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# Inadequate use and regulation of interventions against publication bias decreases their effectiveness: a systematic review

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#### Abstract

**Objectives:** To determine the effectiveness of interventions designed to prevent or reduce publication and related biases. **Study Design and Setting:** We searched multiple databases and performed manual searches using terms related to publication bias and known interventions against publication bias. We dually reviewed citations and assessed risk of bias. We synthesized results by intervention and outcomes measured and graded the quality of the evidence (QoE).

**Results:** We located 38 eligible studies. The use of prospective trial registries (PTR) has increased since 2005 (seven studies, moderate QoE); however, positive outcome-reporting bias is prevalent (14 studies, low QoE), and information in nonmandatory fields is vague (10 studies, low QoE). Disclosure of financial conflict of interest (CoI) is inadequate (five studies, low QoE). Blinding peer reviewers may reduce geographical bias (two studies, very low QoE), and open-access publishing does not discriminate against authors from low-income countries (two studies, very low QoE).

**Conclusion:** The use of PTR and CoI disclosures is increasing; however, the adequacy of their use requires improvement. The effect of open-access publication and blinding of peer reviewers on publication bias is unclear, as is the effect of other interventions such as electronic publication and authors' rights to publish their results. © 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Publication bias; Geographical bias; Trial registration; Open access; Peer review; Conflict of interest

#### 1. Introduction

Despite substantial global efforts to increase the publication of health-related research, about half of clinical studies remain unpublished [1,2]. As a result, published scientific literature represents an incomplete and biased subset of total research findings [3]. Consequently, the nonpublication of research impedes our ability to make objective and balanced decisions about patient care and resource allocation. Publication bias (also sometimes referred to as dissemination bias) occurs when the publication (or nonpublication) of

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research depends on the nature and origin of the research and the direction of the results [1,4].

Numerous examples demonstrate the detrimental effect of publication bias on patient care [5-12] and health expenditures [13]. The case of oseltamivir (Tamiflu) for preventing complications of influenza, for example, illustrates the real-world ramifications of publication bias. Billions of dollars were spent worldwide to stockpile oseltamivir based on a published body of evidence that was missing 60% of patient data [13]. Likewise, clinical decisions based on biased bodies of evidence harmed millions of patients who received rosiglitazone [12], gabapentin [10,11], paroxetine [8,9], rofecoxib [6,7], or reboxetine [14].

Despite examples about the impact of publication bias and overall evidence about the nonpublication of a large proportion of research findings, publication bias is difficult to detect when investigating a specific question of interest. Statistically, current methods for assessing publication bias are characterized by low power and strongly rely on the magnitude of the true treatment effect, the distribution of sample sizes, and a reasonable number of studies [15].

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G.G. and K.T. are Director and Associate Director of the Austrian Branch of the Cochrane Collaboration—an organization that strongly advocates to reduce publication bias and for transparency in clinical pharmaceutical research.

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## What is new?

#### **Key findings**

• The use of clinical trial registries has substantially increased since 2005; however, publication bias is still pervasive (the results of many registered trials are never made available). Likewise, although registries should deter positive outcome reporting, this bias is still prevalent and registry entries are often inadequate for independent systematic reviewers to fully detect this source of publication bias.

### What this adds to what was known?

• Publication bias and selective outcome-reporting bias represent major threats to the validity of systematic reviews and reduce our ability to produce valid conclusions based on a body of evidence. This review highlights that no empirical studies of current interventions have shown that they reduce this bias.

# What is the implication and what should change now?

• Evaluation of the effectiveness of all interventions implemented to reduce publication or related biased is urgently required to focus campaigning and advocacy efforts on those most effective. In addition, for their potential to reduce publication bias to be realized, stricter regulation of trial registries is required, with explicit accountabilities and responsibilities, as well as detailed requirements for entries into mandatory fields and penalties for noncompliance.

Consequently, the absence of a statistically significant correlation or regression does not necessarily indicate the absence of publication bias. Other methods such as the funnel plot and related imputation methods such as trim and fill have low interrated reliability or rely on the assumption that asymmetry is exclusively due to bias [16].

Increased awareness of the harmful and unethical consequences of publication bias has led to the implementation of several measures to reduce the nonpublication of studies and its related publication bias. In 2010, Song et al. [1] published an updated Health Technology Assessment that states that publication bias occurs during different stages of research but mainly before the presentation of findings at conferences and before the submission of manuscripts to journals. Based on their literature review, they list several measures to reduce publication bias that have either been proposed such as a right to publication or already been implemented such as prospective trial registration, mandatory sponsor guidelines, and others. Table 1 provides a summary of the potential mechanisms of measures to reduce publication or related biases as presented by the Song report. Fig. 1 shows the path of trial conception through to the dissemination (or nonpublication) of trial results. The measures identified by Song et al. are shown in light gray shaded boxes, and their point of effect on the pathway is indicated by a light gray dashed line. In this figure, black boxes represent dissemination of results and dashed gray boxes represent nondissemination or publication bias.

To date, however, it remains unclear whether any of these measures achieves its intended goal, that is, to increase the availability of trial results and to reduce publication bias. Therefore, the objective of our systematic review was to identify and appraise empirical studies of interventions designed and implemented to prevent or reduce publication bias to determine their effectiveness.

## 2. Methods

In this review, we concentrated on publication bias in the context of randomized controlled trials (RCTs) in clinical medicine and only included studies that directly measured the effect of an intervention on reducing publication or a related bias. We used the measures identified by Song et al. [1] as a classification framework and summarized our results in terms of the effects on publication bias or related biases, such as outcome-reporting bias, positive outcome bias, geographical or language bias, and so forth.

We included any empirical research study of a measure to reduce publication bias where an analysis was performed that sought to quantify or determine the success of the intervention in preventing or reducing publication bias or related biases. Many studies have demonstrated the existence of publication bias, and these were not the subject of this review. We did not include studies that merely demonstrated the presence of publication bias—such as the number of conference abstracts of RCTs that were subsequently published in full in journals or associations between industry sponsorship and positive results or delay in publication.

We searched MEDLINE (via PubMed), the Cochrane Library, EMBASE, CINAHL, PsycINFO, AMED, and Web of Science. The full search strategy is presented in "Additional material 1." We used medical subject headings and key words, focusing on terms for publication bias, related biases (i.e., "selection bias"), and for the known interventions (i.e., "registry," "prospective registration," "publishing/ethics," "disclosure," "peer review," "electronic publishing," "open access," "right to publication," "CONSORT statement," "conflict of interest," "research sponsor guidelines," and so forth). We initially searched sources from inception up to May 2012. In a second stage in April—June 2014, we performed updated and extended hand and electronic searches using forward and backward citation and reference tracking of pertinent key references

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