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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