKline (GSK) launched in September 2004 a publicly available, internet-based clinical trial register (CSR; www.gsk-clinicalstudyregister.com/) in order to provide results from all GSK-sponsored clinical trials of marketed medicines and vaccines completed since the formation of GSK in 2001 [27]. The aim is to assist physicians in their clinical practice and research, an initiative taken also by other companies and their US trade association. The GSK register contains more than 3000 summaries of published and un-published trials conducted on 52 marketed products.

The objective of this study was to describe the public availability rate and time to publication of studies managed by GSK in Spain, as well as to identify factors that could predict such public availability. The journal impact factor of papers was also determined.

METHODS

Studies

This is a retrospective cohort study based on all scientific studies managed by GSK's Medical Department in Spain. All studies initiated (i.e. first visit of the first subject -or its equivalent, e.g. first in vitro test performed; first clinical history reviewed) in 2001 or later, and completed (i.e. last visit from the last subject -or its equivalent) up to December 31st, 2006, were included. Studies managed by international contract research organisations and all follow-up (extension) safety trials were excluded.

Data collection and definitions

A specific database was designed to contain all data gathered from the review of GSK files. Data were collected after a training session on abstraction of study characteristics; four authors (JL, MGL, RDR and RO) reviewed the data for consistency before entering it to the database. Discrepancies were resolved by consensus of all authors.

Time to publication was defined as the period between study completion (last visit of last patient or its equivalent) and time when first paper on the study's primary end-point, was published. Reason for not publication was captured. "Project" is defined as the group of studies comprising the product development plan for a given indication. "Cancelled projects" (i.e. those prematurely terminated) and the reason for such decision were also recorded.

Results of trials were classified as 'positive' if the protocol-defined hypothesis (primary end-point) was confirmed (i.e. statistically significant difference in favour of the experimental arm), or 'negative' if the hypothesis did not reach statistical significance, (i.e. not significant or significant in favour of the control arm). For non-inferiority trials, results meeting the protocol definition (below the pre-specified significance level, or a

Confidence Interval (CI) excluding the pre-specified difference) were considered 'positive'. When no statistical test was performed, the results were considered as 'positive' if classified by investigators as "important" or "striking", and as 'negative', if classified as of "moderate or "little importance" or "not striking" [28].

Publication was defined only as an original article in a peer-reviewed journal, issued up to March 31st, 2009 (cut-off date). For 'time to publication', only the month/year of publication were considered; an on-line article was included only if no paper publication was available. Journals' impact factors were obtained through ISI Web of Science (http://admin-apps.isiknowledge.com/JCR/JCR) for the year of each publication, between April 1st and 15th, 2009.

Data management and statistical analyses

Quality control was conducted to ensure 100% accuracy and completeness for primary outcomes and main explanatory variables, certifying <1% error in secondary data. Standard descriptive statistics were used for discrete and continuous data. A multivariate logistic regression model was performed to identify factors predicting publication. Two additional models with publication and public availability as outcomes were used only for clinical trials. Factors considered were 'Therapy Area', 'Study being associated to a cancelled project', 'Clinical trial', 'Sample size', 'Positive trial result' (only for clinical trials models) and 'Duration of experimental phase'. Odds Ratio and their 95% CI were calculated. Two multivariate linear regression models were used to identify potential factors explaining time to publication for studies and for clinical trials, respectively. Candidate factors were the same considered above plus the inclusion of 'Impact factor' which was Ln transformed. Non-standardized B coefficients were obtained. Only studies with data in all predicting factors were included in the multivariate models. All candidate factors were maintained in the final models; no stepwise procedures were used for selection. Factors were considered significant if P value <0.05. SPSS statistical software version 15.0 was used.

RESULTS

Studies

Only 3 studies (2 follow-up safety trials and 1 trial not managed by GSK-Spain but by international Contract Research Organizations – this latter was eventually published in an international peer-reviewed journal) were excluded from the analysis. The total sample included 143 studies, two thirds (n=94) being clinical trials. Tables 1 and 2 show the distribution by type of study and therapy area. All study protocols comprising human data, were approved by the relevant REC; clinical trials protocols were also approved by the Spanish Medicines Agency and the relevant competent authorities of the participating countries where appropriate. Six studies (4 clinical trials and 2 prospective, drug-related longitudinal observational studies) were terminated early due to safety (n=3) or recruitment issues (n=3). Twenty projects, accounting for 22 clinical trials (Table 3), were prematurely cancelled, most frequently because of lack of efficacy (16/20; 80%), and usually in phase 2 (15/20, 75%). An additional project was cancelled for lack of efficacy on an animal model, and after conducting an epidemiological longitudinal prospective study.

Most trials (87/94, 93%) were part of the clinical development plans of the investigational medicines and vaccines. Median (range) sample size of clinical trials included in the analysis was 452 (12-5052) subjects. By clinical development phase, these figures were: 13 (12-56), 290 (13-1415), 569 (127-5052) and 458 (120-1395) for phase 1, 2, 3 and 4, respectively

Public availability and Publication rates

a) Total sample (n=143). As shown in Tables 1 and 2, 68% (97/143) of all studies were published in peer-reviewed journals, and 1 was 'in-press', whereas 4 (3%) had already been submitted by the time of study cut-off date. Moreover, there were 17 (Tables 1 and 2) not yet published but posted on CSR. Total public availability (published or posted on GSK CSR) thus reached 80% (114/143). Three out of the 6 studies prematurely terminated were published (2 trials due to safety reasons, and 1 prospective, longitudinal, observational drug-related study due to slow recruitment). GSK was

acknowledged as the study sponsor and/or one, or more, GSK employees were included among study authors in all published manuscripts.

b) Clinical trials (n=94). Sixty one percent (57/94) of trial results were published (Table 1). In addition, 2 manuscripts had been submitted for publication. Results of 43% (16/37) of the non-published trials were posted on CSR, thus reaching 78% (73/94) of public availability rate (Table 1). Reasons for no publication and publication and publicly available rates stratified by positive or negative results are presented in Table 4. Results were publicly available for 87% (55/63) positive versus 58% (18/31) negative trials (Table 4). Results of trials associated with cancelled projects were only publicly available in 41% (9/22) of cases, as compared to 89% (64/72) of trials from non-cancelled projects (Table 3). Results of 21 trials were neither published nor posted on CSR, most of them (13; 62%) belonging to cancelled projects

Time to publication

a) Total sample (n=97/143): Median (range) time from study completion (last visit of the last subject) to publication was 27.3 (6.0-61.9) months. Time (median) to publication by therapy area ranged between 21.3 (Anti-infectives) and 38.5 months (Vaccines). The median (range) window time available for publication (from first study reaching last subject/last visit –or its equivalent- up to cut-off date) was 5.5 (2.5-8.24) years.

b) Clinical trials (n=57/94): Median (range) time from trial completion to publication was 28.4 (6.0-61.9) months. Phase 1 studies were published 16.7 months (median) after study completion. Remarkably, phase 2 (26.4 months) took about 10 or 6 months more (median) for publication than phase 3 (36.0 months) or 4 (30.4 months) trials, respectively. Time (median) to publication by therapy area ranged between 18.2 (Neurosciences) and 39.1 months (Vaccines). Trials with positive and negative results were published 26.9 (6.0-61.9) and 36.5 (8.2-55.8) months after study completion, respectively.

Impact factor

The results of 97 studies were published in 56 different peer-reviewed journals (89 papers in 51 international journals). All journals, except two, are indexed in PubMed; 91% (51/56) indexed by ISI Web of Science. The median impact factors of all published

studies and of clinical trials were 3.6 and 3.9, respectively; negative trials had higher median impact factor (4.5) than positive ones (3.8) (tables 2 and 4).

Predictors for public availability and time to publication

One hundred and nineteen studies were included in the regressions models, i.e. the whole study sample (n=143) except Microbiology (n=20), Systematic Review (n=1), Mathematical Model (n=1) and Pharmacoeconomic (n=2) ones. Among the six factors selected as candidate predictors in the multivariate logistic regression models, 'Study associated to a cancelled project' was the only significant one predicting a lower publication rate for all studies (OR: 0.069; 95% CI 0.02-024; p<0.001) and trials (OR: 0.075; 95% CI 0.016-0.343; p=0.001) and a lower public availability rate (OR: 0.052; 95% CI 0.007-0.382; p=0.004) for trials' results. From the linear models, 'Impact factor' was the only significant contributor reducing the time to publication: papers submitted to journals with higher impact factors resulted in an earlier publication when total sample (B: -5.7; p=0.010) or only clinical trials (B: -6.9; p=0.007) are considered. The results of the multivariate logistic and linear regression models are shown in tables 5 and 6.

DISCUSSION

Despite selective publication being frequently investigated [2-4,6-8,10-13,15-22], this study is the first analysis produced by a pharmaceutical company. Additionally, and as a novelty, it reports not only publication rate, but also availability of non-published study results posted on a website (GSK CSR) as a source of reliable information.

A recent Cochrane review [9] reported that after 9 years 53% of congress abstracts are published (with a median lag time of 17.9 months), this figure increasing to 63% for clinical trials. Our series shows a publication rate of 68% for all studies with a median lag time of 27.3 months; the corresponding figures being 61% and 28.4 months for clinical trials. Thus, GSK-sponsored studies in Spain have similar publication rates but with a shorter time to publication than those included in the Cochrane report (9 vs 5.5 years) [9]. When non-published trial results posted on CSR are added, the 'public availability' rate reaches 78%, (80% when considering the total sample). To put these results in context, only 80% of the Cochrane protocols were published as full reviews

after more than 8 years of completion, with a median time to publication of 2.4 years [29], despite being the most reported systematic reviews [30].

When comparing publication lag time between different studies, a critical element is the time point considered as "start" for each study. We believe that last subject/last visit date is the best milestone for clinical trials, or its equivalent for other types of studies, given its objectivity. Thus, other factors that may influence publication lag time (e.g. database freeze delay) are avoided. Unfortunately, this time point is seldom considered by others, since it is not usually available. The few studies performed using this milestone indicate a median time of 2.4 years to publication for 36 National Institutes of Health-funded Human Immunodeficiency Virus trials [5], or 23 months from dataset finalization to full report publications [31]. These lag times are comparable to the 28.4 months for our 57 published trials. Of note is the fact that most authors when assessing publication rates used different 'start' time points, sometimes not taking into consideration many months or years after study completion; thus, times such as 3-5 years after abstract presentation at congresses [6,7,9,12,15,16,18], or 5-8.5 years after Food and Drug Administration drug approval [10,11] are common.

Although the pharmaceutical industry has been reportedly involved in selective publication [10, 11, 23], this is not an industry-specific issue. Thus, Chan [32] recently stated that "accumulating empiric evidence has shown that selective reporting of results is a systemic problem afflicting all types of trials, including those with no commercial input". It is well documented that positive trials are more likely [1-10, 12, 28, 33] and earlier [4,5,7] published, than negative ones. Hopewell et al [33] reported that positive trials are published in 4 to 5 years whereas negative or null results take 6 to 8 years. In our series, positive trials had higher publication (71%) and public availability (87%) rates; negative trials, were, on the other hand, less frequently published (39%) and publicly available (58%); for non-published studies, the proportion of positive/negative results was 49%/51%. This apparent positive publication bias is however rejected by the logistic regression model showing that the factor 'study associated to a cancelled project' but not 'positive trial result', was the only significant predictor for publication and public availability of a trial result. Hence, positive studies influencing the decision of publication become a confounding factor. Additionally, positive trials were not published significantly earlier.

Although controversial, it is widely accepted that impact factor reflects to some extent the quality and scientific interest of the publication. Median and mean impact factors in our series were 3.9 and 7.5, respectively. Median impact factor ranged from 1.96 to 4.14 [12,16,17], and a mean of around 3 [18] in the few studies reporting this variable. In two studies, 24% and 37% of publications were in journals with an impact factor >4 [17] or >5 [13], respectively. As a comparison, 37% and 20% of the studies results of this study were published in journals with an impact factor > 4 and >5, respectively. On the other hand, we could speculate that the association of higher impact factor with a reduced time to publication may result from higher interest -and hence quicker submission of the paper- on the side of the authors and/or more agile review process by the more important journals.

In this analysis, data from 17 unpublished studies posted on CSR were added to publications. These summary results, as those on other websites, lack the context and interpretation that published papers provide [34] and therefore they should be a complement to publication rather than its substitute. Currently, publishing trial results involving only commercially available medicines – or even approved ones**,** as mandated by the US regulation [14] - is perceived as ethically insufficient. No longer is the aim only to provide information to health care professionals and researchers, but also to honour the implied contracts with study participants that expect their altruistic contribution to render useful information to science, and to prevent repetitive or risky trials with the same or similar compounds: hence, all trials results should be publicly available [35]. This is also a request included in the Declaration of Helsinki that states that positive, negative or inconclusive trial results, "should be published or otherwise made publicly available" [36] . Accordingly, GSK has recently committed to seek publication of results of all clinical trials, observational studies and meta-analyses, including those on prematurely terminated compounds; furthermore, when study results are not published, the CSR summaries will provide context and interpretation of the same [37].

Strengths and limitations

The availability of source documents for all published and unpublished studies is a plus for this internal analysis. Most reviews addressing publication fate of studies have been

performed by external researchers not involved in them, usually without access to protocols and full reports. This uncommon circumstance [23] enabled all conducted studies to be accounted for, from their start until their final fate, with virtually no missing data. In particular, the availability of the study completion date, critical for calculating time lag to publication, is missing in most reviews [10, 21]. This milestone coincides for almost all studies with the Food and Drug Administration requirement as the time point to count the 12-month period to disclose clinical trial results [14]. On the other hand, it could be argued that since the authors participated in the management of the studies and/or their publication, this might compromise their objectivity. Although this bias cannot be completely ruled out, it is tempered by the nature of the information collected, the quality control measures and the fact that most (93%) trials were part of international development projects, and therefore most decisions were made by others.

The external validity of this analysis could be questioned considering the limited number of studies and the even lower number of clinical trials, although greater than those followed until publication reported by others [4,5,13,19,21,23]. Another question is how well this trial sample actually represents the worldwide clinical development of new compounds. Data from the Clinicaltrials.gov database [38] show that in industry-sponsored phase 2-4 trials the activity in Spain ranks parallel to the United Kingdom and Italy. Spain has participated in approximately 25% of all GSK-sponsored international phase 2-4 drug trials during the study period. Despite the limitations of the present analysis, the results could be considered nevertheless as a likely representation of the publication and public availability rates of GSK worldwide. Conversely, no data is provided for other pharmaceutical companies in Spain and, therefore, there is no justification for extrapolating these results to other organisations.

The definitions used in this study of 'positive' and 'negative' trials' results differ from those used by other researchers. In our analysis, the definition of "positive" result correspond to that stated in the protocol for each study, as done by only few other authors [8,9], instead of meeting some specific criteria defined *a posteriori* to be applied to studies [2-7,10-12,28]. By respecting the criteria set by the authors of each protocol, we rated as positive not only the judgement of the investigators but also those accepted by the RECs and regulatory agencies when approving the clinical trials' protocols.

The time lag to publication analysis was applied to a completed set of studies (those with last subject/last visit date <1 Jan,2007). No additional censored data from studies finalizing beyond this date were considered and, therefore, Cox regression models simultaneously considering public availability and time lag to this endpoint were not employed; it should be noted that this model does not allow invariant calculation of publication and public availability rates. Although Cox regression analysis is used when assessing publication rate because of the nature of the datasets considered, we believe, as others did before [26], that our approach for a complete dataset over a defined time period is more informative.

Conclusion

Eighty percent of studies ~~(80%)~~ managed by GSK in Spain are publicly available. When clinical trials are considered, this figure is 78%, comprising a 61% journal publication rate plus an additional 17% of not published trial results posted on CSR –hence, substantially increasing public availability rate. As 93% of these clinical trials are multinational, it seems could be regarded as reasonably representative of what GSK activity is worldwide. Cancellation of projects is the single factor influencing a lower publication and public availability rates. There is, however, room for improvement for attaining a complete public availability of study results conducted by pharmaceutical companies.

Acknowledgements

We thank Dolores Asenjo, Teresa Compañy, Arturo Fueyo, Pilar García Corbeira, José Emilio Martín, Elena Morejón, Felipe Rodríguez-Alcántara and Josefa Samper for data collection, and Pilar Vicente for providing the impact factor of all manuscripts. We also thank Drs A Benbow (London, United Kingdom) and X Carne (Barcelona, Spain) for their critical reading and suggestions on the manuscript.

Financial Disclosure

This study required no funding.

Competing Interests

At the time of conducting the analysis all authors were GlaxoSmithKline SA employees and own stock in GSK.

Abbreviations

REC, research ethics committee.

GSK, GlaxoSmithKline

CSR, clinical study register

CI, confidence interval

References

1.- Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, et al (2008) Systematic Review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE 3(8): e3081. doi:10.1371/journal.pone.0003081

2.- Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR (1991) Publication bias in clinical research. Lancet 337: 867-72

3.- Dickersin K (1990) The existence of publication bias and risk factors for its occurrence. JAMA 263: 1385–1389.

4.- Stern JM, Simes RJ (1997) Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 315: 640-5

5.- Ioannidis JP (1998) Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 279: 281-6

6.- Callaham ML, Wears RL, Weber E, Barton C, Young G (1998) Positive-outcome bias and other limitations in the outcome of research abstracts submitted to a scientific meeting. JAMA 280: 254-7

7.- Krzyzanowska M, Pintilie M, Tannock IF (2003) Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA 290: 495-501

8.- Decullier E, Lheritier V, Chapuis F (2005) Fate of biomedical research protocols and publication bias in France: retrospective cohort study. BMJ. Jul 2; 331(7507):19. Epub 2005 Jun 20.

9.- Scherer RW, Lengenberg P, von Elm E (2007) Full publication of results initially presented in abstracts. Cochrane Database of Systematic Reviews Issue 2, Art No: MR000005. Doi: 10.1002/14651858.MR000005.pub3

10.- Lee K, Bacchetti P, Sim I (2008) Publication of clinical trials supporting successful new drug applications: A literature analysis. PLoS Med 5(9): e191. doi:10.1371/journal.pmed.0050191

11.- Rising K, Bacchetti P, Bero L (2008) Reporting bias in drug trials submitted to the Food and Drug Administration: A review of publication and presentation. PLoS Med 5(11): e217. doi:10.1371/journal. pmed.0050217

12.- Klassen TP, Wiebe N, Russell K, Stevens K, Hartling L et al (2002) Abstracts of randomized controlled trials presented at the society for pediatric reaserach meeting. Arch Pediatr Adolesc Med 156: 474-9

13.- Hall R, Antueno C, Webber A (2007) Publication bias in the medical literature: a review by a Canadian research ethics board. Can J Anesth 54: 331-5

14.- Food and Drug Administration Amendments Act 2007. www.fda.gov/oc/initiatives/HR3580.pdf (accessed January 7th, 2009)

15.- Sanossian N, Ohanian AG, Saver JL, Kim LI, Ovbiagele B (2006) Frequency and determinants of nonpublication of research in the stroke literature. Stroke 37: 2588-92

16.- Montané E, Vidal X (2007) Fate of the abstracts presented at three Spanish clinical pharmacology congresses and reasons for unpublished research. Eur J Clin Pharmacol 63: 103-11

17.- Sanders DS, Carter MJ, Hurlstone DP, Lobo AJ, Hoggard N (2001) Research outcomes in British gastroenterology: an audit of the subsequent full publication of abstracts presented at the British Society of Gastroenterology. Gut 49: 154-5

18.- Carroll AE, Sox CM, Tarini BA, Ringold S, Christakis DA (2003) Does presentation format at the Pediatric Academic Societies' annual meeting predict subsequent publication? Pediatrics 112, 1238-41

19.- Pich J, Carne X, Arnaiz JA, Gomez B, Trilla A, et al (2003) Role of a research ethics committee in follow-up and publications of results. Lancet 361: 1015-6

20.- Turer A, Mahaffey KW, Compton KL, Califf RM, Schulman KA (2007) Publication or presentation of results from multicenter clinical trials: evidence from an academic medical centre. Am Heart J 153: 674-80

21.-Blümle A, Antes G, Schumacher M, Just H, von Elm E (2008) Clinical research projects at a German medical faculty: follow-up from ethical approval to publication and citation by others. J Med Ethics Sep; 34 (9): e20

22.- Von Elm E, Röllin A, Blümle A, Huwiler K, Witschi M, et al (2008) Publication and non-publication of clinical trials: longitudinal study of applications submitted to a research ethics committee. Swiss Med Wkly 138: 197-203

23.- Melander H, Ahlquist-Rastad J, Meijer G, Beermann B (2003) Evidence b(i)ased medicine_ selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ 326: 1171-3

24.- McLennan M, Leong FC, Steele A, Harris J (2008) The influence of industry sponsorship on the acceptance of abstracts and their publication. Am J Obstet Gynecol 198: 579. e1-579.e1-4

25.- Decullier E, Chan AW, Chapuis F (2009) Inadequate dissemination of phase I trials: a retrospective cohort study. PLoS Med 6 (2): e1000034. doi:10.1371/journal.pmed.1000034

26.- Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM (2009) Trial publication after registration in ClinicalTrials.Gov: a cross-sectional analysis. PLoS Med 6 (9): e1000144. doi:10.1371/journal.pmed.1000144

27.- Krall RL, Rockhold F (2006) Reasons for optimism not disillusionment. J Roy Soc Med 99: 435

28.- Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. (2009) Publication bias in clinical trials due to statistical significance or direction of trials results. Cochrane Database Syst Rev Jan 21 (1): MR000006

29.- Tricco AC, Brehaut J, Chen MH, Moher D (2008) Following 411 Cochrane protocols to completion: a retrospective cohort study. PLoS ONE 3 (11): e3684. doi:10.1371/journal.pone.0003684

30.- Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG (2007) Epidemiology and reporting characteristics of systematic reviews. PLoS Med 4 (3): e78. doi:10.1371/journal.pmed.0040078

31.- Ünalp A, Tonascia S, Meinert CL (2007). Presentation in relation to publication of results from clinical trials. Contem Clin Trials 28: 358-69

32.- Chan A-W (2008) Bias, spin, and misreporting: Time for full access to trial protocols and results. PLoS Med 5(11): e230. doi:10.1371/journal.pmed.0050230

33.- Hopewell S, ClarkeMJ, Stewart L, Tierney J (2007) Time to publication for results of clinical trials. Cochrane Database of Systematic Reviews Issue 2. Art. No.: MR000011. DOI: 10.1002/14651858.MR000011.pub2.

34.- Wood AJJ. Progress and deficiencies in the registration of clinical trials (2009). N Engl J Med 360: 824-30

35.- Ghersi D, Clarke M, Berlin J, Gülmezoglu AM, Kush T et al (2008) Reporting the findings of clinical trials: a discussion paper. Bull WHO 86: 492-3

36.- World Medical Association (2008) Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 59th WMA General Assembly, Seoul, October. http://www.wma.net/e/policy/b3.htm (accessed May, 3rd, 2009)

37.- Strahlman E, Rockhold F, Freeman A (2009) Public disclosure of research. Lancet 373: 1319-20

38.- Karlberg JPE. (2008) Industry clinical testing of new medicinal products requires 95000 study sites and 1300000 subjects annually. Clinical Trial Magnifier 1: 101-19 (www.ClinicalTrialMagnifier.com)

Table 1 Study sample (n=143). Public availability of study results: Publications and study results posted on GSK's Clinical Study Register (CSR), by study type.

			N (%)	A: Publication[e] N (%)	B: Non-published but posted on CSR[f] N (%)	A+B: Publication + CSR. N (%)
Type of study	Clinical trial	Phase 1	5	4 (80)	0 (0)	4 (80)
		Phase 2	31	12 (39)	4 (13)	16 (52)
		Phase 3	47	31 (66)	12 (26)	43 (92)
		Phase 4	11	10 (91)	0 (0)	10 (91)
		Total	94 (66)	57 (61)	16 (17)	73 (78)
	Drug-related, observational[a]		9 (6)	4 (44)	1 (11) (*)	5 (56)
	Epidemiology[b]		10 (7)	7 (70)	NA	7 (70)
	Microbiology[c]		20 (14)	20 (100)	NA	20 (100)
	Other[d]		10 (7)	9 (90)	NA	9 (90)
Total			143 (100)	97 (68)	17 (12)	114 (80)

(a) Longitudinal prospective, 5; cross-sectional, 1; retrospective, 2; case-control, 1

(b) Longitudinal prospective, 4; retrospective, 2; cross-sectional, 4

(c) In vitro research, 12: surveillances, 6; animal models, 2

(d) Health Scales Validation, 4; Pharmacoeconomy, 2; Systematic Review, 1; Mathematical Model, 1; Clinical trial on devices and modelling, 1; Health care quality assessment , 1

(e) Publication of full study results in a peer-reviewed journal. Includes paper (n=94) and on-line (n=3) publications.

(f) No of full trials' results posted at GSK's CSR that have not been published yet. Hence, if the results of a trial were published in a journal, it is not included in this figure, regardless if it is, or not, posted in the CSR

N: No of studies

(*) CSR was intended for posting clinical trial results. However, there is a case-control study published and posted on CSR, and a longitudinal, drug-related study, not published but posted on CSR –these were the only non-clinical trials posted on CSR

Table 2. Study sample (n=143). Public availability of study results: Publications and study results posted on GSK's Clinical Study Register (CSR), by therapy area

		N (%)	A: Publication[a] N (%) / Impact factor-median[b]	B: Non-published but posted on CSR[c] N (%)	A+B: Publication + CSR. N (%)
Therapy Area	Neurosciences	22 (15)	13 (59) / 3.13	1 (5)	14 (64)
	C, M & R	24 (17)	16 (67) / 3.00	5 (21)	21 (88)
	Anti-infectives	47 (33)	38 (81) / 3.89	6 (13)	44 (94)
	Oncology	13 (9)	7 (54) / 13.60	2 (15)	9 (69)
	Vaccines	19 (13)	15 (79) / 3.09	3 (16)	18 (95)
	R, U & G	18 (13)	8 (44) / 3.20	0 (0)	8 (44)
	Total	143	97 (68) / 3.61	17 (12)	114 (80)

(a) Publication of full study results in a peer-reviewed journal. Includes paper (n=94) and on-line (n=3) publications.

(b) Impact factor of the year of publication. For papers published on 2008 or 2009, 2007 impact factor is used

(c) No of full trials' results posted at GSK's CSR that have not been published yet. Hence, if the results of a trial were published in a journal, it is not included in this figure, regardless if it is, or not, posted in the CSR

N: No of studies

C, M & R: Cardiovascular, Metabolism and Respiratory

R, U & G: Rheumatology, Urology and Gastroenterology

Table 3. Clinical Trials (n=94). Cancelled projects and fate of results.

Cancelled projects, 20	16 for lack of efficacy: 12 in phase 2, 1 in phase 2/3 and 3 in phase 3; comprising 17 trials[b], of all therapy areas except vaccines 2 for safety reasons: 1 in phase 1, due to animal toxicological findings, 1 in phase 2 ; comprising 3 trials of neurosciences and anti-infectives 2 for manufacturing issues: 1 in Phase 2, and 1 in phase 3 ; comprising 2 vaccine trials
Trials associated to cancelled projects - N (%) Published / Publicly available[a] Not published / Non Publicly available	22 (23) 4 (18) / 9 (41) 18 (82) / 13 (59)
Trials associated to non-cancelled projects - N (%) Published / Publicly available[a] Not published / Non Publicly available	72 (77) 53 (74) / 64 (89) 19 (26) / 8 (11)

"Project" is defined as the group of studies comprising the product development plan for a given indication.

(a) Published or posted on GSK Clinical Study Register (CSR)

(b) And an additional epidemiological longitudinal prospective study

N: No of clinical trials

Table 4. Clinical Trials (n=94). Main characteristics, fate of results and impact factors.

		N (%) (Unless otherwise stated)
One, or more, GSK author in published papers		54 (95)
Window time to publication (years)[a]		Median (range) /Mean 5.6 (2.9-8.2) / 5.7
Positive results[b]		63 (67)
	Phase 1	5 (100)
	Phase 2	9 (29)
	Phase 3	40 (85)
	Phase 4	9 (82)
Positive results[b]		63 (67)
	Published / Publicly available[c]	45 (71) / 55 (87)
	Not Published / Non Publicly available	18 (29) / 8 (13)
Negative results [a]		31 (33)
	Published / Publicly available[c]	12 (39) / 18 (58)
	Not Published / Non Publicly available	19 (61) / 13 (42)
Published papers		57 (61)
	Positive results	45 (79)
	Negative results	12 (21)
Non published papers		37 (39)
	Positive results	18 (49)
	Negative results	19 (51)
Impact factor of published papers (n=53)		Median (range) /Mean 3.9 (0.6-52.6) / 7.5
	Phase 1 (n=4)	3.9 (3.8-5.9) / 4.4
	Phase 2 (n=11)	4.9 (2.0-52.6) / 10.2
	Phase 3 (n=28)	3.3 (0.6-51.3) / 7.8
	Phase 4 (n=10)	3.2 (1.8-11.1) / 5.0
	Positive results (n=42)	3.8 (0.6-52.6) / 7.9
	Negative results (n=11)	4.5 (2.0-15.5) / 6.3
Reasons for no publication (n=37)	Project cancelled	16 (43)
	Lack of time/resources	12 (33)
	Unknown	6 (16)

	Other[d]	3 (8)
Posted on CSR		57 (61)
Marketed products[e]	Published / Publicly available	42 (84) / 50 (100) [f]

(a) Time elapsed from the first clinical trial reaching last subject/last visit until the cut-off date (March 31st, 2009)

(b) See Methods for definitions

(c) Published or posted on GSK Clinical Study Register (CSR)

(d) Submitted with no answer yet (n=2); submitted and rejected (n=1)

(e) Clinical trials conducted with marketed products, i.e. conducted with products that were marketed at the time the trial was run or with a product that was marketed (for the indication, dosage, etc) as of the cut-off date (March 31st, 2009).

(f) All trials were published or posted on GSK CSR, except one which results were posted on Bayer's Website.

N: No of clinical trials (where appropriate)

Table 5 . Factors predicting publication and public availability. Odds Ratios (OR) and 95% Confidence Intervals (95% CI) from multivariate logistic regression models.

		All studies[a]		Clinical Trials; Publication as outcome		Clinical Trials; Public Availablility as outcome	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Factor	Therapy Area		0.488		0.772		0.101
	Study associated to a cancelled project	0.069 (0.02 - 0.24)	0.000	0.075 (0.016 - 0.343)	0.001	0.052(0.007 - 0.382)	0.004
	Clinical trial	1.33 (0.45 - 3.93)	0.606				
	Sample size	1.00 (0.99 - 1.01)	0.979	1.00 (0.999 - 1.001)	0.964	1.00 (0.999 - 1.001)	0.823
	Positive trial result			1.028 (0.286 - 3.691)	0.966	1.118 (0.210 - 5.942)	0.896
	Duration of experimental phase	1.004 (0.96 - 1.05)	0.878	0.996 (0.945 - 1.050)	0.885	1.064 (0.962 - 1.171)	0.231
	Constant	1.17	0.826	2.306	0.373	1.529	0.720

(a) All studies (n= 119) are included, except those belonging to Microbiology (n=20), Systematic Review, (n=1); Mathematical Model (n=1); Pharmacoeconomy (n=2)

OR = Odds ratio; 95% CI = 95% confidence interval

Table 6. Factors predicting time to publication. Coefficients (B) and standard errors (SE) from multivariate linear regression models.

		All studies[a]			Clinical Trials		
		B[c]	SE	P	B[c]	SE	P
Factor	Therapy Area			N.S.			N.S.
	Study associated to a Cancelled Project	2.843	7.646	0.711	-0.068	8.437	0.994
	Clinical trial	0.309	4.110	0.940			
	Sample size	-0.002	0.002	0.366	-0.004	0.002	0.100
	Positive trial result in publication				-5.103	5.038	0.317
	Duration of experimental phase	0.101	0.169	0.552	0.191	0.205	0.356
	Impact factor[b]	-5.739	2.151	0.010	-6.861	2.413	0.007
	Constant	35.495	7.332	0.000	41.11	7.963	0.000

(a) All studies (n= 119) are included, except those belonging to Microbiology (n=20), Systematic Review, (n=1); Mathematical Model (n=1); Pharmacoeconomy (n=2)

(b) Ln transformed

(c) Non-standardized coefficients

Are results from a pharmaceutical company-sponsored studies available to the public?

Rafael Dal-Ré MD, PhD, MPH (*), Alejandro Pedromingo L Sc (a), Manuel García-Losa MD, Juan Lahuerta MD, PhD, MHA, Rafael Ortega MD

Medical Department, GlaxoSmithKline SA, Tres Cantos, Madrid, Spain

(a) Biometry Department, GlaxoSmithKline SA, Tres Cantos, Madrid, Spain

(*) Corresponding author: Dr R Dal-Ré

Current address: Dr R Dal-Ré; Department of Preventive Medicine, Public Health and Medical Immunology and Microbiology, School of Health Sciences, Rey Juan Carlos University, Avda Atenas s/n; 28922 Alcorcón, Madrid, Spain

Phone: +34-91-488 8804; Fax: +34-91-488 8955 ; Email: rafael.dalre@urjc.es

Purpose

Only 53% and 63% of studies and clinical trials results presented at congresses are published.Company-sponsored trials' results are being posted on publicly accessible websites.We analyze the public availability (publication or posting on a website) rate, time to publication and factors predicting public availability of results of studies sponsored by a pharmaceutical company

Methods

Retrospective cohort study analyzing all studies conducted by GlaxoSmithKline in Spain between 2001-2006.Initiation and completion were defined as first subject/first visit and last subject/last visit (or their equivalents).Papers published up to March 31st,2009 were considered. Logistic regression models were used to identify factors predicting public availability of results.

Results

The cohort comprised 143 studies (94 clinical trials, of these,87 were included in international products' clinical development plans). Public availability rate was 80%(114/143) for all studies and 78%(73/94) for clinical trials; publication rates were 68% and 61%, respectively. The median time to publication for all studies and trials was 27.3 and 28.4 months, respectively. 'Study associated to a cancelled project' was the only significant factor associated to lower publication rate for all studies (OR:0.069; 95%CI 0.02-024;p<0.001) and trials (OR:0.075;95%CI 0.016-0.343;p=0.001) and a lower public availability rate (OR:0.052;95%CI 0.007-0.382;p=0.004) for trials' results. Therapy area,sample size,positive trial results,duration of experimental phase and being a clinical trial,did not predict publication or public availability.

Conclusions

80% of studies included in this analysis are publicly available. Website posting increases clinical trial results' public availability rate from 61% to 78%.Cancellation of projects is the single factor negatively influencing publication and public availability rates.

Key words: clinical trials, results, disclosure, sponsor, pharmaceutical company

Publication bias is well recognized [1] with important implications. One of them is that researchers have no access to all the data regarding the intervention of interest. The conclusions of their analyses are therefore bound to be biased but may nevertheless still influence treatment guidelines and decisions. Since it has been shown that positive studies are more likely to be published than negative or inconclusive ones [1-13], reviews tend to overestimate the effects of the intervention. Publication of results could be influenced by investigators, sponsors, journal editors and regulations [14]. Many papers have addressed the publication rate and time to publication of studies and factors influencing these. Most of them are based on abstracts presented at scientific congresses [6,7,12,15-18,24], studies approved by Research Ethics Committees (REC; or Institutional Review Boards in the US) [2-4,8,13, 19-22], studies funded by public agencies [5], or clinical trials submitted to Regulatory Agencies [10,11,23]. To our knowledge, none of them, however, has so far used internal data from a pharmaceutical company.

Indeed, controversy persists about how the industry, as compared to other sponsors, can affect the publication rate of study results. Some authors have found that industry-sponsored studies tend to be less likely published than those funded or sponsored by non-commercial organisations [2,3,22]. This however has not been confirmed by others [15,20,24] Several other factors seem to influence this, with the type of studies under review (e.g. Phase 1 and 2 trials are less likely to be published [2,13,25]) being a critical one. Finally, its worth mentioning a recent report comprising phase 2-4 trials registered in Clinicaltrials.gov showed that industry-sponsored trials (44%) were lees likely to be published than non-industry/non-government-sponsored ones (56%), but there was no difference when compared with government-sponsored trials (40%) [26]

Following a public debate on the publication of trial results, GlaxoSmithKline (GSK) launched in September 2004 a publicly available, internet-based clinical trial register (CSR; www.gsk-clinicalstudyregister.com/) in order to provide results from all GSK-sponsored clinical trials of marketed medicines and vaccines completed since the formation of GSK in 2001 [27]. The aim is to assist physicians in their clinical practice and research, an initiative taken also by other companies and their US trade association. The GSK register contains more than 3000 summaries of published and un-published trials conducted on 52 marketed products.

The objective of this study was to describe the public availability rate and time to publication of studies managed by GSK in Spain, as well as to identify factors that could predict such public availability. The journal impact factor of papers was also determined.

METHODS

Studies

This is a retrospective cohort study based on all scientific studies managed by GSK's Medical Department in Spain. All studies initiated (i.e. first visit of the first subject -or its equivalent, e.g. first in vitro test performed; first clinical history reviewed) in 2001 or later, and completed (i.e. last visit from the last subject -or its equivalent) up to December 31st, 2006, were included. Studies managed by international contract research organisations and all follow-up (extension) safety trials were excluded.

Data collection and definitions

A specific database was designed to contain all data gathered from the review of GSK files. Data were collected after a training session on abstraction of study characteristics; four authors (JL, MGL, RDR and RO) reviewed the data for consistency before entering it to the database. Discrepancies were resolved by consensus of all authors.

Time to publication was defined as the period between study completion (last visit of last patient or its equivalent) and time when first paper on the study's primary end-point, was published. Reason for not publication was captured. "Project" is defined as the group of studies comprising the product development plan for a given indication. "Cancelled projects" (i.e. those prematurely terminated) and the reason for such decision were also recorded.

Results of trials were classified as 'positive' if the protocol-defined hypothesis (primary end-point) was confirmed (i.e. statistically significant difference in favour of the experimental arm), or 'negative' if the hypothesis did not reach statistical significance, (i.e. not significant or significant in favour of the control arm). For non-inferiority trials, results meeting the protocol definition (below the pre-specified significance level, or a

Confidence Interval (CI) excluding the pre-specified difference) were considered 'positive'. When no statistical test was performed, the results were considered as 'positive' if classified by investigators as "important" or "striking", and as 'negative', if classified as of "moderate or "little importance" or "not striking" [28].

Publication was defined only as an original article in a peer-reviewed journal, issued up to March 31st, 2009 (cut-off date). For 'time to publication', only the month/year of publication were considered; an on-line article was included only if no paper publication was available. Journals' impact factors were obtained through ISI Web of Science (http://admin-apps.isiknowledge.com/JCR/JCR) for the year of each publication, between April 1st and 15th, 2009.

Data management and statistical analyses

Quality control was conducted to ensure 100% accuracy and completeness for primary outcomes and main explanatory variables, certifying <1% error in secondary data. Standard descriptive statistics were used for discrete and continuous data. A multivariate logistic regression model was performed to identify factors predicting publication. Two additional models with publication and public availability as outcomes were used only for clinical trials. Factors considered were 'Therapy Area', 'Study being associated to a cancelled project', 'Clinical trial', 'Sample size', 'Positive trial result' (only for clinical trials models) and 'Duration of experimental phase'. Odds Ratio and their 95% CI were calculated. Two multivariate linear regression models were used to identify potential factors explaining time to publication for studies and for clinical trials, respectively. Candidate factors were the same considered above plus the inclusion of 'Impact factor' which was Ln transformed. Non-standardized B coefficients were obtained. Only studies with data in all predicting factors were included in the multivariate models. All candidate factors were maintained in the final models; no stepwise procedures were used for selection. Factors were considered significant if P value <0.05. SPSS statistical software version 15.0 was used.

RESULTS

Studies

Only 3 studies (2 follow-up safety trials and 1 trial not managed by GSK-Spain but by international Contract Research Organizations – this latter was eventually published in an international peer-reviewed journal) were excluded from the analysis. The total sample included 143 studies, two thirds (n=94) being clinical trials. Tables 1 and 2 show the distribution by type of study and therapy area. All study protocols comprising human data, were approved by the relevant REC; clinical trials protocols were also approved by the Spanish Medicines Agency and the relevant competent authorities of the participating countries where appropriate. Six studies (4 clinical trials and 2 prospective, drug-related longitudinal observational studies) were terminated early due to safety (n=3) or recruitment issues (n=3). Twenty projects, accounting for 22 clinical trials (Table 3), were prematurely cancelled, most frequently because of lack of efficacy (16/20; 80%), and usually in phase 2 (15/20, 75%). An additional project was cancelled for lack of efficacy on an animal model, and after conducting an epidemiological longitudinal prospective study.

Most trials (87/94, 93%) were part of the clinical development plans of the investigational medicines and vaccines. Median (range) sample size of clinical trials included in the analysis was 452 (12-5052) subjects. By clinical development phase, these figures were: 13 (12-56), 290 (13-1415), 569 (127-5052) and 458 (120-1395) for phase 1, 2, 3 and 4, respectively

Public availability and Publication rates

a) Total sample (n=143). As shown in Tables 1 and 2, 68% (97/143) of all studies were published in peer-reviewed journals, and 1 was 'in-press', whereas 4 (3%) had already been submitted by the time of study cut-off date. Moreover, there were 17 (Tables 1 and 2) not yet published but posted on CSR. Total public availability (published or posted on GSK CSR) thus reached 80% (114/143). Three out of the 6 studies prematurely terminated were published (2 trials due to safety reasons, and 1 prospective, longitudinal, observational drug-related study due to slow recruitment). GSK was

acknowledged as the study sponsor and/or one, or more, GSK employees were included among study authors in all published manuscripts.

b) Clinical trials (n=94). Sixty one percent (57/94) of trial results were published (Table 1). In addition, 2 manuscripts had been submitted for publication. Results of 43% (16/37) of the non-published trials were posted on CSR, thus reaching 78% (73/94) of public availability rate (Table 1). Reasons for no publication and publication and publicly available rates stratified by positive or negative results are presented in Table 4. Results were publicly available for 87% (55/63) positive versus 58% (18/31) negative trials (Table 4). Results of trials associated with cancelled projects were only publicly available in 41% (9/22) of cases, as compared to 89% (64/72) of trials from non-cancelled projects (Table 3). Results of 21 trials were neither published nor posted on CSR, most of them (13; 62%) belonging to cancelled projects

Time to publication

a) Total sample (n=97/143): Median (range) time from study completion (last visit of the last subject) to publication was 27.3 (6.0-61.9) months. Time (median) to publication by therapy area ranged between 21.3 (Anti-infectives) and 38.5 months (Vaccines). The median (range) window time available for publication (from first study reaching last subject/last visit –or its equivalent- up to cut-off date) was 5.5 (2.5-8.24) years.

b) Clinical trials (n=57/94): Median (range) time from trial completion to publication was 28.4 (6.0-61.9) months. Phase 1 studies were published 16.7 months (median) after study completion. Remarkably, phase 2 (26.4 months) took about 10 or 6 months more (median) for publication than phase 3 (36.0 months) or 4 (30.4 months) trials, respectively. Time (median) to publication by therapy area ranged between 18.2 (Neurosciences) and 39.1 months (Vaccines). Trials with positive and negative results were published 26.9 (6.0-61.9) and 36.5 (8.2-55.8) months after study completion, respectively.

Impact factor

The results of 97 studies were published in 56 different peer-reviewed journals (89 papers in 51 international journals). All journals, except two, are indexed in PubMed; 91% (51/56) indexed by ISI Web of Science. The median impact factors of all published

studies and of clinical trials were 3.6 and 3.9, respectively; negative trials had higher median impact factor (4.5) than positive ones (3.8) (tables 2 and 4).

Predictors for public availability and time to publication

One hundred and nineteen studies were included in the regressions models, i.e. the whole study sample (n=143) except Microbiology (n=20), Systematic Review (n=1), Mathematical Model (n=1) and Pharmacoeconomic (n=2) ones. Among the six factors selected as candidate predictors in the multivariate logistic regression models, 'Study associated to a cancelled project' was the only significant one predicting a lower publication rate for all studies (OR: 0.069; 95% CI 0.02-024; p<0.001) and trials (OR: 0.075; 95% CI 0.016-0.343; p=0.001) and a lower public availability rate (OR: 0.052; 95% CI 0.007-0.382; p=0.004) for trials' results. From the linear models, 'Impact factor' was the only significant contributor reducing the time to publication: papers submitted to journals with higher impact factors resulted in an earlier publication when total sample (B: -5.7; p=0.010) or only clinical trials (B: -6.9; p=0.007) are considered. The results of the multivariate logistic and linear regression models are shown in tables 5 and 6.

DISCUSSION

Despite selective publication being frequently investigated [2-4,6-8,10-13,15-22], this study is the first analysis produced by a pharmaceutical company. Additionally, and as a novelty, it reports not only publication rate, but also availability of non-published study results posted on a website (GSK CSR) as a source of reliable information.

A recent Cochrane review [9] reported that after 9 years 53% of congress abstracts are published (with a median lag time of 17.9 months), this figure increasing to 63% for clinical trials. Our series shows a publication rate of 68% for all studies with a median lag time of 27.3 months; the corresponding figures being 61% and 28.4 months for clinical trials. Thus, GSK-sponsored studies in Spain have similar publication rates but with a shorter time to publication than those included in the Cochrane report (9 vs 5.5 years) [9]. When non-published trial results posted on CSR are added, the 'public availability' rate reaches 78%, (80% when considering the total sample). To put these results in context, only 80% of the Cochrane protocols were published as full reviews

after more than 8 years of completion, with a median time to publication of 2.4 years [29], despite being the most reported systematic reviews [30].

When comparing publication lag time between different studies, a critical element is the time point considered as "start" for each study. We believe that last subject/last visit date is the best milestone for clinical trials, or its equivalent for other types of studies, given its objectivity. Thus, other factors that may influence publication lag time (e.g. database freeze delay) are avoided. Unfortunately, this time point is seldom considered by others, since it is not usually available. The few studies performed using this milestone indicate a median time of 2.4 years to publication for 36 National Institutes of Health-funded Human Immunodeficiency Virus trials [5], or 23 months from dataset finalization to full report publications [31]. These lag times are comparable to the 28.4 months for our 57 published trials. Of note is the fact that most authors when assessing publication rates used different 'start' time points, sometimes not taking into consideration many months or years after study completion; thus, times such as 3-5 years after abstract presentation at congresses [6,7,9,12,15,16,18], or 5-8.5 years after Food and Drug Administration drug approval [10,11] are common.

Although the pharmaceutical industry has been reportedly involved in selective publication [10, 11, 23], this is not an industry-specific issue. Thus, Chan [32] recently stated that "accumulating empiric evidence has shown that selective reporting of results is a systemic problem afflicting all types of trials, including those with no commercial input". It is well documented that positive trials are more likely [1-10, 12, 28, 33] and earlier [4,5,7] published, than negative ones. Hopewell et al [33] reported that positive trials are published in 4 to 5 years whereas negative or null results take 6 to 8 years. In our series, positive trials had higher publication (71%) and public availability (87%) rates; negative trials, were, on the other hand, less frequently published (39%) and publicly available (58%); for non-published studies, the proportion of positive/negative results was 49%/51%. This apparent positive publication bias is however rejected by the logistic regression model showing that the factor 'study associated to a cancelled project' but not 'positive trial result', was the only significant predictor for publication and public availability of a trial result. Hence, positive studies influencing the decision of publication become a confounding factor. Additionally, positive trials were not published significantly earlier.

Although controversial, it is widely accepted that impact factor reflects to some extent the quality and scientific interest of the publication. Median and mean impact factors in our series were 3.9 and 7.5, respectively. Median impact factor ranged from 1.96 to 4.14 [12,16,17], and a mean of around 3 [18] in the few studies reporting this variable. In two studies, 24% and 37% of publications were in journals with an impact factor >4 [17] or >5 [13], respectively. As a comparison, 37% and 20% of the studies results of this study were published in journals with an impact factor > 4 and >5, respectively. On the other hand, we could speculate that the association of higher impact factor with a reduced time to publication may result from higher interest -and hence quicker submission of the paper- on the side of the authors and/or more agile review process by the more important journals.

In this analysis, data from 17 unpublished studies posted on CSR were added to publications. These summary results, as those on other websites, lack the context and interpretation that published papers provide [34] and therefore they should be a complement to publication rather than its substitute. Currently, publishing trial results involving only commercially available medicines – or even approved ones**,** as mandated by the US regulation [14] - is perceived as ethically insufficient. No longer is the aim only to provide information to health care professionals and researchers, but also to honour the implied contracts with study participants that expect their altruistic contribution to render useful information to science, and to prevent repetitive or risky trials with the same or similar compounds: hence, all trials results should be publicly available [35]. This is also a request included in the Declaration of Helsinki that states that positive, negative or inconclusive trial results, "should be published or otherwise made publicly available" [36] . Accordingly, GSK has recently committed to seek publication of results of all clinical trials, observational studies and meta-analyses, including those on prematurely terminated compounds; furthermore, when study results are not published, the CSR summaries will provide context and interpretation of the same [37].

Strengths and limitations

The availability of source documents for all published and unpublished studies is a plus for this internal analysis. Most reviews addressing publication fate of studies have been

performed by external researchers not involved in them, usually without access to protocols and full reports. This uncommon circumstance [23] enabled all conducted studies to be accounted for, from their start until their final fate, with virtually no missing data. In particular, the availability of the study completion date, critical for calculating time lag to publication, is missing in most reviews [10, 21]. This milestone coincides for almost all studies with the Food and Drug Administration requirement as the time point to count the 12-month period to disclose clinical trial results [14]. On the other hand, it could be argued that since the authors participated in the management of the studies and/or their publication, this might compromise their objectivity. Although this bias cannot be completely ruled out, it is tempered by the nature of the information collected, the quality control measures and the fact that most (93%) trials were part of international development projects, and therefore most decisions were made by others.

The external validity of this analysis could be questioned considering the limited number of studies and the even lower number of clinical trials, although greater than those followed until publication reported by others [4,5,13,19,21,23]. Another question is how well this trial sample actually represents the worldwide clinical development of new compounds. Data from the Clinicaltrials.gov database [38] show that in industry-sponsored phase 2-4 trials the activity in Spain ranks parallel to the United Kingdom and Italy. Spain has participated in approximately 25% of all GSK-sponsored international phase 2-4 drug trials during the study period. Despite the limitations of the present analysis, the results could be considered nevertheless as a likely representation of the publication and public availability rates of GSK worldwide. Conversely, no data is provided for other pharmaceutical companies in Spain and, therefore, there is no justification for extrapolating these results to other organisations.

The definitions used in this study of 'positive' and 'negative' trials' results differ from those used by other researchers. In our analysis, the definition of "positive" result correspond to that stated in the protocol for each study, as done by only few other authors [8,9], instead of meeting some specific criteria defined *a posteriori* to be applied to studies [2-7,10-12,28]. By respecting the criteria set by the authors of each protocol, we rated as positive not only the judgement of the investigators but also those accepted by the RECs and regulatory agencies when approving the clinical trials' protocols.

The time lag to publication analysis was applied to a completed set of studies (those with last subject/last visit date <1 Jan,2007). No additional censored data from studies finalizing beyond this date were considered and, therefore, Cox regression models simultaneously considering public availability and time lag to this endpoint were not employed; it should be noted that this model does not allow invariant calculation of publication and public availability rates. Although Cox regression analysis is used when assessing publication rate because of the nature of the datasets considered, we believe, as others did before [26], that our approach for a complete dataset over a defined time period is more informative.

Conclusion

Eighty percent of studies managed by GSK in Spain are publicly available. When clinical trials are considered, this figure is 78%, comprising a 61% journal publication rate plus an additional 17% of not published trial results posted on CSR –hence, substantially increasing public availability rate. As 93% of these clinical trials are multinational, it seems could be regarded as reasonably representative of what GSK activity is worldwide. Cancellation of projects is the single factor influencing a lower publication and public availability rates. There is, however, room for improvement for attaining a complete public availability of study results conducted by pharmaceutical companies.

Acknowledgements

We thank Dolores Asenjo, Teresa Compañy, Arturo Fueyo, Pilar García Corbeira, José Emilio Martín, Elena Morejón, Felipe Rodríguez-Alcántara and Josefa Samper for data collection, and Pilar Vicente for providing the impact factor of all manuscripts. We also thank Drs A Benbow (London, United Kingdom) and X Carne (Barcelona, Spain) for their critical reading and suggestions on the manuscript.

Financial Disclosure

This study required no funding.

Competing Interests

At the time of conducting the analysis all authors were GlaxoSmithKline SA employees and own stock in GSK.

Abbreviations

REC, research ethics committee.

GSK, GlaxoSmithKline

CSR, clinical study register

CI, confidence interval

References

1.- Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, et al (2008) Systematic Review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE 3(8): e3081. doi:10.1371/journal.pone.0003081

2.- Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR (1991) Publication bias in clinical research. Lancet 337: 867-72

3.- Dickersin K (1990) The existence of publication bias and risk factors for its occurrence. JAMA 263: 1385–1389.

4.- Stern JM, Simes RJ (1997) Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 315: 640-5

5.- Ioannidis JP (1998) Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 279: 281-6

6.- Callaham ML, Wears RL, Weber E, Barton C, Young G (1998) Positive-outcome bias and other limitations in the outcome of research abstracts submitted to a scientific meeting. JAMA 280: 254-7

7.- Krzyzanowska M, Pintilie M, Tannock IF (2003) Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA 290: 495-501

8.- Decullier E, Lheritier V, Chapuis F (2005) Fate of biomedical research protocols and publication bias in France: retrospective cohort study. BMJ. Jul 2; 331(7507):19. Epub 2005 Jun 20.

9.- Scherer RW, Lengenberg P, von Elm E (2007) Full publication of results initially presented in abstracts. Cochrane Database of Systematic Reviews Issue 2, Art No: MR000005. Doi: 10.1002/14651858.MR000005.pub3

10.- Lee K, Bacchetti P, Sim I (2008) Publication of clinical trials supporting successful new drug applications: A literature analysis. PLoS Med 5(9): e191. doi:10.1371/journal.pmed.0050191

11.- Rising K, Bacchetti P, Bero L (2008) Reporting bias in drug trials submitted to the Food and Drug Administration: A review of publication and presentation. PLoS Med 5(11): e217. doi:10.1371/journal. pmed.0050217

12.- Klassen TP, Wiebe N, Russell K, Stevens K, Hartling L et al (2002) Abstracts of randomized controlled trials presented at the society for pediatric reaserach meeting. Arch Pediatr Adolesc Med 156: 474-9

13.- Hall R, Antueno C, Webber A (2007) Publication bias in the medical literature: a review by a Canadian research ethics board. Can J Anesth 54: 331-5

14.- Food and Drug Administration Amendments Act 2007. www.fda.gov/oc/initiatives/HR3580.pdf (accessed January 7th, 2009)

15.- Sanossian N, Ohanian AG, Saver JL, Kim LI, Ovbiagele B (2006) Frequency and determinants of nonpublication of research in the stroke literature. Stroke 37: 2588-92

16.- Montané E, Vidal X (2007) Fate of the abstracts presented at three Spanish clinical pharmacology congresses and reasons for unpublished research. Eur J Clin Pharmacol 63: 103-11

17.- Sanders DS, Carter MJ, Hurlstone DP, Lobo AJ, Hoggard N (2001) Research outcomes in British gastroenterology: an audit of the subsequent full publication of abstracts presented at the British Society of Gastroenterology. Gut 49: 154-5

18.- Carroll AE, Sox CM, Tarini BA, Ringold S, Christakis DA (2003) Does presentation format at the Pediatric Academic Societies' annual meeting predict subsequent publication? Pediatrics 112, 1238-41

19.- Pich J, Carne X, Arnaiz JA, Gomez B, Trilla A, et al (2003) Role of a research ethics committee in follow-up and publications of results. Lancet 361: 1015-6

20.- Turer A, Mahaffey KW, Compton KL, Califf RM, Schulman KA (2007) Publication or presentation of results from multicenter clinical trials: evidence from an academic medical centre. Am Heart J 153: 674-80

21.-Blümle A, Antes G, Schumacher M, Just H, von Elm E (2008) Clinical research projects at a German medical faculty: follow-up from ethical approval to publication and citation by others. J Med Ethics Sep; 34 (9): e20

22.- Von Elm E, Röllin A, Blümle A, Huwiler K, Witschi M, et al (2008) Publication and non-publication of clinical trials: longitudinal study of applications submitted to a research ethics committee. Swiss Med Wkly 138: 197-203

23.- Melander H, Ahlquist-Rastad J, Meijer G, Beermann B (2003) Evidence b(i)ased medicine_ selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ 326: 1171-3

24.- McLennan M, Leong FC, Steele A, Harris J (2008) The influence of industry sponsorship on the acceptance of abstracts and their publication. Am J Obstet Gynecol 198: 579. e1-579.e1-4

25.- Decullier E, Chan AW, Chapuis F (2009) Inadequate dissemination of phase I trials: a retrospective cohort study. PLoS Med 6 (2): e1000034. doi:10.1371/journal.pmed.1000034

26.- Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM (2009) Trial publication after registration in ClinicalTrials.Gov: a cross-sectional analysis. PLoS Med 6 (9): e1000144. doi:10.1371/journal.pmed.1000144

27.- Krall RL, Rockhold F (2006) Reasons for optimism not disillusionment. J Roy Soc Med 99: 435

28.- Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. (2009) Publication bias in clinical trials due to statistical significance or direction of trials results. Cochrane Database Syst Rev Jan 21 (1): MR000006

29.- Tricco AC, Brehaut J, Chen MH, Moher D (2008) Following 411 Cochrane protocols to completion: a retrospective cohort study. PLoS ONE 3 (11): e3684. doi:10.1371/journal.pone.0003684

30.- Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG (2007) Epidemiology and reporting characteristics of systematic reviews. PLoS Med 4 (3): e78. doi:10.1371/journal.pmed.0040078

31.- Ünalp A, Tonascia S, Meinert CL (2007). Presentation in relation to publication of results from clinical trials. Contem Clin Trials 28: 358-69

32.- Chan A-W (2008) Bias, spin, and misreporting: Time for full access to trial protocols and results. PLoS Med 5(11): e230. doi:10.1371/journal.pmed.0050230

33.- Hopewell S, ClarkeMJ, Stewart L, Tierney J (2007) Time to publication for results of clinical trials. Cochrane Database of Systematic Reviews Issue 2. Art. No.: MR000011. DOI: 10.1002/14651858.MR000011.pub2.

34.- Wood AJJ. Progress and deficiencies in the registration of clinical trials (2009). N Engl J Med 360: 824-30

35.- Ghersi D, Clarke M, Berlin J, Gülmezoglu AM, Kush T et al (2008) Reporting the findings of clinical trials: a discussion paper. Bull WHO 86: 492-3

36.- World Medical Association (2008) Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 59th WMA General Assembly, Seoul, October. http://www.wma.net/e/policy/b3.htm (accessed May, 3rd, 2009)

37.- Strahlman E, Rockhold F, Freeman A (2009) Public disclosure of research. Lancet 373: 1319-20

38.- Karlberg JPE. (2008) Industry clinical testing of new medicinal products requires 95000 study sites and 1300000 subjects annually. Clinical Trial Magnifier 1: 101-19 (www.ClinicalTrialMagnifier.com)

Table 1 Study sample (n=143). Public availability of study results: Publications and study results posted on GSK's Clinical Study Register (CSR), by study type.

			N (%)	A: Publication[e] N (%)	B: Non-published but posted on CSR[f] N (%)	A+B: Publication + CSR. N (%)
Type of study	Clinical trial	Phase 1	5	4 (80)	0 (0)	4 (80)
		Phase 2	31	12 (39)	4 (13)	16 (52)
		Phase 3	47	31 (66)	12 (26)	43 (92)
		Phase 4	11	10 (91)	0 (0)	10 (91)
		Total	94 (66)	57 (61)	16 (17)	73 (78)
	Drug-related, observational[a]		9 (6)	4 (44)	1 (11) (*)	5 (56)
	Epidemiology[b]		10 (7)	7 (70)	NA	7 (70)
	Microbiology[c]		20 (14)	20 (100)	NA	20 (100)
	Other[d]		10 (7)	9 (90)	NA	9 (90)
Total			143 (100)	97 (68)	17 (12)	114 (80)

(a) Longitudinal prospective, 5; cross-sectional, 1; retrospective, 2; case-control, 1

(b) Longitudinal prospective, 4; retrospective, 2; cross-sectional, 4

(c) In vitro research, 12: surveillances, 6; animal models, 2

(d) Health Scales Validation, 4; Pharmacoeconomy, 2; Systematic Review, 1; Mathematical Model, 1; Clinical trial on devices and modelling, 1; Health care quality assessment , 1

(e) Publication of full study results in a peer-reviewed journal. Includes paper (n=94) and on-line (n=3) publications.

(f) No of full trials' results posted at GSK's CSR that have not been published yet. Hence, if the results of a trial were published in a journal, it is not included in this figure, regardless if it is, or not, posted in the CSR

N: No of studies

(*) CSR was intended for posting clinical trial results. However, there is a case-control study published and posted on CSR, and a longitudinal, drug-related study, not published but posted on CSR –these were the only non-clinical trials posted on CSR

Table 2. Study sample (n=143). Public availability of study results: Publications and study results posted on GSK's Clinical Study Register (CSR), by therapy area

		N (%)	A: Publication[a] N (%) / Impact factor-median[b]	B: Non-published but posted on CSR[c] N (%)	A+B: Publication + CSR. N (%)
Therapy Area	Neurosciences	22 (15)	13 (59) / 3.13	1 (5)	14 (64)
	C, M & R	24 (17)	16 (67) / 3.00	5 (21)	21 (88)
	Anti-infectives	47 (33)	38 (81) / 3.89	6 (13)	44 (94)
	Oncology	13 (9)	7 (54) / 13.60	2 (15)	9 (69)
	Vaccines	19 (13)	15 (79) / 3.09	3 (16)	18 (95)
	R, U & G	18 (13)	8 (44) / 3.20	0 (0)	8 (44)
	Total	143	97 (68) / 3.61	17 (12)	114 (80)

(a) Publication of full study results in a peer-reviewed journal. Includes paper (n=94) and on-line (n=3) publications.

(b) Impact factor of the year of publication. For papers published on 2008 or 2009, 2007 impact factor is used

(c) No of full trials' results posted at GSK's CSR that have not been published yet. Hence, if the results of a trial were published in a journal, it is not included in this figure, regardless if it is, or not, posted in the CSR

N: No of studies

C, M & R: Cardiovascular, Metabolism and Respiratory

R, U & G: Rheumatology, Urology and Gastroenterology

Table 3. Clinical Trials (n=94). Cancelled projects and fate of results.

Cancelled projects, 20	16 for lack of efficacy: 12 in phase 2, 1 in phase 2/3 and 3 in phase 3; comprising 17 trials[b], of all therapy areas except vaccines 2 for safety reasons: 1 in phase 1, due to animal toxicological findings, 1 in phase 2 ; comprising 3 trials of neurosciences and anti-infectives 2 for manufacturing issues: 1 in Phase 2, and 1 in phase 3 ; comprising 2 vaccine trials
Trials associated to cancelled projects - N (%) Published / Publicly available[a] Not published / Non Publicly available	22 (23) 4 (18) / 9 (41) 18 (82) / 13 (59)
Trials associated to non-cancelled projects - N (%) Published / Publicly available[a] Not published / Non Publicly available	72 (77) 53 (74) / 64 (89) 19 (26) / 8 (11)

"Project" is defined as the group of studies comprising the product development plan for a given indication.

(a) Published or posted on GSK Clinical Study Register (CSR)

(b) And an additional epidemiological longitudinal prospective study

N: No of clinical trials

Table 4. Clinical Trials (n=94). Main characteristics, fate of results and impact factors.

		N (%) (Unless otherwise stated)
One, or more, GSK author in published papers		54 (95)
Window time to publication (years)[a]		Median (range) /Mean 5.6 (2.9-8.2) / 5.7
Positive results[b]		63 (67)
	Phase 1	5 (100)
	Phase 2	9 (29)
	Phase 3	40 (85)
	Phase 4	9 (82)
Positive results[b]		63 (67)
	Published / Publicly available[c]	45 (71) / 55 (87)
	Not Published / Non Publicly available	18 (29) / 8 (13)
Negative results [a]		31 (33)
	Published / Publicly available[c]	12 (39) / 18 (58)
	Not Published / Non Publicly available	19 (61) / 13 (42)
Published papers		57 (61)
	Positive results	45 (79)
	Negative results	12 (21)
Non published papers		37 (39)
	Positive results	18 (49)
	Negative results	19 (51)
Impact factor of published papers (n=53)		Median (range) /Mean 3.9 (0.6-52.6) / 7.5
	Phase 1 (n=4)	3.9 (3.8-5.9) / 4.4
	Phase 2 (n=11)	4.9 (2.0-52.6) / 10.2
	Phase 3 (n=28)	3.3 (0.6-51.3) / 7.8
	Phase 4 (n=10)	3.2 (1.8-11.1) / 5.0
	Positive results (n=42)	3.8 (0.6-52.6) / 7.9
	Negative results (n=11)	4.5 (2.0-15.5) / 6.3
Reasons for no publication (n=37)	Project cancelled	16 (43)
	Lack of time/resources	12 (33)
	Unknown	6 (16)

	Other[d]	3 (8)
Posted on CSR		57 (61)
Marketed products[e]	Published / Publicly available	42 (84) / 50 (100) [f]

(a) Time elapsed from the first clinical trial reaching last subject/last visit until the cut-off date (March 31st, 2009)

(b) See Methods for definitions

(c) Published or posted on GSK Clinical Study Register (CSR)

(d) Submitted with no answer yet (n=2); submitted and rejected (n=1)

(e) Clinical trials conducted with marketed products, i.e. conducted with products that were marketed at the time the trial was run or with a product that was marketed (for the indication, dosage, etc) as of the cut-off date (March 31st, 2009).

(f) All trials were published or posted on GSK CSR, except one which results were posted on Bayer's Website.

N: No of clinical trials (where appropriate)

Table 5 . Factors predicting publication and public availability. Odds Ratios (OR) and 95% Confidence Intervals (95% CI) from multivariate logistic regression models.

		All studies[a]		Clinical Trials; Publication as outcome		Clinical Trials; Public Availablility as outcome	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Factor	Therapy Area		0.488		0.772		0.101
	Study associated to a cancelled project	0.069 (0.02 - 0.24)	0.000	0.075 (0.016 - 0.343)	0.001	0.052(0.007 - 0.382)	0.004
	Clinical trial	1.33 (0.45 - 3.93)	0.606				
	Sample size	1.00 (0.99 - 1.01)	0.979	1.00 (0.999 - 1.001)	0.964	1.00 (0.999 - 1.001)	0.823
	Positive trial result			1.028 (0.286 - 3.691)	0.966	1.118 (0.210 - 5.942)	0.896
	Duration of experimental phase	1.004 (0.96 - 1.05)	0.878	0.996 (0.945 - 1.050)	0.885	1.064 (0.962 - 1.171)	0.231
	Constant	1.17	0.826	2.306	0.373	1.529	0.720

(a) All studies (n= 119) are included, except those belonging to Microbiology (n=20), Systematic Review, (n=1); Mathematical Model (n=1); Pharmacoeconomy (n=2)

OR = Odds ratio; 95% CI = 95% confidence interval

Table 6. Factors predicting time to publication. Coefficients (B) and standard errors (SE) from multivariate linear regression models.

		All studies[a]			Clinical Trials		
		B[c]	SE	P	B[c]	SE	P
Factor	Therapy Area			N.S.			N.S.
	Study associated to a Cancelled Project	2.843	7.646	0.711	-0.068	8.437	0.994
	Clinical trial	0.309	4.110	0.940			
	Sample size	-0.002	0.002	0.366	-0.004	0.002	0.100
	Positive trial result in publication				-5.103	5.038	0.317
	Duration of experimental phase	0.101	0.169	0.552	0.191	0.205	0.356
	Impact factor[b]	-5.739	2.151	0.010	-6.861	2.413	0.007
	Constant	35.495	7.332	0.000	41.11	7.963	0.000

(a) All studies (n= 119) are included, except those belonging to Microbiology (n=20), Systematic Review, (n=1); Mathematical Model (n=1); Pharmacoeconomy (n=2)

(b) Ln transformed

(c) Non-standardized coefficients