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

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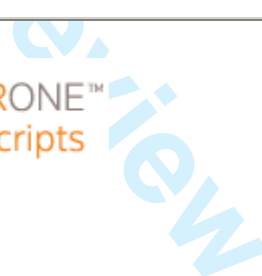
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**Are results from a pharmaceutical company-sponsored studies available to the public?**

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6 **Are results from a pharmaceutical company-sponsored studies available to the**  
7 **public?**  
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### *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 0.02-0.24;  $p < 0.001$ ) 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

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

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30 Indeed, controversy persists about how the industry, as compared to other sponsors, can  
31 affect the publication rate of study results. Some authors have found that industry-  
32 sponsored studies tend to be less likely published than those funded or sponsored by  
33 non-commercial organisations [2,3,22]. This however has not been confirmed by others  
34 [15,20,24] Several other factors seem to influence this, with the type of studies under  
35 review (e.g. Phase 1 and 2 trials are less likely to be published [2,13,25]) being a critical  
36 one. Finally, its worth mentioning a recent report comprising phase 2-4 trials registered  
37 in Clinicaltrials.gov showed that industry-sponsored trials (44%) were less likely to be  
38 published than non-industry/non-government-sponsored ones (56%), but there was no  
39 difference when compared with government-sponsored trials (40%) [26]

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50 Following a public debate on the publication of trial results, GlaxoSmithKline (GSK)  
51 launched in September 2004 a publicly available, internet-based clinical trial register  
52 (CSR; [www.gsk-clinicalstudyregister.com/](http://www.gsk-clinicalstudyregister.com/)) in order to provide results from all GSK-  
53 sponsored clinical trials of marketed medicines and vaccines completed since the  
54 formation of GSK in 2001 [27]. The aim is to assist physicians in their clinical practice  
55 and research, an initiative taken also by other companies and their US trade association.  
56 The GSK register contains more than 3000 summaries of published and un-published  
57 trials conducted on 52 marketed products.  
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5 The objective of this study was to describe the public availability rate and time to  
6 publication of studies managed by GSK in Spain, as well as to identify factors that  
7 could predict such public availability. The journal impact factor of papers was also  
8 determined.  
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## 12 13 14 METHODS

### 15 16 17 Studies

18 This is a retrospective cohort study based on all scientific studies managed by GSK's  
19 Medical Department in Spain. All studies initiated (i.e. first visit of the first subject -or  
20 its equivalent, e.g. first in vitro test performed; first clinical history reviewed) in 2001 or  
21 later, and completed (i.e. last visit from the last subject -or its equivalent) up to  
22 December 31<sup>st</sup>, 2006, were included. Studies managed by international contract research  
23 organisations and all follow-up (extension) safety trials were excluded.  
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### 31 32 Data collection and definitions

33 A specific database was designed to contain all data gathered from the review of GSK  
34 files. Data were collected after a training session on abstraction of study characteristics;  
35 four authors (JL, MGL, RDR and RO) reviewed the data for consistency before entering  
36 it to the database. Discrepancies were resolved by consensus of all authors.  
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42 Time to publication was defined as the period between study completion (last visit of  
43 last patient or its equivalent) and time when first paper on the study's primary end-  
44 point, was published. Reason for not publication was captured. "Project" is defined as  
45 the group of studies comprising the product development plan for a given indication.  
46 "Cancelled projects" (i.e. those prematurely terminated) and the reason for such  
47 decision were also recorded.  
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54 Results of trials were classified as 'positive' if the protocol-defined hypothesis (primary  
55 end-point) was confirmed (i.e. statistically significant difference in favour of the  
56 experimental arm), or 'negative' if the hypothesis did not reach statistical significance,  
57 (i.e. not significant or significant in favour of the control arm). For non-inferiority trials,  
58 results meeting the protocol definition (below the pre-specified significance level, or a  
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3 Confidence Interval (CI) excluding the pre-specified difference) were considered  
4 'positive'. When no statistical test was performed, the results were considered as  
5 'positive' if classified by investigators as "important" or "striking", and as 'negative', if  
6 classified as of "moderate or "little importance" or "not striking" [28].  
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11 Publication was defined only as an original article in a peer-reviewed journal, issued up  
12 to March 31<sup>st</sup>, 2009 (cut-off date). For 'time to publication', only the month/year of  
13 publication were considered; an on-line article was included only if no paper publication  
14 was available. Journals' impact factors were obtained through ISI Web of Science  
15 (<http://admin-apps.isiknowledge.com/JCR/JCR>) for the year of each publication,  
16 between April 1st and 15<sup>th</sup>, 2009.  
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#### 23 24 Data management and statistical analyses

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

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3 studies and of clinical trials were 3.6 and 3.9, respectively; negative trials had higher  
4 median impact factor (4.5) than positive ones (3.8) (tables 2 and 4).  
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#### 8 9 Predictors for public availability and time to publication

10 One hundred and nineteen studies were included in the regressions models, i.e. the  
11 whole study sample (n=143) except Microbiology (n=20), Systematic Review (n=1),  
12 Mathematical Model (n=1) and Pharmacoeconomic (n=2) ones. Among the six factors  
13 selected as candidate predictors in the multivariate logistic regression models, 'Study  
14 associated to a cancelled project' was the only significant one predicting a lower  
15 publication rate for all studies (OR: 0.069; 95% CI 0.02-0.24; p<0.001) and trials (OR:  
16 0.075; 95% CI 0.016-0.343; p=0.001) and a lower public availability rate (OR: 0.052;  
17 95% CI 0.007-0.382; p=0.004) for trials' results. From the linear models, 'Impact  
18 factor' was the only significant contributor reducing the time to publication: papers  
19 submitted to journals with higher impact factors resulted in an earlier publication when  
20 total sample (B: -5.7; p=0.010) or only clinical trials (B: -6.9; p=0.007) are considered.  
21 The results of the multivariate logistic and linear regression models are shown in tables  
22 5 and 6.  
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#### 34 35 DISCUSSION

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38 Despite selective publication being frequently investigated [2-4,6-8,10-13,15-22], this  
39 study is the first analysis produced by a pharmaceutical company. Additionally, and as a  
40 novelty, it reports not only publication rate, but also availability of non-published study  
41 results posted on a website (GSK CSR) as a source of reliable information.  
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48 A recent Cochrane review [9] reported that after 9 years 53% of congress abstracts are  
49 published (with a median lag time of 17.9 months), this figure increasing to 63% for  
50 clinical trials. Our series shows a publication rate of 68% for all studies with a median  
51 lag time of 27.3 months; the corresponding figures being 61% and 28.4 months for  
52 clinical trials. Thus, GSK-sponsored studies in Spain have similar publication rates but  
53 with a shorter time to publication than those included in the Cochrane report (9 vs 5.5  
54 years) [9]. When non-published trial results posted on CSR are added, the 'public  
55 availability' rate reaches 78%, (80% when considering the total sample). To put these  
56 results in context, only 80% of the Cochrane protocols were published as full reviews  
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3 after more than 8 years of completion, with a median time to publication of 2.4 years  
4 [29], despite being the most reported systematic reviews [30].  
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9 When comparing publication lag time between different studies, a critical element is the  
10 time point considered as “start” for each study. We believe that last subject/last visit  
11 date is the best milestone for clinical trials, or its equivalent for other types of studies,  
12 given its objectivity. Thus, other factors that may influence publication lag time (e.g.  
13 database freeze delay) are avoided. Unfortunately, this time point is seldom considered  
14 by others, since it is not usually available. The few studies performed using this  
15 milestone indicate a median time of 2.4 years to publication for 36 National Institutes of  
16 Health-funded Human Immunodeficiency Virus trials [5], or 23 months from dataset  
17 finalization to full report publications [31]. These lag times are comparable to the 28.4  
18 months for our 57 published trials. Of note is the fact that most authors when assessing  
19 publication rates used different ‘start’ time points, sometimes not taking into  
20 consideration many months or years after study completion; thus, times such as 3-5  
21 years after abstract presentation at congresses [6,7,9,12,15,16,18], or 5-8.5 years after  
22 Food and Drug Administration drug approval [10,11] are common.  
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35 Although the pharmaceutical industry has been reportedly involved in selective  
36 publication [10, 11, 23], this is not an industry-specific issue. Thus, Chan [32] recently  
37 stated that “accumulating empiric evidence has shown that selective reporting of results  
38 is a systemic problem afflicting all types of trials, including those with no commercial  
39 input”. It is well documented that positive trials are more likely [1-10, 12, 28, 33] and  
40 earlier [4,5,7] published, than negative ones. Hopewell et al [33] reported that positive  
41 trials are published in 4 to 5 years whereas negative or null results take 6 to 8 years. In  
42 our series, positive trials had higher publication (71%) and public availability (87%)  
43 rates; negative trials, were, on the other hand, less frequently published (39%) and  
44 publicly available (58%); for non-published studies, the proportion of positive/negative  
45 results was 49%/51%. This apparent positive publication bias is however rejected by the  
46 logistic regression model showing that the factor ‘study associated to a cancelled  
47 project’ but not ‘positive trial result’, was the only significant predictor for publication  
48 and public availability of a trial result. Hence, positive studies influencing the decision  
49 of publication become a confounding factor. Additionally, positive trials were not  
50 published significantly earlier.  
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5 Although controversial, it is widely accepted that impact factor reflects to some extent  
6 the quality and scientific interest of the publication. Median and mean impact factors in  
7 our series were 3.9 and 7.5, respectively. Median impact factor ranged from 1.96 to 4.14  
8 [12,16,17], and a mean of around 3 [18] in the few studies reporting this variable. In  
9 two studies, 24% and 37% of publications were in journals with an impact factor >4  
10 [17] or >5 [13], respectively. As a comparison, 37% and 20% of the studies results of  
11 this study were published in journals with an impact factor > 4 and >5, respectively. On  
12 the other hand, we could speculate that the association of higher impact factor with a  
13 reduced time to publication may result from higher interest -and hence quicker  
14 submission of the paper- on the side of the authors and/or more agile review process by  
15 the more important journals.  
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26 In this analysis, data from 17 unpublished studies posted on CSR were added to  
27 publications. These summary results, as those on other websites, lack the context and  
28 interpretation that published papers provide [34] and therefore they should be a  
29 complement to publication rather than its substitute. Currently, publishing trial results  
30 involving only commercially available medicines – or even approved ones, as mandated  
31 by the US regulation [14] - is perceived as ethically insufficient. No longer is the aim  
32 only to provide information to health care professionals and researchers, but also to  
33 honour the implied contracts with study participants that expect their altruistic  
34 contribution to render useful information to science, and to prevent repetitive or risky  
35 trials with the same or similar compounds: hence, all trials results should be publicly  
36 available [35]. This is also a request included in the Declaration of Helsinki that states  
37 that positive, negative or inconclusive trial results, “should be published or otherwise  
38 made publicly available” [36] . Accordingly, GSK has recently committed to seek  
39 publication of results of all clinical trials, observational studies and meta-analyses,  
40 including those on prematurely terminated compounds; furthermore, when study results  
41 are not published, the CSR summaries will provide context and interpretation of the  
42 same [37].  
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### 58 Strengths and limitations

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

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3 performed by external researchers not involved in them, usually without access to  
4 protocols and full reports. This uncommon circumstance [23] enabled all conducted  
5 studies to be accounted for, from their start until their final fate, with virtually no  
6 missing data. In particular, the availability of the study completion date, critical for  
7 calculating time lag to publication, is missing in most reviews [10, 21]. This milestone  
8 coincides for almost all studies with the Food and Drug Administration requirement as  
9 the time point to count the 12-month period to disclose clinical trial results [14]. On the  
10 other hand, it could be argued that since the authors participated in the management of  
11 the studies and/or their publication, this might compromise their objectivity. Although  
12 this bias cannot be completely ruled out, it is tempered by the nature of the information  
13 collected, the quality control measures and the fact that most (93%) trials were part of  
14 international development projects, and therefore most decisions were made by others.  
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26 The external validity of this analysis could be questioned considering the limited  
27 number of studies and the even lower number of clinical trials, although greater than  
28 those followed until publication reported by others [4,5,13,19,21,23]. Another question  
29 is how well this trial sample actually represents the worldwide clinical development of  
30 new compounds. Data from the Clinicaltrials.gov database [38] show that in industry-  
31 sponsored phase 2-4 trials the activity in Spain ranks parallel to the United Kingdom  
32 and Italy. Spain has participated in approximately 25% of all GSK-sponsored  
33 international phase 2-4 drug trials during the study period. Despite the limitations of the  
34 present analysis, the results could be considered nevertheless as a likely representation  
35 of the publication and public availability rates of GSK worldwide. Conversely, no data  
36 is provided for other pharmaceutical companies in Spain and, therefore, there is no  
37 justification for extrapolating these results to other organisations.  
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49 The definitions used in this study of 'positive' and 'negative' trials' results differ from  
50 those used by other researchers. In our analysis, the definition of "positive" result  
51 correspond to that stated in the protocol for each study, as done by only few other  
52 authors [8,9], instead of meeting some specific criteria defined *a posteriori* to be  
53 applied to studies [2-7,10-12,28]. By respecting the criteria set by the authors of each  
54 protocol, we rated as positive not only the judgement of the investigators but also those  
55 accepted by the RECs and regulatory agencies when approving the clinical trials'  
56 protocols.  
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5 The time lag to publication analysis was applied to a completed set of studies (those  
6 with last subject/last visit date <1 Jan,2007). No additional censored data from studies  
7 finalizing beyond this date were considered and, therefore, Cox regression models  
8 simultaneously considering public availability and time lag to this endpoint were not  
9 employed; it should be noted that this model does not allow invariant calculation of  
10 publication and public availability rates. Although Cox regression analysis is used when  
11 assessing publication rate because of the nature of the datasets considered, we believe,  
12 as others did before [26], that our approach for a complete dataset over a defined time  
13 period is more informative.  
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### 24 Conclusion

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

22 At the time of conducting the analysis all authors were GlaxoSmithKline SA employees  
23 and own stock in GSK.  
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32 *Abbreviations*

33 REC, research ethics committee.

34 GSK, GlaxoSmithKline

35 CSR, clinical study register

36 CI, confidence interval  
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For Peer Review

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 <sup>e</sup> N (%)	B: Non- published but posted on CSR <sup>f</sup> 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 <sup>a</sup>		9 (6)	4 (44)	1 (11) (*)	5 (56)
	Epidemiology <sup>b</sup>		10 (7)	7 (70)	NA	7 (70)
	Microbiology <sup>c</sup>		20 (14)	20 (100)	NA	20 (100)
	Other <sup>d</sup>		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 <sup>a</sup> N (%) / Impact factor-median <sup>b</sup>	B: Non-published but posted on CSR <sup>c</sup> 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	<u>16 for lack of efficacy</u> : 12 in phase 2, 1 in phase 2/3 and 3 in phase 3; comprising 17 trials <sup>b</sup> , of all therapy areas except vaccines <u>2 for safety reasons</u> : 1 in phase 1, due to animal toxicological findings, 1 in phase 2 ; comprising 3 trials of neurosciences and anti-infectives <u>2 for manufacturing issues</u> : 1 in Phase 2, and 1 in phase 3 ; comprising 2 vaccine trials
Trials associated to cancelled projects - N (%)	22 (23)
Published / Publicly available <sup>a</sup>	4 (18) / 9 (41)
Not published / Non Publicly available	18 (82) / 13 (59)
Trials associated to non-cancelled projects - N (%)	72 (77)
Published / Publicly available <sup>a</sup>	53 (74) / 64 (89)
Not published / Non Publicly available	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) <sup>a</sup>		Median (range) /Mean 5.6 (2.9-8.2) / 5.7
Positive results <sup>b</sup>		63 (67)
	Phase 1	5 (100)
	Phase 2	9 (29)
	Phase 3	40 (85)
	Phase 4	9 (82)
Positive results <sup>b</sup>		63 (67)
	Published / Publicly available <sup>c</sup>	45 (71) / 55 (87)
	Not Published / Non Publicly available	18 (29) / 8 (13)
Negative results <sup>a</sup>		31 (33)
	Published / Publicly available <sup>c</sup>	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 <sup>d</sup>	3 (8)
Posted on CSR		57 (61)
Marketed products <sup>e</sup>	Published / Publicly available	42 (84) / 50 (100) <sup>f</sup>

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

Factor	Therapy Area	All studies <sup>a</sup>		Clinical Trials; Publication as outcome		Clinical Trials; Public Availability as outcome	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
			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.

Factor		All studies <sup>a</sup>			Clinical Trials		
		B <sup>c</sup>	SE	P	B <sup>c</sup>	SE	P
	Therapy Area			N.S.			N.S.
	Study associated to a Cancelled Project	2.843	7.646	0.711	-	8.437	0.994
	Clinical trial	0.309	4.110	0.940			
	Sample size	-0.002	0.002	0.366	-	0.002	0.100
	Positive trial result in publication				-	5.103	5.038
	Duration of experimental phase	0.101	0.169	0.552	0.191	0.205	0.356
	Impact factor <sup>b</sup>	-5.739	2.151	0.010	-	6.861	2.413
	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

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6 **Are results from a pharmaceutical company-sponsored studies available to the**  
7 **public?**  
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12 Rafael Dal-Ré MD, PhD, MPH (\*), Alejandro Pedromingo L Sc (a), Manuel García-  
13 Losa MD, Juan Lahuerta MD, PhD, MHA, Rafael Ortega MD  
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### *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 0.02-0.24;  $p < 0.001$ ) 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

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

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30 Indeed, controversy persists about how the industry, as compared to other sponsors, can  
31 affect the publication rate of study results. Some authors have found that industry-  
32 sponsored studies tend to be less likely published than those funded or sponsored by  
33 non-commercial organisations [2,3,22]. This however has not been confirmed by others  
34 [15,20,24] Several other factors seem to influence this, with the type of studies under  
35 review (e.g. Phase 1 and 2 trials are less likely to be published [2,13,25]) being a critical  
36 one. Finally, its worth mentioning a recent report comprising phase 2-4 trials registered  
37 in Clinicaltrials.gov showed that industry-sponsored trials (44%) were less likely to be  
38 published than non-industry/non-government-sponsored ones (56%), but there was no  
39 difference when compared with government-sponsored trials (40%) [26]

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49 Following a public debate on the publication of trial results, GlaxoSmithKline (GSK)  
50 launched in September 2004 a publicly available, internet-based clinical trial register  
51 (CSR; [www.gsk-clinicalstudyregister.com/](http://www.gsk-clinicalstudyregister.com/)) in order to provide results from all GSK-  
52 sponsored clinical trials of marketed medicines and vaccines completed since the  
53 formation of GSK in 2001 [27]. The aim is to assist physicians in their clinical practice  
54 and research, an initiative taken also by other companies and their US trade association.  
55 The GSK register contains more than 3000 summaries of published and un-published  
56 trials conducted on 52 marketed products.  
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5 The objective of this study was to describe the public availability rate and time to  
6 publication of studies managed by GSK in Spain, as well as to identify factors that  
7 could predict such public availability. The journal impact factor of papers was also  
8 determined.  
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## 12 13 14 METHODS

### 15 16 17 Studies

18 This is a retrospective cohort study based on all scientific studies managed by GSK's  
19 Medical Department in Spain. All studies initiated (i.e. first visit of the first subject -or  
20 its equivalent, e.g. first in vitro test performed; first clinical history reviewed) in 2001 or  
21 later, and completed (i.e. last visit from the last subject -or its equivalent) up to  
22 December 31<sup>st</sup>, 2006, were included. Studies managed by international contract research  
23 organisations and all follow-up (extension) safety trials were excluded.  
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### 31 32 Data collection and definitions

33 A specific database was designed to contain all data gathered from the review of GSK  
34 files. Data were collected after a training session on abstraction of study characteristics;  
35 four authors (JL, MGL, RDR and RO) reviewed the data for consistency before entering  
36 it to the database. Discrepancies were resolved by consensus of all authors.  
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42 Time to publication was defined as the period between study completion (last visit of  
43 last patient or its equivalent) and time when first paper on the study's primary end-  
44 point, was published. Reason for not publication was captured. "Project" is defined as  
45 the group of studies comprising the product development plan for a given indication.  
46 "Cancelled projects" (i.e. those prematurely terminated) and the reason for such  
47 decision were also recorded.  
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54 Results of trials were classified as 'positive' if the protocol-defined hypothesis (primary  
55 end-point) was confirmed (i.e. statistically significant difference in favour of the  
56 experimental arm), or 'negative' if the hypothesis did not reach statistical significance,  
57 (i.e. not significant or significant in favour of the control arm). For non-inferiority trials,  
58 results meeting the protocol definition (below the pre-specified significance level, or a  
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3 Confidence Interval (CI) excluding the pre-specified difference) were considered  
4 'positive'. When no statistical test was performed, the results were considered as  
5 'positive' if classified by investigators as "important" or "striking", and as 'negative', if  
6 'positive' if classified by investigators as "important" or "striking", and as 'negative', if  
7 classified as of "moderate or "little importance" or "not striking" [28].  
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11 Publication was defined only as an original article in a peer-reviewed journal, issued up  
12 to March 31<sup>st</sup>, 2009 (cut-off date). For 'time to publication', only the month/year of  
13 publication were considered; an on-line article was included only if no paper publication  
14 was available. Journals' impact factors were obtained through ISI Web of Science  
15 (<http://admin-apps.isiknowledge.com/JCR/JCR>) for the year of each publication,  
16 between April 1st and 15<sup>th</sup>, 2009.  
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#### 23 24 Data management and statistical analyses

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

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3 studies and of clinical trials were 3.6 and 3.9, respectively; negative trials had higher  
4 median impact factor (4.5) than positive ones (3.8) (tables 2 and 4).  
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#### 8 Predictors for public availability and time to publication

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10 One hundred and nineteen studies were included in the regressions models, i.e. the  
11 whole study sample (n=143) except Microbiology (n=20), Systematic Review (n=1),  
12 Mathematical Model (n=1) and Pharmacoeconomic (n=2) ones. Among the six factors  
13 selected as candidate predictors in the multivariate logistic regression models, 'Study  
14 associated to a cancelled project' was the only significant one predicting a lower  
15 publication rate for all studies (OR: 0.069; 95% CI 0.02-0.24; p<0.001) and trials (OR:  
16 0.075; 95% CI 0.016-0.343; p=0.001) and a lower public availability rate (OR: 0.052;  
17 95% CI 0.007-0.382; p=0.004) for trials' results. From the linear models, 'Impact  
18 factor' was the only significant contributor reducing the time to publication: papers  
19 submitted to journals with higher impact factors resulted in an earlier publication when  
20 total sample (B: -5.7; p=0.010) or only clinical trials (B: -6.9; p=0.007) are considered.  
21 The results of the multivariate logistic and linear regression models are shown in tables  
22 5 and 6.  
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#### 34 DISCUSSION

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39 Despite selective publication being frequently investigated [2-4,6-8,10-13,15-22], this  
40 study is the first analysis produced by a pharmaceutical company. Additionally, and as a  
41 novelty, it reports not only publication rate, but also availability of non-published study  
42 results posted on a website (GSK CSR) as a source of reliable information.  
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48 A recent Cochrane review [9] reported that after 9 years 53% of congress abstracts are  
49 published (with a median lag time of 17.9 months), this figure increasing to 63% for  
50 clinical trials. Our series shows a publication rate of 68% for all studies with a median  
51 lag time of 27.3 months; the corresponding figures being 61% and 28.4 months for  
52 clinical trials. Thus, GSK-sponsored studies in Spain have similar publication rates but  
53 with a shorter time to publication than those included in the Cochrane report (9 vs 5.5  
54 years) [9]. When non-published trial results posted on CSR are added, the 'public  
55 availability' rate reaches 78%, (80% when considering the total sample). To put these  
56 results in context, only 80% of the Cochrane protocols were published as full reviews  
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3 after more than 8 years of completion, with a median time to publication of 2.4 years  
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5 [29], despite being the most reported systematic reviews [30].  
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9 When comparing publication lag time between different studies, a critical element is the  
10 time point considered as “start” for each study. We believe that last subject/last visit  
11 date is the best milestone for clinical trials, or its equivalent for other types of studies,  
12 given its objectivity. Thus, other factors that may influence publication lag time (e.g.  
13 database freeze delay) are avoided. Unfortunately, this time point is seldom considered  
14 by others, since it is not usually available. The few studies performed using this  
15 milestone indicate a median time of 2.4 years to publication for 36 National Institutes of  
16 Health-funded Human Immunodeficiency Virus trials [5], or 23 months from dataset  
17 finalization to full report publications [31]. These lag times are comparable to the 28.4  
18 months for our 57 published trials. Of note is the fact that most authors when assessing  
19 publication rates used different ‘start’ time points, sometimes not taking into  
20 consideration many months or years after study completion; thus, times such as 3-5  
21 years after abstract presentation at congresses [6,7,9,12,15,16,18], or 5-8.5 years after  
22 Food and Drug Administration drug approval [10,11] are common.  
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35 Although the pharmaceutical industry has been reportedly involved in selective  
36 publication [10, 11, 23], this is not an industry-specific issue. Thus, Chan [32] recently  
37 stated that “accumulating empiric evidence has shown that selective reporting of results  
38 is a systemic problem afflicting all types of trials, including those with no commercial  
39 input”. It is well documented that positive trials are more likely [1-10, 12, 28, 33] and  
40 earlier [4,5,7] published, than negative ones. Hopewell et al [33] reported that positive  
41 trials are published in 4 to 5 years whereas negative or null results take 6 to 8 years. In  
42 our series, positive trials had higher publication (71%) and public availability (87%)  
43 rates; negative trials, were, on the other hand, less frequently published (39%) and  
44 publicly available (58%); for non-published studies, the proportion of positive/negative  
45 results was 49%/51%. This apparent positive publication bias is however rejected by the  
46 logistic regression model showing that the factor ‘study associated to a cancelled  
47 project’ but not ‘positive trial result’, was the only significant predictor for publication  
48 and public availability of a trial result. Hence, positive studies influencing the decision  
49 of publication become a confounding factor. Additionally, positive trials were not  
50 published significantly earlier.  
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5 Although controversial, it is widely accepted that impact factor reflects to some extent  
6 the quality and scientific interest of the publication. Median and mean impact factors in  
7 our series were 3.9 and 7.5, respectively. Median impact factor ranged from 1.96 to 4.14  
8 [12,16,17], and a mean of around 3 [18] in the few studies reporting this variable. In  
9 two studies, 24% and 37% of publications were in journals with an impact factor >4  
10 [17] or >5 [13], respectively. As a comparison, 37% and 20% of the studies results of  
11 this study were published in journals with an impact factor > 4 and >5, respectively. On  
12 the other hand, we could speculate that the association of higher impact factor with a  
13 reduced time to publication may result from higher interest -and hence quicker  
14 submission of the paper- on the side of the authors and/or more agile review process by  
15 the more important journals.  
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26 In this analysis, data from 17 unpublished studies posted on CSR were added to  
27 publications. These summary results, as those on other websites, lack the context and  
28 interpretation that published papers provide [34] and therefore they should be a  
29 complement to publication rather than its substitute. Currently, publishing trial results  
30 involving only commercially available medicines – or even approved ones, as mandated  
31 by the US regulation [14] - is perceived as ethically insufficient. No longer is the aim  
32 only to provide information to health care professionals and researchers, but also to  
33 honour the implied contracts with study participants that expect their altruistic  
34 contribution to render useful information to science, and to prevent repetitive or risky  
35 trials with the same or similar compounds: hence, all trials results should be publicly  
36 available [35]. This is also a request included in the Declaration of Helsinki that states  
37 that positive, negative or inconclusive trial results, “should be published or otherwise  
38 made publicly available” [36] . Accordingly, GSK has recently committed to seek  
39 publication of results of all clinical trials, observational studies and meta-analyses,  
40 including those on prematurely terminated compounds; furthermore, when study results  
41 are not published, the CSR summaries will provide context and interpretation of the  
42 same [37].  
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### 58 Strengths and limitations

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

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3 performed by external researchers not involved in them, usually without access to  
4 protocols and full reports. This uncommon circumstance [23] enabled all conducted  
5 studies to be accounted for, from their start until their final fate, with virtually no  
6 missing data. In particular, the availability of the study completion date, critical for  
7 calculating time lag to publication, is missing in most reviews [10, 21]. This milestone  
8 coincides for almost all studies with the Food and Drug Administration requirement as  
9 the time point to count the 12-month period to disclose clinical trial results [14]. On the  
10 other hand, it could be argued that since the authors participated in the management of  
11 the studies and/or their publication, this might compromise their objectivity. Although  
12 this bias cannot be completely ruled out, it is tempered by the nature of the information  
13 collected, the quality control measures and the fact that most (93%) trials were part of  
14 international development projects, and therefore most decisions were made by others.  
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26 The external validity of this analysis could be questioned considering the limited  
27 number of studies and the even lower number of clinical trials, although greater than  
28 those followed until publication reported by others [4,5,13,19,21,23]. Another question  
29 is how well this trial sample actually represents the worldwide clinical development of  
30 new compounds. Data from the Clinicaltrials.gov database [38] show that in industry-  
31 sponsored phase 2-4 trials the activity in Spain ranks parallel to the United Kingdom  
32 and Italy. Spain has participated in approximately 25% of all GSK-sponsored  
33 international phase 2-4 drug trials during the study period. Despite the limitations of the  
34 present analysis, the results could be considered nevertheless as a likely representation  
35 of the publication and public availability rates of GSK worldwide. Conversely, no data  
36 is provided for other pharmaceutical companies in Spain and, therefore, there is no  
37 justification for extrapolating these results to other organisations.  
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49 The definitions used in this study of 'positive' and 'negative' trials' results differ from  
50 those used by other researchers. In our analysis, the definition of "positive" result  
51 correspond to that stated in the protocol for each study, as done by only few other  
52 authors [8,9], instead of meeting some specific criteria defined *a posteriori* to be  
53 applied to studies [2-7,10-12,28]. By respecting the criteria set by the authors of each  
54 protocol, we rated as positive not only the judgement of the investigators but also those  
55 accepted by the RECs and regulatory agencies when approving the clinical trials'  
56 protocols.  
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5 The time lag to publication analysis was applied to a completed set of studies (those  
6 with last subject/last visit date <1 Jan,2007). No additional censored data from studies  
7 finalizing beyond this date were considered and, therefore, Cox regression models  
8 simultaneously considering public availability and time lag to this endpoint were not  
9 employed; it should be noted that this model does not allow invariant calculation of  
10 publication and public availability rates. Although Cox regression analysis is used when  
11 assessing publication rate because of the nature of the datasets considered, we believe,  
12 as others did before [26], that our approach for a complete dataset over a defined time  
13 period is more informative.  
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### 25 Conclusion

26 Eighty percent of studies managed by GSK in Spain are publicly available. When  
27 clinical trials are considered, this figure is 78%, comprising a 61% journal publication  
28 rate plus an additional 17% of not published trial results posted on CSR –hence,  
29 substantially increasing public availability rate. As 93% of these clinical trials are  
30 multinational, it seems could be regarded as reasonably representative of what GSK  
31 activity is worldwide. Cancellation of projects is the single factor influencing a lower  
32 publication and public availability rates. There is, however, room for improvement for  
33 attaining a complete public availability of study results conducted by pharmaceutical  
34 companies.  
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17 This study required no funding.  
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*Competing Interests*

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

34 REC, research ethics committee.

35 GSK, GlaxoSmithKline

36 CSR, clinical study register

37 CI, confidence interval  
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For Peer Review

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 <sup>e</sup> N (%)	B: Non- published but posted on CSR <sup>f</sup> 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 <sup>a</sup>		9 (6)	4 (44)	1 (11) (*)	5 (56)
	Epidemiology <sup>b</sup>		10 (7)	7 (70)	NA	7 (70)
	Microbiology <sup>c</sup>		20 (14)	20 (100)	NA	20 (100)
	Other <sup>d</sup>		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 <sup>a</sup> N (%) / Impact factor-median <sup>b</sup>	B: Non-published but posted on CSR <sup>c</sup> 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	<u>16 for lack of efficacy</u> : 12 in phase 2, 1 in phase 2/3 and 3 in phase 3; comprising 17 trials <sup>b</sup> , of all therapy areas except vaccines <u>2 for safety reasons</u> : 1 in phase 1, due to animal toxicological findings, 1 in phase 2 ; comprising 3 trials of neurosciences and anti-infectives <u>2 for manufacturing issues</u> : 1 in Phase 2, and 1 in phase 3 ; comprising 2 vaccine trials
Trials associated to cancelled projects - N (%)	22 (23)
Published / Publicly available <sup>a</sup>	4 (18) / 9 (41)
Not published / Non Publicly available	18 (82) / 13 (59)
Trials associated to non-cancelled projects - N (%)	72 (77)
Published / Publicly available <sup>a</sup>	53 (74) / 64 (89)
Not published / Non Publicly available	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) <sup>a</sup>		Median (range) /Mean 5.6 (2.9-8.2) / 5.7
Positive results <sup>b</sup>		63 (67)
	Phase 1	5 (100)
	Phase 2	9 (29)
	Phase 3	40 (85)
	Phase 4	9 (82)
Positive results <sup>b</sup>		63 (67)
	Published / Publicly available <sup>c</sup>	45 (71) / 55 (87)
	Not Published / Non Publicly available	18 (29) / 8 (13)
Negative results <sup>a</sup>		31 (33)
	Published / Publicly available <sup>c</sup>	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 <sup>d</sup>	3 (8)
Posted on CSR		57 (61)
Marketed products <sup>e</sup>	Published / Publicly available	42 (84) / 50 (100) <sup>f</sup>

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

Factor	Therapy Area	All studies <sup>a</sup>		Clinical Trials; Publication as outcome		Clinical Trials; Public Availability as outcome	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
			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.

Factor		All studies <sup>a</sup>			Clinical Trials		
		B <sup>c</sup>	SE	P	B <sup>c</sup>	SE	P
	Therapy Area			N.S.			N.S.
	Study associated to a Cancelled Project	2.843	7.646	0.711	-	8.437	0.994
	Clinical trial	0.309	4.110	0.940			
	Sample size	-0.002	0.002	0.366	-	0.002	0.100
	Positive trial result in publication				-	5.103	5.038
	Duration of experimental phase	0.101	0.169	0.552	0.191	0.205	0.356
	Impact factor <sup>b</sup>	-5.739	2.151	0.010	-	6.861	2.413
	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