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Cancer randomized trials showed that dissemination bias is still a problem to be solved

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Abstract

Objective: The objective of the present study was to determine the publication rate of cancer randomized controlled trial (RCTs) and to analyze the determinants of the publication, as well as to estimate the possible existence of a location and time lag bias. We also described the bibliometric characteristics of the publications.

Study design and Setting: We conducted an observational study that identified publications resulting from RCTs involving cancer-related drug products. These studies were authorized and registered by the Spanish Agency of Medicines and Medical Devices between 1999 and 2003.

Results: We identified 168 publications of 303 RCTs, resulting in a publication rate of 55.4% after a mean follow-up of 12 years. The only factor associated to the likelihood of nonpublication was the study setting favoring only national RCTs (odds ratio 2.7; 95% confidence interval 1.5–4.8). Type of sponsor did not seem to be associated, although the largest volume of nonpublished trials is international, industry-sponsored. Positive results seemed to be associated to a publication in a higher impact factor journal and a shorter time-to-publication.

Conclusions: About half of the cancer RCTs during the target period have not been published. The national setting is a factor associated to nonpublication, whereas the direction of results determines its dissemination (impact factor and timely publication).

Keywords: Dissemination bias; Publication bias; Publication rate; Location bias; Cancer; Randomized controlled trial

1. Introduction

A randomized controlled trial (RCT) should only be considered completed once it is published, being its results available for health care professionals, patients, regulatory agencies, and ethics committees [1,2]. However, a significant proportion of RCTs will never be published or will be only partially reported [3–5]. Furthermore, published RCTs appear in journals with a highly variable access and dissemination extent and are published with a varying degree of readiness. This phenomenon is usually related to the nature and direction of the results, thus representing a distortion in the dissemination process of research findings [6]. Dissemination bias, which is a broader term to include all the various types of bias related with this problem [6], tends to hide part of the available information, usually entailing an overestimation of the effect of interventions and underestimation of the adverse events, an unnecessary

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What is new?

Key findings

- Only about half (55.4%) of all cancer trials authorized in Spain have been published after a mean follow-up of 12 years after approval.
- The national setting (Spain) compared with the international was associated with a higher risk of non-publication.
- Among the non-published national trials, a high proportion were prematurely interrupted due to logistic difficulties. Many of them were non-commercial studies sponsored by cooperative clinical groups.
- Published studies reporting favourable results were associated to being published in a higher impact factor journal and a shorter time-to-publication than negative ones.

What is the implication and what should change now?

- There is a need of further developing measures that guarantee a complete research transparency, which go beyond registering RCTs in public access registries. Local ethics committees and regulatory agencies should play a leading role.
- There is a need to promote policies that support independent research that is clinically relevant as well as avoiding early discontinuation.

replication of allegedly unperformed studies, and a distortion of clinical and health care decision making for considering partial and often biased evidence [7–10]. Among potential dissemination bias, publication bias occurs when the probability of publishing research findings depends on the nature and direction of the results, whereas location bias refers to the publication in journals with greater impact, and therefore easier access based on these results [11]. On the other hand, time lag bias refers to the rapid or delayed publication of research findings, also influenced by the nature and direction of the results [11]. In addition, some authors have suggested that sample size ($\geq$100 participants) and the funding source (pharmaceutical industry) also influence the publication rate [12–14].

The objective of the present study was to determine the publication rate of cancer RCTs and to analyze the determinants of the publication, as well as to estimate the possible existence of location and time lag bias. In addition, we also described the bibliometric characteristics of the publications. In a future article, we will analyze the selective reporting of outcomes and the differences between protocols and published articles regarding the end points of the study.

2. Methods

The unit of analysis of this retrospective cohort observational study was any protocol and publication resulting from RCTs involving cancer-related drug products authorized and registered by the Spanish Agency of Medicines and Medical Devices (AEMPS), between 1999 and 2003. This period was established to assure a minimal length of time (at least 10 years) for the study to be completed and published.

The process of study identification and protocol description has already been described elsewhere [15]. We tried to locate all the articles deriving from each RCT, considering as the index publication the one reporting the results of the primary end point. We searched electronic databases including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar search engine, until March 2015. Our search strategy essentially involved keywords included in the RCT title (related to the type of cancer and the treatment), the acronym of the study when existing, and sometimes the code of the protocol, the sponsor, and the name of the national principal investigator for those studies conducted exclusively in Spain (information on the principal investigator for international studies was not available). Whenever the database searches were unsuccessful, the national coordinator in Spain and the study sponsor were contacted via postal mail, and also the research ethics committee of the coordinating institution when no response was obtained. In all cases, communications in conferences proceedings were also considered by searching keywords in the American Society of Clinical Oncology and the European Society for Medical Oncology web sites. We were not able to inquiry the Spanish Society Medical Oncology because it does not have a similar search engine.

Furthermore, we checked if each RCT had been registered in ClinicalTrials.gov and also thorough the International Clinical Trials Registry Platform.

The publication rate was computed using the number of index publications out the number of RCTs authorized by the AEMPS. To detect other dissemination forms different from index publications, we also considered any other publications, including conferences proceedings, registration in the mentioned clinical trials platforms, or any reference to the trials (not necessarily on results) in any web site [16]. Factors assessed as determinants of the nonpublication were type of sponsor (pharmaceutical industry vs. others sources), sample size, study settings (national vs. international), and type of hypothesis tested (superiority vs. noninferiority).

We obtained the impact factor (average amount of times that articles from a scientific journal published within the

past 2 years are cited in the Journal Citation Report) and Eigenfactor score (number of times that articles from a scientific journal have been cited within the past 5 years in the Journal Citation Report, considering whether the articles have been cited in with highly ranked journals, is not influenced by self-citation). We also obtained the number of citations in systematic reviews from each index publication in the Thomson Reuters Web of Knowledge^{SM} platform (searched in March 2015). The impact factor was calculated for all studies where an index publication was retrieved ($n = 168$), whereas the Eigenfactor score was obtained only for 101 studies, as this indicator was computed on the basis of web site from 2007 onward. We measured the location bias through the correlation of the impact factor and the Eigenfactor score with the direction of the results (for or against the study hypothesis). Moreover, the time interval from the authorization until the publication of the study was estimated depending on the study setting, type of sponsor, direction of the results, and sample size.

We defined the primary end point as the one reported in the protocol and corresponding to the primary objective of the study. However, when this variable was not explicitly reported, we considered the variable used to calculate the sample size. To assess the potential risk of misclassification of the primary end point, two authors (M.B. and G.U.) randomly evaluated a sample of 30 studies; the agreement was measured with the kappa statistic. The primary end point was classified as favorable when P value was <0.05 and/or the 95% confidence interval (CI) of the effect measure excluded the null value (1 for the relative measures of the effect [risk ratio (RR) or hazard ratio (HR)] or 0 for the difference of means) [7,17]. In the case of noninferiority RCTs, this was considered whenever the lower bound of the CI was under the prespecified delta value. The degree of thoroughness in the report of the primary end point could be assessed and was defined as complete when the reported information would eventually allow using it in a meta-analysis [18].

Measures of central tendency (mean and median) and of dispersion (standard deviation and range) were used to perform the descriptive analysis of quantitative parameters; proportions were used for qualitative variables. We did univariate analysis to identify the studies characteristics that were statistically associated to their publication. The analysis was conducted using the Pearson chi-squared test or the Spearman nonparametric correlation coefficient for the categorical variables and the Student t-test for continuous variables. Significant variables (P value ≥ 0.1) were selected from the univariate analysis to include them in a multivariate model of logistic regression. The association of the study results (favorable or nonfavorable) with certain characteristics of the RCTs was also explored using a univariate analysis. All analyses were conducted in SPSS 17 (SPSS Inc., Chicago, IL, USA).

To test the relationship between impact factor or Eigenfactor and study characteristics, we used a Mann-Whitney test and also a Student t-test.

Because this research project did not involve patients or the use of clinical data, we did not request approval form our institution's ethics committee, which is in agreement with the Spanish Legislation on biomedical research (Ley 14/2007).

3. Results

We identified 168 index publications (in form of a journal article) of 303 RCTs on cancer-related drugs registered during the target period (1999–2003), which is a publication rate of 55.4% after a mean follow-up period of 12 years. Including other forms of dissemination such as conference proceedings, registration in a clinical trial registry, or any web site, 61 additional studies were identified. Only five of them published results, increasing the rate of publication to 57.1%. Therefore, without considering the mandatory registration of trials by the competent regulatory authority, we could only detect the existence of 75.6% of studies by some sort of accessible resource. The rest of trials, 24.4% (74/303), could not be traced at all, which means that they are completely hidden to public access.

In Table 1, we present the publication rates of RCTs by sponsorship and setting. The great majority of studies approved and consequently the derived publications were international (78.2% [237/303] and 85.7% [144/168], respectively) and sponsored by the pharmaceutical industry (74.6% [226/303] and 75.0% [126/168], respectively).

The publication rate was higher for international studies (60.8%) [144/237] compared to Spanish studies (36.4%) [24/66] and was very similar for those sponsored by the pharmaceutical industry (55.8%) [126/226] compared to those funded by others than the industry (54.5%) [42/77]. Table 1 illustrates that although the highest rate of nonpublished trials are national, in absolute terms, the main core of the problem is among the international industry-sponsored trials.

The only factor associated to the likelihood of publication which turned out to be significant in the multivariable logistic model was the study setting (odds ratio 2.7; 95% CI 1.5–4.8), with the national studies being at higher risk of nonpublication. By contrast, the type of

Table 1. Characteristics of RCTs (all RCTs and published RCTs) according to sponsor and setting

	Sponsor		
Setting	**Pharmaceutical industry**	**Other sponsor**	**Total**
International	204 (119)	33 (25)	237 (144)
National	22 (7)	44 (17)	66 (24)
Total	226 (126)	77 (42)	303 (168)

Abbreviation: RCT, randomized controlled trial.

Table 2. Reasons why studies remained unpublished

Rationale for not publishing	*N* (%)
Early closure (*N*)	38 (66.6)
Low recruitment rate (18)	
Lack of efficacy (7)	
No patients recruited (3)	
No reason stated (3)	
Sponsor's decision (2)	
Efficacy proven by a different study (1)	
Adverse events (1)	
Adverse events plus lack of efficacy (1)	
Lack of resources (1)	
National Health entity's decision (1)	
Being the study completed, the sponsors gave no reason for the nonpublication	5 (8.7)
Negative results or with little interest to the sponsor	7 (12.2)
Under publication	2 (3.5)
Ongoing study	2 (3.5)
A report was published with the study results in the pharmaceutical company's web site, but the study was not published in a scientific journal	3 (5.2)
Total	57

sponsor, sample size, and type hypothesis tested did not seem to be related to the likelihood of being published.

Of note, among the published RCTs, 22 (13.1%) reported study data from prematurely closed trials (six due to low rate of recruitment, nine to the proof of study drug efficacy in another published study, five due to safety issues, four due to lack of efficacy, and two could not determine the reason). As for the 135 (44.5%) studies with no index publication, we were able to determine the cause of nonpublication in 57 (42.2%), 38 of them (66.6%) having been closed prematurely for different reasons (Table 2). This information was obtained from the postal mail survey address to sponsor and PI in which a single reason was selected among several options.

The overall mean length of time since the authorization to the publication in the journal was 6.5 years (ranging from 2 to 14 years). We found differences in the time-to-publication, being shorter for studies that were sponsored by the pharmaceutical industry (6.1 years vs. 7.6 years, respectively; P value = 0.002), those with a favorable result according to the study hypothesis (6.1 years vs. 7.0 years, respectively; P value = 0.04), and those involving less than 1,000 patients (6.3 years vs. 7.9 years, respectively; P value = 0.03). No differences were seen according to the study setting (6.3 years for international vs. 7.5 years for national studies) but with a trend (P value = 0.08). These results did not essentially differ when we applied a survival analysis (median time-to-publication for studies with favorable results was 5 years vs. 6 years for nonfavourable; P value = 0.039).

All index publications were disseminated in international journals, 78.6% of them in specialized oncology journals. Of these RCTs, 36.3% (61) were published in the *Journal of Clinical Oncology*, 9.5% (16) in the *Annals of Oncology*, and 7.1% (12) in the *New England Journal of Medicine*. The remaining studies were published in a total of 25 scientific journals.

The mean impact factor of the index publications was 13.3 (ranging from 1.3 to 53.4). Using a parametric approach, RCTs with favorable results to the study hypothesis (53.1%) were published in higher impact factor or Eigenfactor factor (P value = 0.0), which suggests a possible location bias. However, the association was not significant in the nonparametric analysis (impact factor distribution was skewed, with several outlier values well above). However, it is noteworthy that seven of the eight outliers correspond to studies with favorable results that were published in high impact factor. No association was observed with type of sponsor (P value = 0.213) nor study setting (P value = 0.071) although with a trend for international RCTs.

The agreement about classification of the primary end point was high (K = 0.90). The degree of the primary end point report was considered complete in 96.8% of cases, whereas the remaining failed to report the CI, the P value, or the estimate of effect.

As at March 2015, the articles had been cited a mean of 151.7 times (ranging from 0 to 2,377; median of 51.5 times). The mean number of citations of those RCTs in systematic reviews were 46.8 (ranging from 0 to 647). We found differences in the number of citations according to the type of journal (oncology vs. general; P value = 0.00), the direction of the results (favorable vs. nonfavorable) and the setting (international vs. national) (P value = 0.00).

The first author belonged to an institution based in Spain (n = 31), United States (n = 31); United Kingdom (n = 20); Germany (n = 14); France (n = 13); Belgium (n = 9); Canada (n = 6); and Italy (n = 6), to a total of 24 countries.

4. Discussion

No research study should be considered as finished until its results have been published in a scientific journal. This is even more compelling in case of RCTs where investigators appealed to the trust of the study participants on the assumption that the generated knowledge would be disseminated regardless of the nature and direction of results. Only under this premise, RCTs will contribute to the advancement of knowledge, by eventually providing its results for future systematic reviews, avoiding the redundant research and at the end favoring a better health care.

This article describes the publication rate and their determinants, the location and time lag bias, as well as the bibliometric characteristics of the publications of cancer RCTs taking as the study ingredients those trials authorized in Spain. This work is part of a broader project that has described the RCTs [15] and which will also

analyze the selective reporting bias and risk of bias of published RCTs.

The observed publication rate was 55.4%, which means that near half of cancer RCTs fails to be published (primary end point), which is in coincidence with other authors using similar methodology (weighted pooled proportion of RCTs published 60.3%; 95% CI 45.4–73.6) [19] although none was found using a national regulatory agency database as a source nor they were restricted to cancer trials. That rate is undoubtedly low, considering that the mean length of follow-up was about 12 years, and, moreover, taking into account that the importance of dissemination bias and its harmful consequences had been widely claimed and demonstrated before that period [12,20,21]. When we included other forms of partial dissemination [11,16] such as trials registries, congresses, and nonindex publications, we detected 61 additional studies which means that globally we had at least some information of only 75.6% of all performed RCTs and none of about a 24.4%. In other words, nearly a quarter of the studies remain completely hidden from the public because they cannot be traced at all.

As expected, because they represent most authorized RCTs, those studies that finally came published are mainly international (85.7%) and sponsored by the pharmaceutical industry (75.0%). According to our multivariate analysis, national trials are at higher risk of not being published although this is not suggested for those trials sponsored by the pharmaceutical industry. This is in contradiction with the findings of a recent systematic review of methodological studies investigating on publication rate of research studies [19]. However, this discrepancy may be due to the limited number of studies available for the analysis in the review, by methodological differences between the studies included in the review and ours (designs other than RCTs were included in the review, which covered a variety of medical disciplines, that were identified in different sources and periods, with a narrower follow-up period, among others).

Being only a national study could be a determinant factor for nonpublication due to the fact that national trials had a smaller sample size compared to the international ones (mean of 341 vs. 646, respectively) and a greater tendency to early closure as a result of patient recruitment difficulties (52.9% of those discontinued vs. 34.3%, respectively). This suggests the difficulties of conducting noncommercial clinical trials with sparse resources, as well as the need to promote policies that support independent research that can avoid early discontinuation. The discontinuation rate found in our study was 12.5%, lower than that found in other recent reports [22,23]. However, this seems to be an underestimate because we do not know the final status of 78 RCTs, which suggests that the actual figure is close to that reported by these authors (between 24.9% and 27% for medical RCTs, mostly because of slow recruitment). This is a phenomenon with important ethical implications that should be studied further in the future as some of the associated factors are probably preventable, causing waste of resources and an unnecessary involvement of many patients in these studies [24]. However, as summarized in Table 1, the main focus of concern should be the international industry-sponsored trials because they represent the largest number of unpublished studies in absolute terms.

As in previous reports, the systematic review by Schmucker found a positive association between negative results and risk of nonpublication [19]. We were not able to confirm this hypothesis as initially planned because of the lack of access to pertinent data either at the nonexisting publication, at the final report of the study, or because of nonresponses by authors and sponsors to our requirements. Only access to the final trial report, which should ideally be readily available to the corresponding ethics committees and to the regulatory agencies, or mandatory posting of results in trial registries, would allow a thorough analysis of all determinant factors of nonpublication [1,25–27].

Among the published studies, 50% of them provided results that support the study hypothesis (whether it was a superiority or noninferiority study). However, although this high percentage of negative results published is higher than that reported by other authors [28], it does not allow us to make assumptions on the results of unpublished studies, information to which we had no access.

Regarding the index articles (168 articles reporting the results of the primary outcome), they were published in 28 different journals (with a mean impact factor of 13.3), with a predominance of general journals over specialized in the field of oncology. The average number of citations received per article was high, although the observed variability was very large (0 to 2.377 times). All studies were published in international indexed journals independently of the study setting and the sponsor. This means that any trial, either national or international, sponsored by the industry or by other entities, has been published in an indexed national journal. Handsearching of nonindexed journals, such as that promoted by the Cochrane Collaboration [11], can provide information about any possible trial published in them. However, no study has been found either so far among the 7,000 trials identified by handsearching many Spanish nonindexed journals.

We observed that RCTs with favorable results tended to be published in journals with greater impact factor, had a greater number of citations, and were published promptly compared to the RCTs with unfavorable results, suggesting a location and a lag time biases. On the other side, we observed a more timely publication when either RCTs had been sponsored by the pharmaceutical industry, maybe because of its greater resources invested in the study conduction and publication, compared with trials sponsored by others than the industry where a higher rate of discontinuation was found.

As a strength of this study, it is remarkable that we were able to have access to cancer protocols of all RCTs authorized by a regulatory agency, ensuring the total representativeness at a national level of the sample. The follow-up to detect any related publication of all studies has been long enough and very comprehensive, which gives a reasonable confidence about the derived publication and location rates. However, we also faced some important limitations. First, we were unable to explore the publication bias because it was not possible to consult any result or circumstance in 25.7% of the studies, despite thoroughly searching in different databases, web sites, and contacting principal investigators, sponsors, and ethics committees. Unfortunately, a large proportion of the studies had not been registered in accessible databases and the ones that were registered had outdated information regarding the situation of the study and the eventually published articles. However, we believe that these limitations do not substantially change the main conclusions of the study.

Our results reinforce the need of further developing measures that guarantee a complete research transparency, which go beyond the register of RCTs in public access registries (e.g., encouraging policies that promote an explicit publishing commitment, forbiddance of restrictive clauses in research contracts, allowance of independent researchers to audit RCTs databases, close monitoring of investigators' and sponsors' commitments by regulatory agencies and ethics committees until the final results are published, etc.). These measures should affect all the parties involved in the conduction of clinical trials, as well as to the professional associations [29,30]. A recent study has developed evidence-informed general and targeted recommendations addressing the various stakeholders involved in knowledge generation and dissemination to help overcome the problem of dissemination bias (OPEN-To Overcome failure to Publish nEgative fiNdings). Hopefully following these recommendations will help increase transparency in biomedical research [31]. It should also be noted that the World Health Organization has recently published a new statement on the public disclosure of clinical trial results where it defines reporting timeframes, calls for results reporting of older but still unpublished trials, and outlines steps to improve linkages between clinical trial registry entries and their published results [32]. However, as some have correctly pointed, previous calls for registration have not been enough to fix publication bias, and positive statements like this one will require practical implementation such as auditing, providing better data for individual accountability [33].

In conclusion, about half of the cancer studies authorized in Spain during the study period remain unpublished and a quarter are completely opaque, despite the long time spent since the date of authorization. The observed low publication rate is unlikely to change substantially even with a more extended follow-up period. An exclusively national study setting was a factor associated to nonpublication, where a high rate of discontinuation was observed, whereas sponsorship by the pharmaceutical industry and favorable results are associated to a more rapid and wider dissemination. The existing proposals to reduce publication and location bias seem to be still ineffective which justify that further actions must be taken.

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