April 2013

UNCOVER is an FP7-funded project under Contract No 282574

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The effectiveness of interventions for reducing publication bias

A systematic review

This report should be cited as follows:

Thaler K, Nußbaumer B, Van Noord M, Kien C, Griebler U, Gartlehner G. Deliverable 3.1 of the UNCOVER FP7-funded project under contract number 282574: The Effectiveness of interventions for reducing publication bias: a systematic review. March 2013.

Publication bias occurs when the publication of research depends on the nature and direction of the results – a study's positive, negative, or null result can influence its chances of publication. The objective of this systematic review was to evaluate the effectiveness of interventions designed and implemented to prevent and reduce publication bias related to the publishing of study results from clinical trials. This deliverable presents the results of the review.

This deliverable was prepared for the UNCOVER project consortium:

AIT Austrian Institute of Technology
Department for Foresight & Policy Development
Coordinating partner

Vienna, Austria

DUK Danube University Krems
Department for Evidence-based Medicine and Clinical Epidemiology

Krems, Austria

UNC University of North Carolina at Chapel Hill
Gillings School of Global Public Health

Chapel Hill, North Carolina, United States

Contact
Dr. Manuela KIENEGGER

Technology Management
Department for Foresight & Policy Development
AIT Austrian Institute of Technology GmbH
Donau-City-Straße 1
A-1220 Vienna
Austria

T +43(0) 50550-4530
F +43(0) 50550-4599

manuela.kienegger@ait.ac.at

www.ait.ac.at

The effectiveness of interventions for reducing publication bias

A systematic review

This deliverable was prepared by:
Kylie Thaler, MD, MPH
Barbara Nußbaumer, BSc, MSc
Megan G. Van Noord, MSIS
Christina Kien, MA
Ursula Griebler, PhD, MPH
Gerald Gartlehner, MD, MPH

Other contributions to the deliverable by:
Maria Flamm, MD, MPH (Peer Reviewer)

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Executive Summary

Background

The UNCOVER project aims to identify and evaluate strategies and ways to overcome non-publication of clinical trials that have been designed and executed as randomized controlled trials. Publication bias occurs whenever a study's positive, negative, or null result influences its chances of publication. This report aims to evaluate the effectiveness of interventions to prevent and reduce publication bias and to conduct a thematic analysis of the literature to identify factors acting as barriers or facilitators in the implementation of such interventions.

Objectives

- To identify and appraise empirical studies on interventions to reduce publication bias, specifically with respect to prospective study registration.
- To identify personal, social, organizational, and structural factors that can act as barriers or serve as facilitators in the implementation of interventions to prevent and reduce publication bias.

Methods

The following electronic databases were searched: MEDLINE (via PubMed), the Cochrane Library, EMBASE, CINAHL, PsycINFO, AMED, and Web of Science. The main literature search was conducted in May 2012. We also manually searched reference lists of pertinent reviews, included studies, and background articles.

We retrieved all results from studies and performed an independent dual review of the titles and abstracts. We then retrieved and dually reviewed full-text publications, identifying articles eligible for inclusion.

We allocated the identified studies to KQ1 or KQ2. For KQ1, we abstracted data from the included publications and performed a risk of bias assessment. We synthesized the results and graded the strength of the evidence. For KQ2, we extracted data and performed a thematic analysis.

Results

Overall, we found 15 articles that were eligible for KQ1 and 42 articles that were eligible for KQ2. We located little evidence that showed that current measures are actually succeeding in reducing the problem of publication bias.

1 Introduction

1.1 Background

The UNCOVER project, funded by the European Union (Grant Number: 282 574), aims to identify and evaluate strategies and ways to overcome non-publication of clinical studies that have been designed and executed as randomized controlled trials (RCTs). UNCOVER is divided into seven Work Packages – this report is the deliverable for Work Package 3, Task 3.2.

RCTs are currently the gold standard for assessing drug and device efficacy as they are designed to avoid or minimize both systematic and random errors in clinical studies. They are the building blocks of systematic reviews – a cornerstone of evidence-based medicine for improved safety and effectiveness of patient outcomes. However, the inherent value of an RCT is dependent on knowledge of the trial's existence and accessibility to the trial's findings. Publication bias is the term used whenever a study's positive, negative, or null result influences its chances of publication.(1, 2) A study examining the patterns of publication of clinical trials funded by the National Institutes of Health (NIH) and registered with ClinicalTrials.gov <www.clinicaltrials.gov> found that fewer than half of a sample of registered trials were published within 30 months of trial completion.(3) Non-publication (i.e., not disseminating results) of RCT results may decisively reduce the benefit of systematic reviews of drugs, medical devices, or procedures because the research that is available, "differs in its results from the results of *all* the research that has been done in an area [and] readers and reviewers of that research are in danger of drawing the wrong conclusion about what that body of research shows".(4)

For example, in 2009 a Cochrane review on neuraminidase inhibitors was in its third update (following the outbreak of influenza A/H1N1) and the Cochrane review team conducing the update did not expect a change to the previous finding that oseltamivir (Tamiflu®) was effective in reducing serious complications of influenza such as pneumonia, "Oseltamivir 150 mg daily is effective in preventing lower respiratory tract complication in influenza cases (OR 0.32, 95% CI 0.18 to 0.57)".(5-7) However, a comment from Keiji Hayashi, a pediatrician in Japan, was submitted to the Cochrane Collaboration that questioned why, in their 2005 review, the Cochrane researchers were able to make that conclusion solely on the basis of a single peer-reviewed, manufacturer-funded study by Kaiser et al. that had meta-analyzed 10 phase III trials on oseltamivir, eight of which were unpublished.(5, 6, 8) The Cochrane review team thus began the task of attempting to verify the data themselves and requested the unpublished study data from Roche, the

manufacturers of oseltamivir. However, despite numerous attempts, the authors have been unable to obtain the full set of clinical study reports or obtain verification of data from Roche.(6) The data that has been obtained (i.e., documents from regional regulatory agencies and partial trial reports) has led the Cochrane review team to conclude that there were, "substantial problems with the design, conduct and availability of information from many of the trials" and that oseltamivir is effective only for the prevention and treatment of symptoms of influenza and not on other effects (e.g., prevention of pneumonia).(6)

Why does this matter? Based on the limited evidence that was available, governments have spent billions of dollars stockpiling oseltamivir in the belief that the drug can reduce the rate of complications from influenza and not just the duration of influenza symptoms.(9) The World Health Organization (WHO) included oseltamivir in its 2011 "WHO Model List of Essential Medicines", essential medicines being defined as those that "satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness".(10, 11) The U.S. Center for Disease Control (CDC) recommends oseltamivir as one of two medications for treating regular flu in the U.S., stating in its 2012-2013 *Influenza Antiviral Medications: Summary for Clinicians* that: "Influenza antiviral prescription drugs can be used to **treat** influenza or to prevent influenza" and "Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever and illness symptoms, and may reduce the risk of complications from influenza (e.g., otitis media in young children, pneumonia, respiratory failure) and death, and shorten the duration of hospitalization".(12) However, regulatory agencies such as the U.S. Food and Drug Administration (FDA), who have access to trial data for use in the drug approval process, have only approved oseltamivir to reduce the duration of influenza symptoms in people two weeks of age and older who have been symptomatic for no more than two days, and to prevent the flu in people who are 1 year of age and older.(5, 13)

As awareness has grown about the problem of publication bias, research has been conducted to examine the root causes and to identify preventative measures. In 2010, Song et al. published an updated Health Technology Assessment (HTA) that identified and appraised studies on publication and related biases, assessed methods to deal with publication and related biases, and examined measures taken to prevent, reduce and detect dissemination bias.(2) In Chapter 7 of the HTA, six measures were identified for the prevention of publication bias: 1) Changes in publication process, 2) Prospective registration of trials, 3) Open access policy, 4) Right to publication, 5) Research sponsors' guidelines, and 6) Confirmatory large-scale trials.

Changes in publication process: peer review process, disclosure of commercial interest, electronic publication

Peer review process: The peer review process was developed in order to improve the quality of published studies and screen out articles with flawed methodology or conclusions.(2) However, peer review can sometimes lead to publication bias; for example, when reviewers select studies with positive results for publication over those with null or negative findings.

Disclosure of commercial interest: Many journals require authors to complete conflict of interest forms in which authors disclose any commercial interests they may have, so as to acknowledge competing interests.(2) This increased transparency is an intervention in reducing publication bias as researchers may receive industry funding.

Electronic publication: The trend away from paper publishing to lower-cost electronic journals has resulted in the establishment of journals with the sole purpose of allowing researchers to publish ambiguous or null findings. Examples include, the *Journal of Pharmaceutical Negative Results*, the *Journal of Unsolved Questions* (JUNQ), and the *Journal of Negative Results in BioMedicine*, which are all peer-reviewed journals that publish negative results in an effort to allow researchers a larger platform to share their research findings. Electronic journals also often use an open-access system where their published articles are available free of charge to all readers.

Prospective registration of trials

Registration of clinical trials is at the forefront of reducing publication bias. The European Medicines Agency (EMA) has implemented a phased approach to support the pharmaceutical industry with the implementation of the electronic submission of information on medicines.(14) The National Library of Medicine (NLM) maintains the ClinicalTrials.gov database where, as a result of a U.S. law, clinical trials are registered and results are meant to be reported within two years of study completion.(15) Trial registries largely exist to strengthen and legitimize the scientific evidence base; however, there are some opponents to registries who believe that due to the competitiveness of the medical research field, information about trials should be proprietary.(16)

Open access policy

Open access policies are created to allow public access to results of clinical studies, either through access to raw trial data or to study publications without journal access fees. Mandating trial reporting and allowing access to negative, null, or positive study results without the barrier of pay-walls (i.e., journal access fees) is an intervention for reducing publication bias.

Right to publication

Right to publication refers to the right of scientists to publish any and all study findings – the industry should not suppress negative results of trials they have sponsored. Supporting a researcher's right to publish negative and null results may help reduce publication bias.

Research sponsors' guidelines

Guidelines such as the EU Clinical Trials Directive, the Declaration of Helsinki, and the CONSORT Statement have been developed so that researchers can follow the same sets of standards. Guidelines that stress the importance of reporting both positive and negative findings can help prevent selective reporting of outcomes and reduce publication bias.<

Confirmatory large-scale trials

An additional intervention to reduce publication bias is the use of confirmatory, multicenter, large-scale trials when the existence of publication bias is likely and the impact is clinically important.

1.2 Objectives

The aim of this systematic review is to evaluate the effectiveness of interventions to prevent and reduce publication bias, specifically with respect to prospective study registration as well as to conduct a thematic analysis of the literature to elicit the personal, social, organizational, and structural factors acting as barriers or facilitators in the implementation of such interventions.
The two key questions that will be addressed in this report are:

- **KQ1.** What is the effectiveness of interventions to prevent and reduce publication bias, specifically with respect to prospective study registration?
- **KQ2** What personal, social, organizational and structural factors can act as barriers or serve as facilitators in the implementation of interventions to prevent and reduce publication bias?

2 Methods

2.1 Search Strategy

To identify articles relevant to each Key Question, we searched MEDLINE (via PubMed), the Cochrane Library, EMBASE, CINAHL, PsycINFO, AMED, and Web of Science. The full search strategy is presented in **Appendix A**. We used Medical Subject Headings (MeSH) and key words, focusing on terms that most relevantly described this topic. Sources were searched up to May 2012. We manually searched reference lists of pertinent reviews, included studies, and background articles on this topic to look for any relevant citations that our searches might have missed. We imported all citations into an EndNote® X4 electronic database.

2.2 Eligibility Criteria

Table 1 lists the eligibility criteria for this report. We included studies on interventions to reduce publication bias where an analysis was performed that sought to quantify or determine the success of the intervention in reducing publication bias overall. Additionally, we looked at how these interventions reduced related biases (defined in Appendix B).

Figure 1 provides an analytic framework for this report.

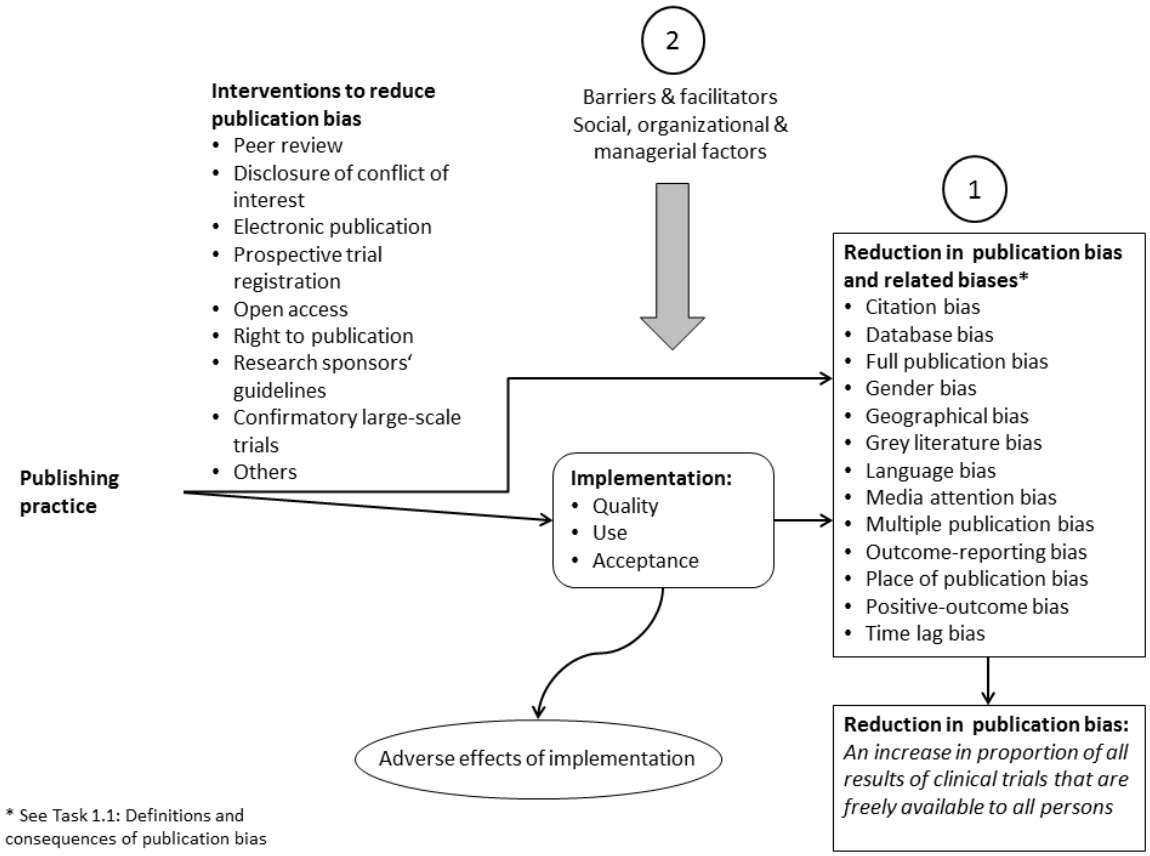


Figure 1: Analytic framework indicating the relationship of KQ1 and KQ2 in the process of implementing interventions to reduce publication bias

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 considered the following categories of intervention:

- Changes in publication process (i.e., peer review process, disclosure of commercial interest, electronic publication)
- Prospective registration of trials
- Open access policy
- Right to publication
- Research sponsors guidelines
- Confirmatory large-scale trials

Table 1: Study eligibility criteria

Outcome	Study eligibility criteria
KQ1 Outcomes: • Effectiveness in increasing the proportion of results of clinical trials that are available to all persons (reduction in publication bias) • Effectiveness in reducing related biases, such as: o Citation bias o Database bias o Full publication bias o Gender bias o Geographical bias o Grey literature bias o Language bias o Media attention bias o Multiple publication bias o Outcome-reporting bias o Place of publication bias o Positive-outcome bias o Time lag bias • Use and uptake of interventions	Any empirical research study with a comparison: • Randomized trials • Controlled cohort studies • Before and after studies • Cross sectional studies
KQ2 • Barriers and facilitators of the implementation of interventions	Any empirical research study: • Interviews • Focus groups • Survey • Document Review When no evidence is available from empirical studies then: • Discussion/Perspective and experiences of authors of studies • Editorials, Commentaries, Letters to the editor

2.3 Study Selection

We retrieved all results from searches and performed an independent dual review of the titles and abstracts for all citations. We then retrieved all full-text publications and dually reviewed these for inclusion (and allocation to KQ1 or KQ2) or for relevance as background material. The full-text review process was also conducted independently and disagreements were resolved between the two reviewers or with a third reviewer.

We used Endnote® X4 for managing citations and organized the citation review process using Microsoft Excel®.

2.4 Data Extraction

For KQ1, one reviewer abstracted data from the included studies or publications. A second reviewer checked the abstractions for correctness. For KQ2, a thematic analysis was performed, which included a data extraction component and is described in detail in section 2.8.

2.5 Risk of Bias Assessment

A single reviewer performed an assessment of the risk of bias of all empirical studies, which was confirmed by a second reviewer. For randomized controlled trials, we used the Cochrane Collaboration risk of bias tool.(1) We assessed adequacy of randomization, allocation concealment, the impact of attrition, and incomplete reporting. We based the risk of bias assessment for observational studies on criteria outlined by Deeks et al.(17)

We assessed risk of bias only for the section evaluating the effectiveness of interventions (KQ1). We refrained from doing a risk of bias assessment for articles included for KQ2 because our aim was to give an overview of possible barriers and facilitators of the implementation of interventions to counter publication bias, not their effectiveness.

We rated both RCTs and observational studies as being of low, unclear, or high risk of bias. We included studies with a high risk of bias in the results. Importantly, although this three-tier rating scale is the same for both types of studies, the inherent risk of bias in the design of RCTs and observational studies differs (as it does within categories of observational studies, i.e., whether a control group existed). This is reflected in the grading of the strength of the evidence for each outcome (see section 2.7).

2.6 Synthesis of Results

We examined interventions in the following categories: changes in publication process (i.e., peer review process, disclosure of commercial interest, electronic publication), prospective registration of trials, open access policy, right to publication, research sponsors' guidelines, and confirmatory large-scale trials.

For KQ1, we then classified the results of studies as to whether they evaluated the use or quality of use of the intervention, or by the mechanism by which they sought to reduce a certain aspect of publication bias (i.e., by reducing geographical bias or outcome reporting bias). We summarized the results qualitatively. For KQ2, we performed a thematic analysis, which is fully described in section 2.8.

2.7 Quality of the Evidence

For the results of KQ1, we graded the quality of the available evidence in a four-part hierarchy based on an approach devised by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group.(18) As shown in Table 2 we used four grades: high, moderate, low, and very low.

The four categories reflect the quality of the evidence for a particular outcome and are based on the design of the available studies, an assessment of the risk of bias of those studies, the consistency of the result, the directness of the outcomes presented in the studies (i.e., whether only surrogate outcomes are available), and the overall precision of the results. Other factors that influence the rating of the quality of the evidence are: the impact of potential publication bias; whether a large effect is present; if a dose-response relationship is observed; and the nature and direction of plausible confounding. A single reviewer graded the evidence and allocated a rating and a second, senior reviewer confirmed the rating.

Table 2: Definitions of the grades of the overall quality of evidence

++++ **HIGH**	We are very confident that the true effect lies close to that of the estimate of the effect
+++ **MODERATE**	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
++ **LOW**	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
+ **VERY LOW**	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Source: Adapted from the GRADE working group.(19)

We rated the quality of the evidence for multiple outcomes for each intervention. A statement regarding the direction of the result for an outcome (i.e., whether the intervention DOES or DOES NOT improve this outcome) is associated with a rating of the quality of the evidence for that statement. This indicates the certainty of our conclusion. We present our GRADE ratings in summary tables at the end of each intervention subchapter for KQ1.

For KQ2, we performed a thematic analysis (qualitative research). We extracted personal opinion pieces, ideas, and suggestions of authors stated in the discussion part of a study or within editorials, commentaries, or letters to the editor. Because the majority of the data

included in the thematic analysis are not results of studies we did not rate the quality of the evidence.

2.8 Thematic Analysis

We conducted a document analysis of all studies included for KQ2. To identify barriers and facilitators, we performed an inductive thematic analysis as described by Braun & Clarke.(20) A thematic analysis is a method to identify, analyze, and report themes by searching across a data set – in our case a range of texts. The identified themes (barriers and facilitators) emerged inductively from the data and were not predetermined before we started the analysis.

As a first step, we familiarized ourselves with the data by thoroughly reading all included articles. One author extracted all relevant data (i.e., text passages referring to barriers or facilitators to counter publication bias) from the articles into an excel sheet (Microsoft Excel®). In the second phase, we generated initial codes (e.g., “personal interest of researcher”) to describe the data extracted and organized the data into meaningful groups. As a third step, similar and repeating codes were grouped together, consolidated, and categorized into descriptive themes (e.g., “competing interests of stakeholders”) and subthemes. Next, we reviewed the generated themes by re-reading all data extractions evaluating whether they fit into the themes. Also, because thematic analysis is an iterative process, the whole dataset (all articles) were read again in order to find additional data. After this step, data within themes should cohere together meaningfully and all themes should be clearly distinguishable.(20) Where possible, themes were then clustered into higher-ranking themes: main categories subsuming descriptive themes. The higher-ranking themes are presented in the results section and supported by direct or indirect citations from authors of trials, studies, or editorials.

Based on the results of the thematic analysis we categorized all identified barriers and facilitators into personal, social, organizational, and structural factors.

3 Results

3.1 Results Introduction

This chapter is divided into two sections corresponding to the two key questions:

- **KQ1.** What is the effectiveness of interventions to prevent and reduce publication bias, specifically with respect to prospective study registration?
- **KQ2.** What personal, social, organizational and structural factors can act as barriers or serve as facilitators in the implementation of interventions to prevent and reduce publication bias?

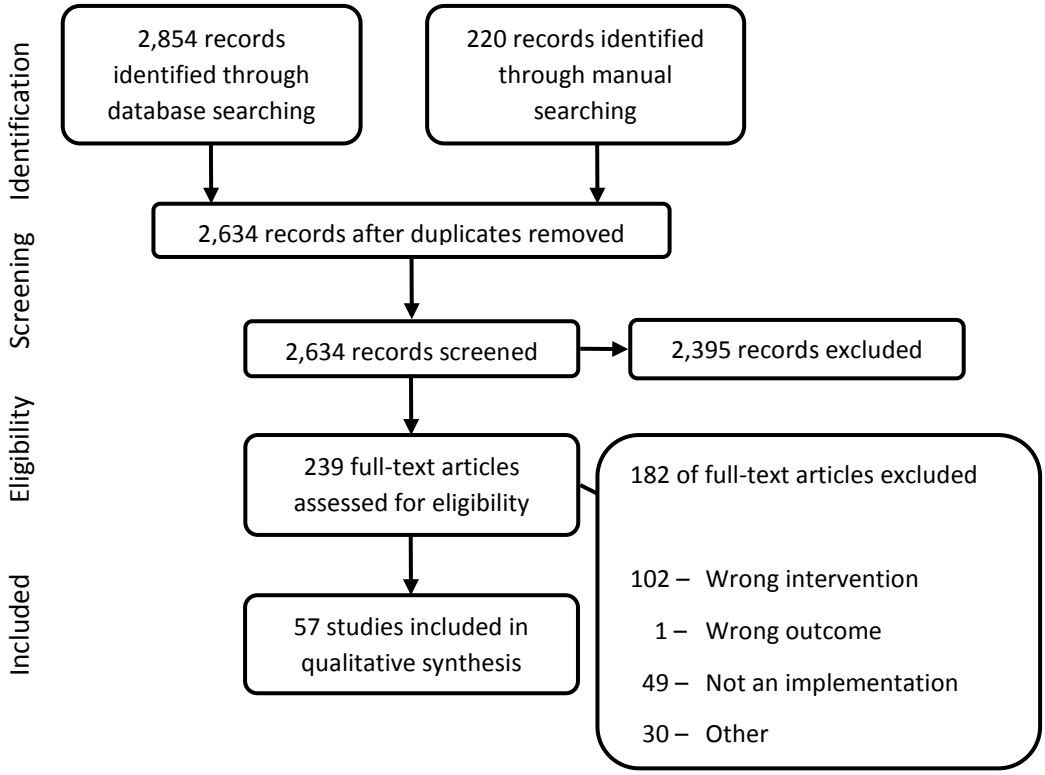
For each key question we present a qualitative summary of the literature pertaining to that question. Results are also presents in tabular form (see Tables 3-16).

3.2 Results of the Literature Search

We identified 3,074 citations from searches and reviews of reference lists and screened 2,634 records, after removal of duplicates.

Figure 2 documents the disposition of the 239 articles retrieved for full-text review for this report. Overall, we included 57 articles – 15 for KQ1 and 42 for KQ2.

Figure 2: PRISMA diagram of the study selection process.



3.3 Key Question 1: Interventions to Prevent and Reduce Publication Bias

We located 15 articles that analyzed the effectiveness of interventions to prevent or reduce publication bias.(21-35) We present the evidence for each type of intervention in separate sections. We found eight studies that evaluated the success of prospective trial registration,(21-28) and six studies that examined changes in publication process: five studies that looked at interventions in the peer review process,(29-33) and one study that explored electronic publication.(35) We found one study that evaluated open access publishing systems (with author publication fees; i.e., authors are charged a fee to publish).(34) We did not locate any evidence on disclosure of commercial interest (changes in publication process), right to publication, research sponsors' guidelines, or confirmatory large-scale trials.

Most of the studies we located were observational and did not incorporate a control group. Where randomized trials or controlled observational trials were available (i.e., for blinded peer review) they were often too small to provide adequate statistical power to detect small but important differences. High attrition was a problem for many studies and this contributed to the rating of unclear or high risk of bias.

3.3.1 Key Results

3.3.1.1 Changes in Publication Process: Peer Review Process

- Open peer review is well accepted *(one cross-sectional study, very low quality of evidence)*
- Blinded peer review may decrease geographical bias against non-US authors *(one RCT and one before-after study, low quality of evidence)* but does not reduce gender bias *(one before-after study, very low quality of evidence)*
- Blinding peer reviewers affects their decisions to accept, revise, or reject a manuscript *(three RCTs, low quality of evidence)* and improves their ability to detect mistakes *(one RCT, very low quality of evidence)*
- We did not locate any evidence regarding changes to the peer review process to reduce selective outcome reporting or positive outcome reporting bias.

3.3.1.2 Changes in Publication Process: Electronic Publishing

- One electronic journal, *Trials*, increased the number of published protocols and reports of failed RCTs over five years (2006-2011), but not raw data from RCTs, negative RCTs, or expanded reports of RCTs *(one qualitative summary, very low quality of evidence)*

3.3.1.3 Prospective Registration of Trials

- The number and proportion of clinical trials being prospectively registered has increased by 73% since the ICMJE policy was implemented in 2005 *(one before-after study, low quality of evidence)*
- Where not mandatory, details provided in trial registries regarding outcomes and methods was missing or vague and do not provide adequate data to detect and reduce outcome reporting bias *(seven cross-sectional studies, moderate quality of evidence)*
- Clinical trial registries do not reduce positive-outcome reporting bias *(one cross-sectional study, very low quality of evidence)*

3.3.1.4 Open-access Policy

- Implementing an open access system where authors pay publication fees for publishing articles might reduce the number of articles published by authors from developing countries and on public health and epidemiology *(one observational study, very low quality of evidence)*

3.3.2 Changes in Publication Process: Peer Review Process

Critics of the peer-reviewing process claim that it increases geographical bias (reviewers tending to rate manuscripts from their own country more favorably),(36, 37) and gender

bias against submissions from women.(38) We did not include studies that evaluated the effect of changes to the peer-review process on the quality, timeliness, or proportion of persons willing to peer review a manuscript. We limited included studies to those reporting on factors directly associated with publication bias, such as gender bias, or geographical bias (including against developing countries or authors from countries where English is not the native language). We did not locate any studies that evaluated changes to the peer review process to reduce selective outcome reporting or positive outcome reporting bias.

We located five studies that evaluated the effectiveness of interventions or changes in the peer review process for reducing publication bias.(29-33) One study implemented a system of open, public peer review where articles and the peer-review comments were available online for commentary from the public prior to paper publication,(29) and four studies looking at blinded or un-blinded peer-review processes.(30-33) The study on open peer review only evaluated the acceptance and uptake of this method of peer review, while the other four evaluated the impact on geographic and gender bias as well as the proportion of reviewers who advised to accept a manuscript and their ability to detect mistakes in a manuscript.

Table 3 provides a description of the characteristics and results of the included studies.

Table 3: Studies evaluating the peer review process

Study	Study Design & Intervention	Results	Risk of Bias
Acceptance of open peer review			
Bingham et al., 1998(29)	Uncontrolled cohort study of an open peer review system appealing for commentary from the public on original articles and their reviews (*The Medical Journal of Australia*)	Only 2% of internet readers also supplied comments on articles. All comments were supportive of the peer reviewers, 90% were sensible and useful.	high[1]
Blinded peer review			
Ross et al., 2006(30)	Before and after study of blinded peer review of abstracts submitted to AHA meeting.	Blinding peer review significantly improved the acceptance rate of abstracts from outside the US, from non-English speaking countries, and less prestigious institutions.	high[2]
Alam et al., 2011(31)	RCT: Four reviewers randomly allocated to perform blinded or unblinded peer review or 40 manuscripts	No significant differences were seen for acceptance rates between blinded and unblended peer review of US or non-US manuscripts.	unclear[3]
Fisher et al., 1994(32)	RCT: Four reviewers randomly allocated to perform blinded or unblinded peer review of 57 manuscripts	No significant differences in scoring (recommendation to accept/reject)	high[4]

Study	Study Design & Intervention	Results	Risk of Bias
Godlee et al., 1998(33)	RCT: 221 reviewers randomly allocated to blinded vs. unblinded review and open vs. anonymous review of a manuscript with 8 weaknesses	No significant differences in ability to detect mistakes, blinded reviewers less likely to recommend rejection	unclear[5]

RCT: randomized controlled trial; RoB: risk of bias; US: United States of America
[1] Study uncontrolled, 50% of articles excluded from study by editors, 19% of authors refused to take part.
[2] Cannot rule out effect of different time periods and role of increasing awareness of geographical bias
[3] Inadequate description of randomization and allocation concealment. No analysis of whether blinding was maintained
[4] Reviewers guessed author identity in 46% of cases.
[5] Response rate of 53%.

3.3.2.1 Acceptance of open peer review

In the uncontrolled cohort study of an open, public peer-review process, editors of *The Medical Journal of Australia* (MJA) asked all peer reviewers in a period during 1996 and 1997 to allow online publication of their comments on an article that was subsequently accepted for publication.(29) These peer review reports were published simultaneously with the article in electronic form, and the interested public was able to make further comments. Reviewers were allowed to remain anonymous. Open peer review had a high acceptance; 81% of authors agreed to participate, while 92% of reviewers participating, with 62% of those choosing to sign their reports. The participation of the general public was disappointing. Of 2,880 Internet users who accessed the articles, only 25% also accessed the peer reviewers' comments, and less than 2% provided an e-mail comment themselves. Of the 52 comments, 90% were sensible and potentially useful.

Table 4 shows the quality of the evidence for open peer review.

Table 4: Quality of the evidence for open peer review

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
Open peer review is well accepted						
1, cross-sectional study	Yes[1]	NA	Serious[2]	none	Large effect	+ VERY LOW
Open peer review reduces geographical bias, gender bias, outcome reporting bias and positive outcome reporting bias						
No evidence						

[1] high attrition (refusal to participate or exclusion of articles by the editors)
[2] study conducted in 1996-7 and may not be applicable anymore

3.3.2.2 Blinded peer review to reduce geographical bias, gender bias, and influence decisions regarding manuscripts

Four studies evaluated blinded peer review, three small randomized trials(31-33) and one large before and after study.(30) The largest study compared the acceptance of 67,273 abstracts submitted to the American Heart Association's annual Scientific Sessions meeting in 2000 and 2001, when reviewers were aware of the name and institution of submitting authors, with the years 2002 through 2004 when abstracts were submitted anonymously.(30) Blinding of the peer review process for abstracts submitted to a major US cardiology conference significantly reduced the likelihood of preferential acceptance of abstracts from US-authors, from countries with English as the official language, and from prestigious institutions ($P<0.001$ for all comparisons). The acceptance rate of abstracts from women or men was not affected by blinding the peer review process.

The three smaller randomized trials of blinded peer review failed to detect significant differences between the blinded and unblinded reviewers. In the study of 40 manuscripts submitted to the journal *Dermatologic Surgery*, four reviewers were randomly assigned to conduct blinded or unblinded peer review of submitted articles.(31) The authors compared the recommendations of the two groups of reviewers for US and non-US manuscripts. All peer reviewers were from the US. No significant differences were detected between rates of recommendations to accept, accept with revisions, or reject manuscripts from US or non-US authors between blinded and unblinded peer reviewers. This study was powered to detect a 25% difference in acceptance rates to a significance of $P<0.10$ and therefore may have failed to detect a smaller, but relevant effect. Another small, randomized study of 57 manuscripts submitted to *The Journal of Developmental and Behavioral Pediatrics* showed that for two blinded and two unblinded peer reviewers the score given to a manuscript (indication of whether to publish, revise, or reject) did not differ significantly.(32) An analysis of the effect of blinding on the acceptance rate for manuscripts submitted from highly published authors indicated that blinding increased the acceptance rate of papers from authors with more previously published articles. Finally, a trial of 221 reviewers randomly assigned them to blinded or unblinded review and open or anonymous review of a manuscript for the *British Medical Journal*.(33) Reviewers were sent a modified manuscript with eight areas of weakness. The study failed to detect a significant difference in the ability of reviewers to detect mistakes, although blinded reviewers were less likely to recommend rejection.

Table 5 shows the quality of the evidence for blinded peer review.

Table 5: Quality of the evidence for blinded peer review

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
Blinded peer review reduces geographical bias						
2, one before-after study and one RCT	no	Serious[1]	Serious[2]	none	none	++ LOW
Blinded peer review does not reduce gender bias						
1, before and after study	no	NA	Serious[2]	none	none	+ VERY LOW
Blinding peer reviewers changes their decision to accept, revise or reject a manuscript						
3, RCTs	Yes[3]	none	none	Serious[4]	none	++ LOW
Blinding peer reviewers improves their ability to detect mistakes in a manuscript						
1, RCT	Yes[3]	NA	none	Very serious[4]	none	+ VERY LOW
Blinded peer review reduces outcome reporting bias and positive outcome reporting bias						
No evidence						

NA: not applicable
[1] RCT indicated no difference between blinded and non-blinded reviewers, before-after study showed significant improvement in geographical bias with blinding
[2] abstracts submitted to a cardiology conference in the US, may not be applicable to other specialties and to conferences outside the US or to journals
[3] RCTs at high risk of bias
[4] Trials were small and not adequately powered to detect an important difference

3.3.3 Changes in Publication Process: Electronic Publishing

We located one study that evaluated the impact of an electronic journal on reducing factors that are known to be associated with publication bias. This summary showed that the use of electronic publishing with unlimited space has increased the number of published protocols and reports on failed RCTs, but not achieved other goals.

The journal *Trials* was launched in 2006 with the explicit aim of publishing "manuscripts on any aspect of the design, performance, and findings of RCTs in any discipline related to health care".(39) In addition, *Trials* actively encourages the publication of protocols of RCTs and of "negative" results.

Table 6 provides a description of the characteristics and results of the included studies for electronic publication.

Table 6: Studies evaluating electronic publishing

Study	Study Design & Intervention	Results	Risk of Bias
Altman et al., 2011(35)	Electronic journal that actively publishes protocols, raw data and negative results.	Increase in number of protocols of RCTs published and reports of failed RCTs. No improvement in publication of raw results, RCTs with negative results, or expanded reports of RCTs.	high[1]

[1] **Qualitative analysis, often not accompanied by concrete numbers of cases or any comparisons with other journals**

3.3.3.1 Electronic journal to reduce outcome-reporting and positive-outcome bias

One article presented a qualitative summary of the success of *Trials* over the first five years of its existence.(35) *Trials* was successful in increasing the number of published protocols of RCTs which can help expose and reduce outcome-reporting bias and selective reporting of subgroups; in the first year 21 protocols were published, and by 2011 that number had increased to over 100. The journal rejected less than 20% of RCT protocols submitted for publication. Likewise, *Trials* published "numerous" reports of failed RCTs in order to convey information to the general research community on "lessons learned". In contrast, the attempt to publish raw data from RCTs, extended reports of RCTs published in abbreviated form elsewhere, and RCTs with negative results failed. In five years only one RCT was published with raw data available for re-analysis (albeit a large trial on acute stroke – the International Stroke Trial IST-1). *Trials* published no expanded report of a trial previously published elsewhere; although "several" expanded protocols previously published in other journals were accepted. Only "a small number" of RCTs with negative results were published, despite the explicit policy of considering manuscripts rejected by other journals post peer-review for reasons of space or interest level (considered synonyms for negative results).

Table 7 shows the quality of the evidence for electronic publishing.

Table 7: Quality of the evidence for electronic publishing

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
Electronic publishing increases the number/proportion of published protocols						
1, qualitative summary	Yes[1]	NA	None	Serious[2]	None	+ VERY LOW
Electronic publishing DOES NOT increase the publication of negative results (reduce positive outcome reporting bias)						
1, qualitative summary	Yes[1]	NA	None	Serious[2]	None	+ VERY LOW
Electronic publishing DOES NOT increase the amount of information provided on RCTs (improved ability to assess risk of bias, reduces selective outcome reporting bias)						
1, qualitative summary	Yes[1]	NA	None	Serious[2]	None	+ VERY LOW

NA: not applicable
[1] Qualitative analysis, often not accompanied by concrete numbers of cases or any comparisons with other journals
[2] no quantitative analysis possible

3.3.4 Prospective Trial Registration

We located eight studies that evaluated aspects of prospective trial registration related to publication bias, seven cross-sectional studies(21-27) and one before and after study.(28) One controlled before and after study analyzed the effect of the ICMJE policy requiring the registration of clinical trials as a prerequisite of publication on the number and quality of entries in trial registries.(28) Seven studies measured the adequacy of information provided in trial registries or compared published and registry data,(21-24, 27, 28) and one study reported on the adherence to the CONSORT (Consolidated Standards of Reporting Trials) guidelines in the published reports of registered trials vs. non-registered trials.(25) One study evaluated the impact of prospective trial registration on positive outcome reporting bias by comparing the favorable reporting of study drugs in publications of registered versus non-registered trials.(26)

Table 8 provides a description of the characteristics and results of the included studies.

Table 8: Studies evaluating trial registration

Study	Study design	Results	Risk of Bias
ICMJE policy on prospective trial registration (increasing the use of trial registries)			
Zarin et al., 2005(28)	Before and after study of records from *clinicaltrials.gov* after ICMJE policy began in Sep 2005	Number of entries increased by 73%	low

Study	Study design	Results	Risk of Bias
Adequacy of information in trial registries & comparison with published data (reducing the potential for outcome reporting bias)			
Ross et al., 2009(27)	Cross-sectional study of 7,515 entries in *clinicaltrials.gov* in 2007	66% provided details of primary outcome and 56% of secondary outcomes.	low
Zarin et al., 2011(21)	Cross-sectional study of 2,178 records from *clinicaltrials.gov* that had results available.	Of 100 randomly selected trial entries 61% provided only vague information on outcomes	low
Zarin et al., 2005(28)	Before and after study of records from *clinicaltrials.gov* after ICMJE policy began in Sep 2005	31% of records from pharmaceutical companies provided specific details on outcomes.	low
Mathieu et al., 2009(23)	Cross-sectional study of 323 RCTs published 40 high-impact factor journals in 2008	55% were not or inadequately registered. Trials were registered in clinicaltrials.gov (84%) or ISRCTN (12%). 31% presented a different primary outcome.	low
Huic et al., 2011(24)	Cross-sectional study of 152 registered trials from *clinicaltrials.gov* and their published reports	Differences between registry and publication: 78% for reported target sample size; 39% primary outcome; and 65% secondary outcomes	unclear[1]
Reveiz et al., 2010(22)	Cross-sectional study of 265 entries from the WHO ICTRP* search portal evaluating the adequacy of reporting of methodological study details in	No useful information or insufficient detail on allocation concealment (98%), blinding (86%) or harms (90%). Explicit reporting of sample size calculations was adequate in only 1% of entries.	unclear[2]
Reveiz et al., 2010(25)	Cross-sectional study of 144 RCTs compared the adherence to the CONSORT guidelines in prospectively registered RCTs**	Reporting of participant flow and randomization implementation was significantly better in publications of RCTs that had been prospectively registered (flow: 76% vs. 38%, randomization: 48% vs. 22%).	unclear[3]
Trial registration and favorable results (reducing positive outcome bias)			
Rasmussen et al., 2009(26)	Cross-sectional study of 137 reports of RCTs in oncology to determine if prior registration was associated with reporting favorable results***	The proportion of RCTs prospectively registered increased from 0% to 80% from 2002 to 2008. There was no relationship between registration and favorable results.	low

CONSORT: Consolidated Standards of Reporting Trials; ICMJE: International Committee of Medical Journal Editors; ISRCTN: International Standard Randomized Controlled Trial Number Register; RCT: randomized controlled trial; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform

*** The WHO ICTRP portal indexes clinicaltrials.gov plus six primary registries from Australia, China, India, Germany, ISRCTN, and the Netherlands**

**** registered in any international clinical trial registry, unspecified**

***** included the US national Institutes of Health registry, the ISRCTN, the WHO ICTRP, the US National Cancer Institute PDQ Comprehensive Cancer database, and corporate trial registries and databases.**

1 sample of published trials not taken randomly for smaller journals

2 sample from trial registries not proportional to the use of those registries in real world (over-sampling of smaller registries)

3 unclear which trial registries were included

3.3.4.1 Increasing use of trial registries: the ICMJE policy on prospective trial registration

One before and after study analyzed the impact of the ICMJE policy requiring the registration of clinical trials as a prerequisite of publication.(28) The authors analyzed the number of records and completeness of information on "Intervention Name" and "Primary Outcome Measure" in the trial registry *clinicaltrials.gov* in the six months around the implementation of the ICMJE policy on September 13 2005. From May 2005 to October 2005 the number of trials registered in *clinicaltrials.gov* increased by 73% from 13,153 to 22,714. All persons entering intervention names for non-industry trials used specific details during the entire study period. For industry records the percentage of nonspecific entries (e.g., "investigational drug") for intervention name decreased from 10% to 2%, indicating the ICMJE policy had a positive effect.

Table 9 shows the rating of the quality of the evidence for the effectiveness of prospective trial registration.

Table 9: Quality of the evidence for prospective trial registration

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
The ICMJE policy on mandatory registration encourages the use of CT registries						
1, before and after study	No	NA	None	Serious	Large effect	++ LOW

3.3.4.2 Adequacy of information in trial registries & comparison with published data (reducing outcome-reporting bias)

Prospective trial registries could assist systematic reviewers or other independent persons to detect and discourage outcome-reporting bias by allowing them to crosscheck planned primary and secondary outcomes and potential subgroup analyses with those presented in the publications of result of trials. For this to be possible the data in trial registries must be accurate and complete.

Six studies provide evidence that trial registries contain missing or faulty information regarding important methodological and design aspects or that the information about clinical trials is changed between initial registration and publication.(21-24, 27, 28) One study examined the difference in adherence to good reporting of methods in registered versus non-registered studies.(25)

One large cross-sectional study of 7,515 registered clinical trials in *clinicaltrials.gov* conducted in 2007 indicated that only 66% provided details on the primary outcome and only 56% described secondary outcomes.(27) Likewise, for 657 records entered by the top 10 pharmaceutical companies around the time of the implementation of the ICMJE compulsory trial registration policy, only 31% provided specific information on the primary

outcome including the measure and the time frame.(28) Four studies of 2,964 registry entries provide evidence that between 30% and 40% of primary outcomes and up to 65% of secondary outcomes are changed between first and last entry of study information in clinical trial registries or that reported primary and secondary outcomes in the trial registries or in journal publications differ from those initially registered for the trials.(21, 23, 24, 27) Similarly, reported outcomes measures and time for follow up of outcomes as well as the methodological characteristics of trials are vaguely described.(21, 22, 27) These results indicate that even when trials are prospectively registered, publications remain vulnerable to selective outcome reporting bias.

Both studies additionally analyzed the adequacy of the information provided on the primary outcome and population of 311(27) and 100(21) randomly selected registered trials. When persons registering details of a trial are allowed to provide vague details then the registry details do not provide adequate information to ensure that outcome-reporting bias has not occurred in subsequent publications. Vague entries include: providing an outcome such as “anxiety” but no measurement scale, or providing a measurement (specific rating scale) but no time frame or method of analysis (e.g., categorical, change from baseline, period of follow up). In the smaller, more recent sample 61% of entries specified only a domain (symptom) or measurement scale.(21) Likewise, in a sample of 684 records, only 31% included all participants in all analyses and 24% of trials reported results for less than 90% of the original study population for at least one outcome. The larger sample of 311 trials registered in *clinicaltrials.gov* by 2005 and subsequently published in journals confirmed that the quality and specificity of data on outcomes varied considerably and was often too sparse to allow controls of subsequent publications.(27)

Two small cross sectional studies looked specifically at discrepancies between clinical trial registry records and published reports of trials.(23, 24) One cross-sectional study evaluated whether 323 RCTs published in 2008 in 40 high-impact factor journals in general medicine, cardiology, rheumatology, and gastroenterology had been adequately registered prior to publication and whether the primary outcome reported in the registry corresponded to that presented in the journal article.(23) The authors included both journals with a policy of requiring registration for publication and those that did not mandate prior registration. Of 323 published reports of RCTs 28% were not registered, 15% were registered after study completion, and 12% had no or an unclear description of the primary outcome in the registration record. (Many trials began before the ICMJE policy implantation deadline of July 2005.) Most trials were registered in *clinicaltrials.gov* (84%) or International Standard Randomized Controlled Trial Number Register (ISRCTN) (12%). Of the 147 trials where registration was performed before enrolment of participants and the primary outcome was adequately described in the registry, 31% presented a different primary outcome in the published report; 41% of these discrepancies favored statistically significant results.

The other study assessed the completeness of RCT data in *clinicaltrials.gov* and the nature of changes to the registry entries and compared the registry data with published records of trials for all 482 reports of clinical trials published in ICMJE journals in the 2.5 years after September 15, 2005.(24) The authors present an analysis of a random sample of 149 articles (152 RCTs) from seven journals. Between the first and last registration records 17% of records showed a major change in the information provided on the primary outcome and 15% changed the details of secondary outcomes. Fifteen percent of records did not include a sample size calculation by the time of the last data entry before publication. Many discrepancies were detected between the last change to the registry record and publication: 78% differed in the reported target sample size; 39% had discrepancies in the primary outcome, including newly introduced primary outcomes not declared in the trial registry data (30%); and 65% differed in the secondary outcomes.

Two studies looked at the adequacy of the description of the methods of trials in registries,(22) and in published reports of registered vs. non-registered trials.(25) The first study evaluated the adequacy of reporting of key methodological study details in 265 records of RCTs retrieved from the seven registries accessible through the WHO ICTRP search portal (*clinicaltrials.gov* plus six primary registries from Australia, China, India, Germany, ISRCTN, and the Netherlands).(22) The majority of records provided no useful information or insufficient detail on allocation concealment (98%), blinding (86%) or harms (90%). Likewise, explicit reporting of sample size calculations was adequate in only 1% of entries. In general, the Australian and Indian registries had a higher proportion of adequate reporting of methods, and these registries also provided specific fields for most of the methodological items assessed.

The second cross-sectional analysis of 144 RCTs published in the top 55 ranked medical journals in 2007 compared the adherence to the CONSORT guidelines in RCTs that reported prospective trial registration (36%) with those that did not (64%).(25) The authors determined that the reporting of participant flow and randomization implementation was significantly better in publications of RCTs that had been prospectively registered (flow: 76% vs. 38%, randomization: 48% vs. 22%). These results indicate that prospectively registering trials may have a role in improving the quality and comprehensiveness of the final publications of trial results even if details in the registries are not always adequate.

Table 10 shows the rating of the quality of the evidence for the effectiveness of prospective trial registration.

Table 10: Quality of the evidence for prospective trial registration

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
Prospective trial registration DOES NOT provide adequate data to detect and reduce discrepancies with published reports (reducing the potential for outcome reporting bias)						
7, cross-sectional studies	No	none	none	none	Large effect	+++ MODERATE

3.3.4.3 Evidence of positive outcome reporting bias in registered vs. non-registered trials

Rasmussen and colleagues conducted a cross-sectional analysis of 137 published reports of 115 distinct RCTs that evaluated the 25 oncology drugs newly approved for use by the FDA in the period 2000-2005 and compared those that were prospectively registered with those not registered.(26) All articles were published between 1996 and 2008; no trials were prospectively registered before 2002, while 80% of those published in 2007-2008 were registered. The authors did not find any difference between the likelihood of registered studies to favor the test drug as compared with non-registered RCTs (OR 1.29 95%CI 0.54 to 3.08). These results confirm that the use of trial registries is increasing; however no effect on reducing positive outcome reporting bias could be seen.

Table 11 shows the rating of the quality of the evidence for the effectiveness of prospective trial registration.

Table 11: Quality of the evidence for prospective trial registration

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
Clinical trial registries DO NOT reduce positive outcome reporting bias						
1, cross-sectional study	No	None	Serious[1]	Serious	Supported by other evidence[2]	+ VERY LOW

[1] **Only trials in oncology**

[2] **One study did not show a difference in positive outcomes for registered vs. non-registered trials, in addition, several other studies indicated that the reporting of primary and secondary outcomes in trial registries is poor and therefore they cannot be used to deter/reduce positive outcome reporting bias.**

3.3.5 Open-access Policy

"Open-access" describes two interventions: mandatory open access for all persons to all data resulting from clinical trials; and free access for all persons to publications of clinical trials (a system where users of the scientific literature have unlimited access to publications without paying subscription fees to the publishers of journals). We did not locate any studies on open access to all data from clinical trials. We located one study on

open access to peer-reviewed journals publishing articles on clinical trials in infectious diseases.(34) In order to fund open-access journals authors of scientific publications are asked to pay publication fees to have their study published. Hence the burden of cost for publication is shifted from the user to the authors. Costs for authors are usually between one and two thousand Euros and journals often offer discounts for authors from developing countries.(40) Several funders of clinical research in Europe mandate open access to the results of studies that they sponsor.(2)

See Table 12 for a description of the characteristics and results of the included studies.

Table 12: Studies evaluating open access publishing

Study	Study Design & Intervention	Results	Risk of Bias
Liyanage et al., 2006(34)	Cross-sectional study of four journals with alternative models – subscription vs. author pays. Additional before and after data provided for two journals.	Authors from developing countries and articles about public health or epidemiology were less likely to be published in author-pays journals. Articles on basic science were more frequent in author-pays journals.	high[1] The difference was no longer statistically significant looking at the same journal pre- and post-implementation of author-pays system.

[1] **Not clear how comparable the scopes of the journals are and how this influences the decision to accept different types of manuscripts. No before and after comparison provided for subscription-based journals.**

3.3.5.1 Open-access publishing disadvantages authors from developing countries

We located one publication that performed a cross-sectional study and a before and after study.(34) In the cross-sectional analysis authors evaluated the implementation of publication fees and open access publishing for reducing publication bias in the field of infectious diseases by comparing four journals similar in scope; two with a traditional subscription-based funding model and two with publication fees for authors and where electronic access to articles was “open” (free of charge for all users) after 12 months. For a ten-page article with one colored figure authors are asked to pay $1,230 U.S. dollars. The study compared 463 original articles published in the journals in 2003 and 2004 and found that significantly fewer articles written by authors from developing countries and concerning public health and epidemiology were published in journals with publication fees (OR 0.25 95%CI 0.15 to 0.41, OR 0.5 95%CI 0.33 to 0.74, respectively). Likewise, articles concerning basic science (animal studies or cellular, genetic or biochemical studies) were more likely to be published in the journals with publication fees (OR 5.2 95%CI 2.73 to 9.87). No significant difference was seen for the number of publications funded by the pharmaceutical industry (OR 1.11 95%CI 0.69 to 1.79). In their before and after analysis the

authors of this study also compared the same two journals before and after implementation of the author-pays model (1998 and 1999 vs. 2003 and 2004) and the difference in rates of publications from developing countries and on public health and epidemiology was no longer statistically significant (OR 1.33 95%CI 0.7 to 2.52, OR 1.06 95%CI 0.74 to 1.52, respectively). This may indicate that these results are more dependent on the scope/direction of the journal and less on the model, or that the scope/direction of the journal may also influence a decision to move to an author-pays system.

One additional short report (published as a letter to the editor) compared the characteristics of 216 articles published in 2007 and 2008 as extended reports in the journal *Annals of the Rheumatic Diseases*.(41) This journal offers a voluntary option for authors to "unlock" their articles for readers, i.e., make them free open-access. In the period studied factors significantly associated with unlocked articles were: industry funding (OR 2.48 95%CI 1.03 to 5.94); employment at a pharmaceutical company 8OR 4.02 95%CI 1.62 to 9.98); equity provided by pharmaceutical company (OR 7.22 95%CI 2.29 to 22.70); other grants (OR 12.73 95%CI 4.57 to 35.46); and fees to individual researchers (OR 16.78 95%CI 5.95 to 47.30). The type of study was not significantly associated with the decision to unlock; randomized controlled trials vs. other study types (OR 2.92 95%CI 0.86 to 9.84). As this study was published as a letter to the editor we were not able to perform a critical appraisal of the methods used and it was formally excluded from our review; however the results contrast with the other study which showed no association with industry sponsorship and an author-pays or subscription-based funding system.

Table 13 shows the quality of the evidence for open access publishing.

Table 13: Quality of the evidence for open access publishing

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
Open access publishing improves access to trial results						
No evidence						
Open access publishing increases bias against authors from developing countries (harm)						
1, observational study (cross-sectional analysis and a before-after analysis)	Yes[1]	Serious[2]	Serious[3]	Serious[2]	none	+ VERY LOW

[1] **Not clear how comparable the scopes of the journals are and how this influences the decision to accept different types of manuscripts. No before and after comparison provided for subscription-based journals**
[2] **Results of cross-sectional comparison and before-and-after analysis were inconsistent**
[3] **Study only looked at four infectious disease journals**

3.4 Key Question 2: Qualitative Synthesis

The uniqueness of KQ2 required a qualitative approach and therefore the style of this section differs from the previous chapter. This chapter presents the results of a qualitative thematic analysis focusing on barriers and facilitators of the implementation of interventions aimed at reducing publication bias. Barriers and facilitators can be personal, social, organizational, or structural factors that impact the implementation of interventions to counter publication bias. As previously discussed, we used the following categories to present our findings: Changes in publication process, Prospective registration of trials, Open access policy, Right to publication, Research sponsors' guidelines, and Confirmatory large-scale trials.

We wanted to gain a broad overview of all possible barriers and facilitators influencing measures to reduce publication bias. We thus included empirical research studies such as expert interviews and surveys, literature reviews, and the discussion part of studies. We also incorporated editorials, commentaries, and letters to the editor into our analysis in order to identify expert opinions, new ideas, and common themes about facilitators and barriers.

We included 42 articles for the thematic analysis. Some articles mentioned barriers and/or facilitators for more than one intervention to counter publication bias, others focused on one intervention (summarized in Table 14). We did not identify publications concerning right to publication and research sponsors' guidelines.

We located two articles that conducted qualitative expert interviews - one on the peer review process and one on factors influencing the publication process.(42, 43) We found one study in which a web-based survey about academic researchers' opinions on registering trial details was performed and we identified one article that presented an explanatory framework of factors influencing peer review.(44, 45) We also included seven research studies where barriers/facilitators of peer review, prospective trial registration, and disclosure of financial interest was mentioned in the discussion part of the article.(46-52) We found six narrative literature reviews,(16, 53-57) 13 commentaries,(58-69) seven editorials,(70-77) three letters to the editor,(78-80) and two articles that describe specific trial registries.(81, 82)

Table 14: Types of articles and interventions addressed in studies included for KQ2

Publication	Type of article	Intervention
Abaid et al., 2007(58)	Commentary	- Prospective trial registration - Open access policy (mandatory reporting of results)

Publication	Type of article	Intervention
Abaid et al., 2007(59)	Commentary	- Prospective trial registration
Antonelli & Mercurio, 2009(53)	Narrative literature review	- Prospective trial registration - Open access policy (mandatory reporting of results)
Berger, 2008(60)	Commentary	- Changes in publication process: Disclosure of conflict of interest
Bock, 2002(61)	Commentary	- Changes in publication process: Peer review process
Bonita et al., 2011(54)	Narrative literature review	- Prospective trial registration - Open access policy (mandatory reporting of results)
Bourgeois et al., 2010(52)	Analysis of registered trials/ discussion part	- Prospective trial registration - Open access policy (mandatory reporting of results)
Calnan et al., 2006(43)	Empirical Research Study: Expert Interview (n=6)	- Prospective trial registration - Confirmatory large scale trial
Chalmers, 2002(80)	Letter to the editor	- Open access policy (mandatory reporting of results)
Connor, 2008(62)	Commentary	- Changes in publication process: Peer review process
De Melo-Martin & Intemann, 2009(63)	Commentary	- Changes in publication process: Disclosure of conflict of interest
Deangelis et al., 2005(70)	Editorial	- Prospective trial registration
Dickersin & Rennie, 2003(55)	Narrative literature review	- Prospective trial registration
Dubben & Beck-Bornholdt, 2004(57)	Narrative literature review	- Prospective trial registration
Easterbrook, 1987(79)	Letter to the editor	- Open access policy (mandatory reporting of results)
Gibbs & Wager, 2000(82)	Description of a pharmaceutical trial registry	- Prospective trial registration
Glymour, 2005(78)	Letter to the editor	- Changes in publication process: Peer review process

Publication	Type of article	Intervention
Gøtzsche, 2009(77)	Commentary	- Open access policy (mandatory open access to trial data)
Hall et al., 2007(46)	Analysis of data from protocols submitted to REB/ discussion part	- Prospective trial registration
Henderson, 2002(64)	Commentary	- Changes in the publication process: peer review process - Open access policy (mandatory open access to trial data)
Joober et al., 2012(71)	Editorial	- Open access policy (Open access journals) - Changes in Publication Process: Electronic Publication
Koletsi et al., 2009(47)	Analysis of type of result & impact factor of journals/ discussion part	- Changes in publication process: Peer review process
Laine, 2007(72)	Editorial	- Prospective trial registration
Levy, 1997(65)	Commentary	- Prospective trial registration - Open access policy (mandatory reporting of results)
Liesegang, 2009(66)	Commentary	- Changes in publication process: Peer review process - Changes in publication process: Disclosure of conflict of interest
Lipworth et al., 2006(42)	Empirical Research Study: Expert Interviews (n=35)	- Changes in publication process: Peer review process
McGee et al., 2011(48)	Analysis if published trials have been registered	- Prospective trial registration
Newton, 2010(45)	Explanatory framework of factors influencing peer review	- Changes in publication process: Peer review process
Phillips, 2011(73)	Editorial	- Changes in publication process: Peer review process
Reveiz et al., 2006(81)	description of a specific trial registry	- Prospective trial registration
Reynolds, 2003(74)	Editorial	- Prospective trial registration - Open access policy (mandatory reporting of results)

Publication	Type of article	Intervention
Rising et al., 2008(49)	Analysis of registered trials and their publication/ discussion part	- Open access policy (mandatory reporting of results)
Rochon et al., 2011(50)	Email survey of clinical trial investigators (n=732)/ discussion part	- Changes in publication process: disclosure of conflict of interest
Savitz, 2011(67)	Commentary	- Prospective trial registration
Scherer & Trelle, 2008(44)	Web-based survey of academic researchers (n=282)	- Prospective trial registration - Open access policy (mandatory reporting of results)
Seigel, 2003(56)	Narrative literature review	- Peer Review - Disclosure of conflict of commercial interest
Somberg, 2003(75)	Editorial	- Prospective trial registration
Staessen, 2003(69)	Commentary	- Changes in publication process: Peer review process
Steinbrook, 2004(68)	Commentary	- Prospective trial registration - Open access policy (mandatory reporting of results)
Strech, 2011(16)	Narrative literature review	- Prospective trial registration
Tonks, 1999(76)	Editorial	- Prospective trial registration
Viergever & Ghersi, 2011(51)	Analysis of registered trials/discussion party	- Prospective trial registration

3.4.1 Key Results

In the following chapter we will refer to parties who are involved in the research process as stakeholders, including researchers, representatives of the pharmaceutical industry, journal editors and lawmakers as stakeholders.

3.4.1.1 Changes in Publication Process: Peer Review Process

As the main barriers for peer review, we identified the resource intensity of the process, competing interests of reviewers and editors, different cultural norms, and inconsistencies in the peer review process - in particular reviewers' and editors' lack of consistent qualifications.

As possible solutions to overcome these barriers, we identified required conflict of interest statements from peer reviewers, strategies to enforce transparency and objectivity, the use of full-time experienced peer reviewers and editors, training for reviewers and editors, and the option to base an article's acceptance for publication by a peer review of only the introduction and methods sections.

3.4.1.2 Changes in Publication Process: Disclosure of Commercial Interest

Many physicians who have financial contracts with pharmaceutical companies are convinced that they have no resulting conflict of interest. This personal perception of the situation might mean that they do not disclose this "conflict of interest". As conflict of interest statements are rarely verified for truthfulness, the **credibility of such statements** can be questioned.

The use of comprehensive checklists, aimed at identifying investigators' conflict of interest, should be used in the preparation stage of a trial in order to determine if there are any competing interests that could influence the trial. Support of external agencies (e.g., enforcement of conflict of interest disclosure) could facilitate the implementation of these statements.

3.4.1.3 Changes in Publication Process: Electronic Publishing

Public funding was identified as a possible facilitator for journals that publish negative/neutral results because public funding or charitable support could help divide the publication process from currently existing financial constraints.

3.4.1.4 Prospective Registration of Trials

As the main barriers for trial registration, we identified competing interests of stakeholder groups, different national legal systems, lack of a mechanism to enforce trial registration, and a lack of resources for researchers to complete trial registration.

Proposed solutions to overcome these barriers include mandatory trial registration, coordination between trial registries so that a unique registration number is assigned to a study regardless of the registry it is registered in, the creation of one single registry, the provision of financial support for trial registries through industry and governments, improvement of trial registries' usability, and raising stakeholders' awareness of the consequences of publication bias. Stakeholders involved in prospective registration of trials are primarily researchers and pharmaceutical companies.

3.4.1.5 Open Access Policy

Because open access policy refers to open journals as well as to open data we summarize the following three interventions under the subheading open access policy.

3.4.1.6 Open access journals

One identified barrier for open access journals is the demand for publication fees.

3.4.1.7 Mandatory reporting results

The main barrier of mandatory reporting of results (for example to ethic committees, trial registries or funding agencies) is the reluctance of researchers and pharmaceutical companies to report all of their results.

3.4.1.8 Mandatory open access to trial data

One of the main barriers of this intervention is also the reluctance of researchers and sponsors to release all trial data as well as the lack of quality control of the released data.

3.4.1.9 Confirmatory large scale trial

Lack of recognition can act as a barrier to implement confirmatory large-scale trials, because researchers get too little recognition if they take part in a large-scale trial, compared to their own small trial.

3.4.2 Changes in Publication Process: Peer Review Process

As described in this section, a properly conducted peer review may help to prevent publication bias.(83)

3.4.2.1 Barriers

We identified **inconsistencies in the process** of peer review as one barrier.(42, 66) For instance, codes of practice among medical journal editors are voluntary and not widespread.(73) Consistent criteria does not exist for the selection of peer reviewers, so editors may be subjective in their choice of peer reviewers.(47, 64) Bock mentions the lack of agreed-upon standards by which manuscripts are judged.(61) Lipworth and colleagues state that the review process itself is not consistent or reproducible because there is no clear definition of good and bad manuscripts.(42) Appraisals and decisions are often highly subjective and "intuitive" which leads to another barrier: **biased reviewers.** Reviewing is highly subjective and therefore sometimes the private interests of reviewers, such as professional affinities or rivalries, their sense of their own authority, moral responsibility, or unavoidable prejudices can affect the review process.(42, 66) Personal knowledge, understanding and ability, personality and beliefs can influence decisions of reviewers.(45) This can cause reviewers to fail to be objective, consistent, critical and/or clear about their reasoning processes.(42) Reviewers can also be biased against manuscripts that contradict their own thinking or mainstream opinion.(45, 73) Some reviewers value the significance of results higher than the validity of the methods. Reviewers also prefer interesting topics and favorable results.(47)

The interests of editors can also play an important role and may lead to the barrier of **biased editors**. Similar to peer reviewers, editors can be influenced by their personal beliefs and attitudes, society's norms, and ethical considerations.(45) This can lead to editors failing to be objective and clear about their decision making process.(42) Studies with failed treatments are less likely to be cited which can influence the impact factor of the journal it is published in. Since journals are interested in obtaining high impact factors and part of an editors' job is to pursue the goals of the journal, editors are less likely to publish studies that do not demonstrate positive findings and prefer to publish studies with statistically significant results.(43, 62)

A **lack of consistent qualifications** for editors and reviewers was identified as a barrier. A training manual for editors is missing and most editors do not have proper training (especially within smaller medical journals).(66) Likewise, the lack of training for peer reviewers is identified in the literature as a barrier.(43)

Another identified barrier was the **resource intensity** of the review process. The peer review process takes significant academic time. Many people are involved in the process which makes it a costly, often slow, inefficient, and ineffective endeavor.(66)

Peer review is also influenced by cultural **norms and behavior**. The cultural climate in a country influences editors' and reviewers' behaviors.(45) Experts within different disciplines may have different standards and criteria when reviewing an article, which influences the peer review process.(42) It is a norm within the scientific community that participating in peer review is part of being a scientist. While some see it as a moral and civic obligation, others perceive it as an unwanted burden.(42) This could influence the motivation of the reviewer and as a consequence the proper implementation of peer review.

3.4.2.2 Facilitators

To overcome the problem of inconsistencies in the peer review process, **enforcing transparency** was identified as a possible solution. Publishing the abstract along with an explanation for the rejection could enforce transparency in the peer review process.(73)

Enforcing objectivity is another possible solution to inconsistencies in the peer review process. Incorporating opinions from a wide range of experts could lead to more objective reviews and minimize single-reviewer bias.(73) An agreed upon quantitative measurement, familiar to all manuscript authors, would make the peer review process more objective and consistent.(61)

Possible solutions to overcome biased reviewers and editors were identified, such as a **statement of conflict of interest.** Lipworth et al. and Phillips recommend that peer reviewers should identify any potential conflict of interests, such as personal relationships,

academic rivalries or personal, political, or ideological persuasions in order to minimize the problem of biased reviewers.(42, 73)

The use of fulltime, experienced professional peer reviewers and editors could also facilitate the proper implementation of peer review. Liesegang recommends a full-time experienced professional editorial board, which would guarantee that the editors are competent and experienced.(66) Bock et al. suggest an independent panel of professional reviewers who have no personal benefits in accepting or rejecting a manuscript.(61)

Training for peer reviewers and editors was also identified as a possible facilitator. Phillips suggests more guidance and training for **editors** as well as raising awareness of reviewer bias throughout the scientific community.(73) Lipworth et al. and Liesegang recommend training in scientific appraisal for **reviewers.**(42, 66) Peer reviewers should be able to measure manuscripts on clinical research against guidelines such as CONSORT and if the analyses are wrong they should be trained to realize it.(56) Training reviewers and editors should raise their awareness that manuscripts presenting neutral or negative results have value and that the quality of the study should be the focus, not just positive outcomes.(43, 47)

Another proposal found in the literature was to **peer review only the introduction and methods sections** of a submitted paper. In this case, reviewers' decisions wouldn't be influenced by the outcomes. Reviewers could be blinded to results in a first phase of the review process.(78) An innovative idea, already utilized by the journal "the Lancet", is to review the protocol of a study in order to avoid being influenced by "positive" or "negative" results. If a protocol is peer reviewed and determined to be good, the journal commits to at least send the manuscript of the study out for peer-review. This way an editorial commitment is made before the results are known.(69)

3.4.3 Changes in Publication Process: Disclosure of Conflict of Interest

Conflict of interest disclosure is where an individual or organization fills out a document disclosing any details about any potential conflicts of interest concerning employment, financial concerns, and public appearances to ensure that there is no potential bias that could affect an individual or organization's work.

3.4.3.1 Barriers

Many physicians who have financial contracts with pharmaceutical companies are convinced that they have no resulting conflict of interest or that their financial relationship to a company may result in a change in their behavior.(66) This **personal perception** of the situation might mean that they do not disclose this "conflict of interest". Many researchers also insist that as scientists, they can remain objective at all times.(56) The disclosure of

commercial conflict of interest is largely reliant upon the honesty and good faith of researchers and industry - conflicts of interest are rarely verified for truthfulness - and therefore the **credibility of such statements** can be questioned.(60) Current emphasis on disclosure policies may even provide a false sense of security that the problems that might result from conflict of interests have been solved.(63)

3.4.3.2 Facilitators

One way to improve the implementation of disclosure of conflict of interest is the development and use of **checklists**. Comprehensive checklists aimed at identifying investigators' conflicts of interest should be used in the preparation stage of a trial in order to determine if there are any competing interests that could influence the design of a trial.(50) **Support by external agencies**, such as the enforcement of disclosing conflicts of interest by external agents, could facilitate appropriate disclosure of conflicts of interest.(50) The World Association of Medical Editors (WAME), the International Committee of Medical Journal Editors (ICMJE) and the Committee on Publication Ethics (COPE) have already developed guidelines that recommend financial disclosure policies for authors, staff, peer reviewers, and editors.(66)

3.4.4 Changes in Publication Process: Electronic Publication

As described in the previous section, journals have been created with the sole purpose of encouraging researchers to publish their null or negative findings in an effort to enlarge the body of scientific knowledge. To facilitate the maintenance of such journals, **public funding** or charitable support could separate the publication process from financial constraints.(71)

3.4.5 Prospective Trial Registration

Prospective registration of all clinical trials in a searchable and comprehensive registry can help to reduce publication bias by ensuring that information about all existing trials is accessible to the public, independent of the results.(59)

3.4.5.1 Barriers

Competing interests of different stakeholder groups was identified as a potential barrier to the implementation of trial registration. Pharmaceutical companies pursue commercial interests that can keep them from registering their trial in advance because publishing confidential information concerning entrepreneurial developments can result in a competitive disadvantage and remove the sought-after exclusivity.(16, 55, 58, 75) Trial registries require disclosure of sensitive information, and proprietary knowledge in an asset for pharmaceutical companies. They perceive trial data as their own private property

that has to be protected.(16) Publishing this information could be detrimental for their future financial success.(44, 76, 82) Trial registration and publishing information at an early stage is seen as potentially damaging if not all companies register their trials.(82) McGee and colleagues mention that some economists argue that prospective trial registration could result in fewer trials being conducted because each trial becomes public knowledge and therefore the investment necessary to conduct a trial will be more vulnerable to market forces as companies will have to assess possible opportunity costs (cost of an investment in terms of the value of the second best alternative) of such an investment.(48) Although McGee et al. disagree with this fear, they mention it as a possible reason for the reluctance of representatives of a pharmaceutical industry to register their trials. Academic researchers also have competing interests, such as the right for exclusivity of their research idea, and therefore lack the willingness to completely register their trials.(16, 44, 75) Scherer (2008) conducted a web-based survey of academic researchers (n=282) and found out that there is a reluctance of researchers to disclose study details, especially details about planned subgroup analysis and sample size calculation.

Other barriers to prospective trial registration are factors such as different legal systems and multiple trial registries. **Many trial registries** exist worldwide that differ in their coverage, are run by different organizations, and are at different stages of development, especially those in developing countries.(74, 76, 81) Some registries (e.g., the meta-registry http://www.controlled-trials.com) charge a fee for registration, which limits the number of trial registrations among researchers and sponsors.(53) Registries often have different purposes (administrative, enrollment, scientific database, etc.), which makes a single, unique registry difficult to achieve.(55) Nevertheless, Abaid et al. argue that a centralized registry is needed.(58) Tonks and Abaid et al. also argue that the use of many different registries make it difficult to capture all trials from a variety of sources and make it difficult to find trials.(59, 76)

Different legal systems between countries hinder a worldwide uniform trial registry.(76) In some countries registration of trials is required by law and in others it is not. In some countries trial registries are open to the public while in others they are confidential and only accessible to agencies.(53, 74) The European Clinical Trials Directive (Directive 2001/20/EC) required that all clinical trials conducted in member states of the European Union have to be registered in the EudraCT database. EudraCT is only accessible to regulatory agencies and research funding institutions, not to researchers. The general public has limited access to information on registered trials via the EU Clinical Trials Register.(53)

Lack of mechanisms to enforce trial registration is another barrier we identified. Although trial registration is required by law in countries such as the U.S., neither funding nor mechanisms of enforcement have been implemented.(53, 55, 68, 74) A formal system for

monitoring or imposing penalties for failure to register is missing.(59) As entering data in a trial registry takes time, a lack of incentive for researchers to spend time registering their trials could be a barrier too.(76)

A **lack of provided resources** is another barrier to proper prospective trial registration. Sustaining good quality of a trial registry needs quality control and management of data, which is very expensive. It is not clear who will bear the costs in the future.(53, 55)

Another identified barrier is the **lack of awareness** of the problem and consequences of publication bias. According to Dickersin & Rennie this lack of awareness is prominent within different stakeholder groups (e.g., researchers, pharmaceutical industry, editors etc.).(55)

Even if trials are registered other problems can occur that weaken the purpose of trial registration. **Imperfect data quality** was found to be a problem in adequate implementation of prospective trial registration. A common criticism is that incomplete or vague data is entered in trial registries.(51, 52, 70) Abaid et al. argue that pharmaceutical companies enter intentionally vague terms to protect their information which leads to unclear entries.(59)

The **type of study** conducted could influence the willingness to register the trial prospectively. Trial registration is not optimal for every study type. Prior specification of the hypothesis of observational studies can be seen as burdensome and hinders the process of scientific discovery.(67)

3.4.5.2 Facilitators

Within the literature many suggestions and ideas to overcome barriers in the implementation of prospective trial registration are mentioned.

One suggested way to facilitate the implementation of prospective trial registration was to make **trial registration a prerequisite** for crucial decisions within research. Many authors suggest that ethic committees should mandate registration as a condition for trial approval. Ethic committees are in a good position to evaluate the proper registration because they always see the study protocol and have the necessary financial and human resources.(16, 46, 65, 68, 74) Registration as a prerequisite for consideration of publication by the journal editors has already been implemented, but this policy should be adopted and enforced by more journal editors.(16, 48, 51, 53, 58, 70) Dickersin recommends requiring registration as a condition of funding trials.(55)

Phase 1 trials explore the safety of experimental drugs. At the moment these trials don't have to be registered in the U.S. Since this information could be important for other researchers, it should be mandatory to register all clinical trials no matter what phase they are in.(46, 68)

The implementation of **mechanisms to enforce adequate trial registration** could help overcome the problem of missing trial registrations and poor data quality. Penalties should be enforced for those who register their trials, but intentionally use vague terms and enter meaningless information so as to avoid publishing too much information, as well as for those who fail to register their trials altogether.(16, 55, 75) Journals should also enforce their trial registration policies; although registration is becoming a more common requirement for publication, in reality the policy is often not enforced and manuscripts of non-registered trials are published.(48) To improve the quality of reported data, an agreement on international norms and standards for clinical trial registration and reporting is required.(70, 81) Strech suggests that a new regulation system should initially be instituted for a fixed period of time. This also includes making principle investigators aware of an obligation to register trials and consequences of non-compliance so that there are trial registries of sufficient quality. Noncompliance in trial registration could result in funding being withheld, monetary penalties, or public notices of noncompliance.(54) To facilitate investigators' accountability and transparency, clearly assigned responsibility to a named principal investigator in all registered records of clinical trials is necessary.(51)

The simplification of the registration process could be realized through better usability of trial registries and one comprehensive trial registry. **Better usability** could improve the willingness of researchers to register their trials. Therefore a trial registry should be easy to understand and practical to use.(53, 55) This includes improvement of the explanatory text for the trial registration data set, so that requirements for registration are clearer to researchers.(51) Having **one comprehensive trial registry** for all trials would simplify trial registration. A possible solution could be merging several registries to achieve a comprehensive registry, or creating a single comprehensive trial registry.(55, 74) Antonelli & Mercurio recommend worldwide legislation that mandates international linked registries that are able to exchange information among countries and avoid unnecessary duplication of efforts.(53)

To utilize the information of trial registries easily a **unique registration number** could help. Many commentators insist that trials be allocated one unique identifier to differentiate between multiple studies and multi-center trials and to easily find trials and avoid duplication.(53, 55, 59, 68) Journal editors should require unique registration numbers for every report of a trial and publish the number together with the article.(52, 55)

Provision of resources to maintain trial registries are called for in the literature. Appropriate efforts (financial and personal) for registration are needed.(16) Governments in all countries should fund and enforce trial registration.(53, 68) According to Antonelli & Mercurio pharmaceutical companies and governments should share the costs of trial registration.(53) In order to guarantee independence from the pharmaceutical industry, an independent fund for trial registries with blind financial support from different sources could help to eliminate the bias of investments of pharmaceutical companies, which could

compromise the independence of trial registries. Appropriate software to manage such a huge amount of information is a necessary resource.(53, 76) Questions arise such as who is responsible for providing resources: the pharmaceutical industry or government?

As there are many different stakeholder groups involved in research, **support of stakeholders** is needed to facilitate prospective trial registration. Individuals in the highest positions at institutions and organizations that conduct research must require registration of trials. Industry leaders must agree to and insist upon comprehensive registration.(55) Journals should support the reporting of study results in trial registries and should not treat "registry publication" in the same sense as "manuscript publication"; authors should not have to worry that journals won't accept their manuscripts because the results were previously published in a registry (and journals only accept manuscripts if the results have not been published elsewhere).(72) It is lawmakers' duty to protect the public by requiring comprehensive trial registration through ethics committees.(55) Although freedom of research is a core element of national legislation, Strech argues that unconditional basic rights should be restricted when they negatively impact other constitutional values such as an individual's physical health and wellbeing, which can be endangered by publication bias (e.g., when negative results are not published, leading to the wrong conclusion about a therapy or medication, which ends up doing more harm than good).(16) Therefore it is an ethical responsibility to share all results.(58)

Raising awareness and educating stakeholders about the problem of publication bias is crucial to facilitate trial registration. More awareness of the problem and its significance could increase the willingness to register trials and publish all types of results in a timely manner.(16)

3.4.6 Open Access Policy

"Open-access" describes two interventions: free access for all persons to publications of clinical trials (open access journals - a system where users of the scientific literature have unlimited access to publications without paying subscription fees to the publishers of journals); and open access for all persons to all data resulting from clinical trials. This can be achieved by mandatory reporting of results and mandatory open access to trial data.

3.4.6.1 Open access journals

An open access publication is one that is freely available for redistribution and reuse. Publishers sometimes create online-only journals designed to disseminate barrier-free research results rapidly; these publications are peer reviewed, fully open access and are designed to publish new scientific or academic findings. (84) (84)

Only one barrier in the included literature was identified for the implementation of open access publications. Open access journals often **rely on publication fees**, where authors

have to pay to publish their articles. This keeps authors from publishing negative results, since these manuscripts probably would not be highly rewarded through citation and therefore paying for publishing such manuscripts doesn't seem very attractive.(71)

3.4.6.2 Mandatory reporting of results

The call for mandatory reporting of results was prominent in the literature. Abaid and colleagues even argue that it is an ethical responsibility to share all results.(58) However, authors had different ideas about how this could be attained. Some stated that it should be part of **trial registries** to demand reporting of results (at least all primary outcomes) as soon as they are available.(49, 52, 53, 68) Dubben et al. suggest that researchers, when registering a trial, should be bound to publish an article as soon as possible.(57)

Ethic committees are considered by some authors to be in the ideal position to enforce the dissemination of trial results. They could require comprehensive reports of findings no later than three years after completion. They could then send reports to a central, comprehensive, and multidisciplinary registry.(65, 79) This central registry could publish abstracts in a quarterly journal and supply copies of the complete documents for a fee.(65) Chalmers suggests that ethic committees should keep a registry of all proposals, that a final report should be requested within three months of study completion, and that both should be made publicly available.(80) If ethic committees take on this role, it will be important that they receive appropriate resources that will permit them to do their work and ensure proper dissemination of results.(74) We also found the suggestion that **funding organizations** should ensure that the results of funded trials are publicly disseminated.(74) Funding organizations should encourage investigators to publish all results, independent of the type of results, and reward investigators for their efforts.(71) Bonita et al. mention that any trial that is supported by NIH funds is already required to produce publicly available summaries of their results, which are widely accessible through an online database.(54) One barrier to the implementation of this intervention is the **reluctance of researchers** to publish their results before submission to a peer-reviewed journal, even if the journal would accept this pre-publication of results.(44) As another barrier we identified the **reluctance of companies** to publish negative results because this may lead to large economic disadvantages.(53)

3.4.6.3 Mandatory open access to trial data

Access to all raw trial data, not just through publication in journals, is a potential facilitator. Gøtzsche suggests that raw data from all trials should be published on a public website.(77) It would offer the possibility to detect errors and flaws in publications. This kind of data sharing could also help to save costs, since research projects could be performed using data that was collected for another purpose. However, this would require a change in culture, which at the moment is characterized by proprietary thinking and ownership of data.(77) A barrier to the mandatory release of trial data is the **reluctance of**

researchers and sponsors to publish sensitive data like study protocols and financial agreements.(44) Another barrier identified in the use of data repositories was the **missing quality check**. If editors and peer review are missing, the risk of bias and misconduct exists. Some readers could confuse summaries of this publicly available data with peer reviewed articles in scientific journals.(64)

3.4.7 Confirmatory large scale trials

To avoid biases and random errors, a large number of patients are necessary for RCTs. It is therefore a widespread assumption that confirmatory large-scale trials are less vulnerable to publication bias because due to the larger number of participants, confirmatory, large-scale trials may avoid some bias, thus providing more convincing evidence than small trials.(83)

3.4.7.1 Barrier

For this intervention only one barrier and no suggested facilitators could be identified in the included literature. Lack of recognition can act as a barrier to implement confirmatory large-scale trials, because researchers get too little recognition if they take part in a large-scale trial, compared to their own small trial. This may keep them from participating in large-scale trials.(43)

3.4.8 Personal, Social, Organizational and Structural Factors

Since barriers and facilitators are factors influencing interventions to counter publication bias, we categorized them into four types of influencing factors that will be presented in Table 15 and organized by intervention and then by type of factor. Within this report a personal factor derives from an individual or a group of people, like e.g., competing interests of different stakeholder groups. A social factor is created by society, its norms and culture, like e.g., behavior in a culture. Organizational factors relate to all influences emerging from organizational processes, e.g., the usability of a registry. Structural factors describe local conditions and realities, like differing legal systems.

Table 15: Influencing Factors

Type of factor	Description	Barrier/Facilitator
Prospective trial registration		
Personal factor	Competing interests of different stakeholder groups	Barrier
Personal factor	Imperfect data quality	Barrier

Type of factor	Description	Barrier/Facilitator
Social factor	Lack of awareness/raising awareness	Barrier/facilitator
Social factor	Support of stakeholders	Facilitator
Organizational factor	Many inconsistent registries/one comprehensive registry	Barrier/facilitator
Organizational factor	Better usability of trial registries	Facilitator
Organizational factor	Unique registration number	Facilitator
Structural factor	Lack of mechanisms to enforce trial registration/mechanisms to enforce adequate trial registration	Barrier
Structural factor	Lack of provided resources/ Provision of resources to maintain trial registries	Barrier
Structural factor	Type of study	Barrier
Structural factor	Different legal systems	Barrier
Structural factor	Trial registration as a prerequisite (ethic committee approval, journal publication, funding)	Facilitator
Peer review		
Personal factor	Interests of reviewers	Barrier
Personal factor	Interests of editors	Barrier
Personal factor	Statement of conflict of interest	Facilitator
Social factor	Norms and behavior in a culture	Barrier
Organizational factor	Enforcing transparency	Facilitator
Organizational factor	Enforcing objectivity	Facilitator
Organizational factor	Resource intensity	Barrier
Organizational factor	The engagement of fulltime experienced professionals	Facilitator
Organizational factor	Peer review only the introduction and methods part	Facilitator
Organizational factor	Training for reviewers and editors	Facilitator
Structural factor	Lack of a consistent qualification	Barrier
Structural factor	Inconsistency of the process	Barrier
Open Access Journals		

Type of factor	Description	Barrier/Facilitator
Organizational factor	Rely on publication fees	Barrier
Disclosure of conflict of commercial interest		
Personal factor	Personal perception	Barrier
Personal factor	Credibility of such statements	Barrier
Organizational factor	Checklists	Facilitator
Organizational factor	Support by external agencies	Facilitator
Journal of negative/neutral results		
Structural factor	Public funding	Facilitator
Mandatory reporting results (by ethic committees, trial registries, funding agencies)		
Personal factor	Reluctance of researchers	Barrier
Personal factor	Reluctance of companies	Barrier
Mandatory release of trial data		
Personal factor	The reluctance of researchers and sponsors	Barrier
Organizational factor	Missing quality check	Barrier
Confirmatory large scale trials		
Personal factor	Lack of recognition	barrier

4 Discussion

4.1 Key Findings and Strength of the Evidence

The research and scientific community has been aware of and calling for solutions to address the problem of publication bias for many decades.(85, 86) Despite several major steps forward and the implementation of policies to increase the availability of all clinical trial results, we located little evidence that showed that current measures are actually succeeding in reducing this problem. Indeed the only conclusion that we can support with a moderate rating for the quality of the body of evidence is that clinical trial registries *do not* provide comprehensive and accurate information about the methods and pre-specified outcomes of the registered clinical trials that would allow the detection and deterrence of selective outcome reporting, even if their use has increased markedly since 2005.

Competing interests of sponsors and researchers are seen as a major barrier to prospective trial registration. Although within the last years laws and regulations were developed to require trial registration, a lack of mechanisms to enforce adequate trial registration was mentioned in the literature. Facilitators to overcome these barriers could be the implementation of enforcement mechanisms, like sanctions or penalties for not complying as well as clear rules of what data has to be entered. Winning the support from stakeholders is essential within this process. Another difficulty seems to be the existence of many different inconsistent registries all over the world within different legal systems. The desire for one open access comprehensive trial registry and worldwide legislation that mandates international linked registries that are able to exchange information among countries is often expressed in the literature. The use of a unique registration number could help to identify all studies. The fact that registering trials is time consuming for researchers and there is a lack of awareness of the importance of publication bias within the scientific community can also be seen as barriers. In order to overcome this barrier trial registration should be made as easy and practical to use as possible. Raising awareness of the impact of publication bias through education may also be helpful. In order to implement an enforcement mechanism, create one comprehensive trial registry, and make it easy and practical to use. Financial and personnel resources are essential and have to be provided by state bodies or through a central fund supported by all stakeholders, including industry.

Likewise, although the quality of the evidence is very low, it seems as if electronic publishing has not been able to increase the number of negative results or the amount of

information provided regarding the results of all outcomes of RCTs (again, an attempt to minimize positive outcome reporting bias) and that open access to scientific journals serves to discriminate against authors from developing countries without providing any benefit to reduce publication bias (very low strength of evidence).

The main barriers we identified concerning the peer review process were biased reviewers and editors as well as the inconsistency of the peer reviewing process. Facilitators named that could overcome these barriers included training for reviewers and editors, employment of experienced full-time professionals and enforcement of transparency and objectivity. Basing the decision about a manuscript solely on the introduction and methods could work as a facilitator to overcome the problem of overrating "positive findings" but we did not locate any empirical evidence on this approach. The peer review process seems to be influenced by social factors like norms and behavior in a culture and disciplinary cultures or personal factors like interests of the reviewer.

The evidence we found on the effectiveness of changes to the process of peer reviewing was limited. While blinding peer reviewers may decrease geographical bias against non-US authors (low strength of evidence) it is not clear that blinding reviewers reduces gender bias. We found no evidence that changing the peer reviewing process can reduce reporting or positive outcome bias (e.g., procedures for cross-checking all submitted manuscripts against protocols or registry entries) or on the role of ethics commissions in ensuring protocols and publications are consistent. Even if one saw potential here for interventions against publication bias to be implemented, the poor quality of the information in trial registries and the tendency for this information to be altered over time currently prohibits accurate cross-checking by third parties such as reviewers or ethic commissions.

4.2 Limitations

This report has some limitations. We searched several databases and conducted extensive searches; however we cannot be sure if we have detected every study of an intervention to reduce publication bias. For the identification of barriers and facilitators, we preferentially included findings from focus groups and interviews, but due to a lack of data, we also included editorials and discussions from authors of interventions studies. We reported on opinions and editorials where they presented new thoughts or ideas about barriers and facilitators. Many other publications not cited in this report have also discussed the topic of publication bias and attempts to reduce it and it was impossible to include all articles with any reference to publication bias here. We believe we have provided a thorough overview of the discussion of publication bias in the scientific literature; however, we acknowledge that other stakeholders, such as industry or funders, may not be as well represented as authors and researchers.

4.3 Recommendations and Future Research

This report has several implications. Firstly, many interventions that should supposedly reduce publication bias and that have been advocated by researchers and organizations over many years are not supported by any study data. We require more and larger controlled studies of systems or interventions, for example new processes for ethics commissions, journals, or peer reviewers, or on the potential for open access or electronic publication to reduce publication bias.

Secondly, the one intervention that has been successful in its uptake (trial registries) is weakened by lack of mandatory fields and lack of regulation to ensure that all data provided is complete and accurate and not altered during the course of a trial or after trial completion but before publication. In addition to mandating their use, some policing of the quality of information entered into trial registries is required. We recommend that fully complete data in the mandatory fields of a trial registry should also be a prerequisite for ethic commission approval, for being considered for publication, and of funding for future clinical trials.

Cultural and legal differences between countries make the establishment of one worldwide comprehensive trial registry a difficult goal to realize. However, it is necessary that there is one registry to find all conducted trials. Therefore a meta-registry, like the WHO ICTRP, where each trial has a unique identifier number, is necessary as well as consistent worldwide legislation concerning prospective trial registration. The question concerning funding a central registry remains open; should governments provide funding for trial registries alone or can this be done through a central agency where the pharmaceutical industry are also expected to contribute?

Lastly, we did not locate any evidence regarding the mandatory disclosure of all trial data. This would be the ultimate panacea for the problem of publication bias, allowing independent persons to evaluate, interpret, and summarize the results of clinical trials.

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Appendices

Appendix A: Literature Searches:

PubMed:

Search	Query	Items found
#1	Search "Publication Bias"[Mesh]	1747
#2	Search "Bias (Epidemiology)"[Mesh]	44583
#3	Search "Selection Bias"[Mesh]	3159
#4	Search "Prejudice"[Mesh]	20912
#5	Search "bias"[tiab]	64678
#6	Search #1 OR #2 OR #3 OR #4 OR #5	122639
#7	Search "Research/ standards"[Mesh]	19170
#8	Search "Publishing/standards"[Mesh]	5410
#9	Search "Quality Control"[Mesh]	36731
#10	Search "Writing/standards"[Mesh]	1168
#11	Search "Journalism, Medical/ standards"[Mesh]	584
#12	Search #7 OR #8 OR #9 OR #10 OR #11	59526
#13	Search #6 AND #12	3044
#14	Search "Registries"[Mesh]	46060
#15	Search "Evidence-Based Medicine"[Mesh]	45157
#16	Search "Clinical Trials as Topic"[Mesh]	250161
#17	Search "Review Literature as Topic"[Mesh]	6050
#18	Search "Practice Guidelines as Topic"[Mesh]	65868
#19	Search "Meta-Analysis as Topic"[Mesh]	11809
#20	Search "Periodicals as Topic"[Mesh]	31483
#21	Search #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	424261
#22	Search #13 AND #21	1018

EMBASE:

No.	Query	Results
#1	'bias':ti OR 'bias':ab	**73,191**
#2	'publication'/exp	**108,591**
#3	'types of study'/exp	**19,509,350**
#4	'medical literature'/exp	**113,548**
#5	'outcome assessment'/exp	**159,312**
#6	#3 OR #4 OR #5	**19,550,408**
#7	#1 AND #2 AND #6	**975**

The Cochrane Library:

ID	Search	Hits
#1	"Publication Bias"[Mesh]	10284
#2	"Bias (Epidemiology)"[Mesh]	542
#3	"Selection Bias"[Mesh]	4103
#4	"Prejudice"[Mesh]	287
#5	"bias"[tiab]	26095
#6	(#1 OR #2 OR #3 OR #4 OR #5)	26299
#7	"Research/ standards"[Mesh]	64
#8	"Publishing/standards"[Mesh]	11
#9	"Quality Control"[Mesh]	1090
#10	"Writing/standards"[Mesh]	6
#11	"Journalism, Medical/ standards"[Mesh]	1
#12	(#7 OR #8 OR #9 OR #10 OR #11)	1160
#13	(#6 AND #12)	254
#14	"Registries"[Mesh]	1463
#15	"Evidence-Based Medicine"[Mesh]	3024
#16	"Clinical Trials as Topic"[Mesh]	35167
#17	"Review Literature as Topic"[Mesh]	91
#18	"Practice Guidelines as Topic"[Mesh]	1403
#19	"Meta-Analysis as Topic"[Mesh]	548
#20	"Periodicals as Topic"[Mesh]	71

ID	Search	Hits
#21	(#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)	41128
#22	(#13 AND #21)	57

CINAHL, AMED, PsycINFO:

#	Query	Results
S11	S5 or S10	604
S10	S8 and S9	85
S9	S2 or S7	101193
S8	S1 and S6	1102
S7	(MH "Publishing+")	100879
S6	(MH "Bias (Research)+")	6823
S5	S3 or S4	550
S4	S1 and S2	56
S3	(MH "Publication Bias")	515
S2	(DE "PUBLICATIONS") OR (DE "PUBLISHING")	5208
S1	TI bias OR AB bias	43752

Appendix B: Definitions of Bias:

Term	Definition
Bias	Bias refers to types of systematic errors in the collection, analysis, or interpretation of research data that distort the outcomes; bias at times may be either unrecognized or intentional, but both negate the validity of the study.(87) In statistics, the bias of an estimator is the difference between this estimator's expected value and the true value of the parameter being estimated.
Citation bias	Occurs when the chance of a study being cited by others is associated with its result. For example, authors of published articles may tend to cite studies that support their position. Thus, retrieving literature by scanning reference lists may produce a biased sample of articles and reference bias may also render the conclusions of an article less reliable.(2)
Database bias (indexing bias)	Occurs when there is biased indexing of published studies in literature databases. A literature database, such as MEDLINE or EMBASE, may not include and index all published studies on a topic. The literature search will be biased when it is based on a database in which the results of indexed studies are systematically different from those of non-indexed studies.(2)
Dissemination bias	Occurs when the dissemination profile of a study's results depends on the direction or strength of its findings. The dissemination profile is defined as the accessibility of research results or the possibility of research findings being identified by potential users. The spectrum of the dissemination profile ranges from completely inaccessible to easily accessible, according to whether, when, where and how research is published.(2)
Full publication bias	Occurs when the full publication of studies that have been initially presented at conferences or in other informal formats is dependent on the direction and/or strength of their findings.(2)
Grey literature bias	Occurs when the results reported in journal articles are systematically different from those presented in reports, working papers, dissertations or conference abstracts.(2)

Term	Definition
Language bias	Occurs when languages of publication depend on the direction and strength of the study results.(2) Rationale: Authors having completed a clinical trial yielding negative results might be less confident about having it published in a large diffusion international journal written in English and would then submit it to a local journal. If these investigators work in a non-English speaking country the paper will be published in their own language in a local journal. Positive results by authors from non-English speaking countries are thus more likely to be published in English, and negative results in the investigators language.(84)
Media attention bias	Occurs when studies with striking results are more likely to be covered by the media (newspapers, radio and television news).(2)
Multiple publication bias (duplicate publication bias)	Occurs when studies with significant or supportive results are more likely to generate multiple publications than studies with non-significant or unsupportive results. Duplicate publication can be classified as 'overt' or 'covert'. Multiple publication bias is particularly difficult to detect if it is covert, when the same data are published in different places or at different times without providing sufficient information about previous or simultaneous publication.(2)
Non-publication	See "publication bias" the term we use for non-publication of the results of clinical trials.
Outcome reporting bias	Occurs when a study in which multiple outcomes were measured reports only those that were significant.(2) Selective [outcome] reporting bias in a study is defined as the selection, on the basis of the results, of a subset of analyses to be reported. Selective reporting may occur in relation to outcome analyses, subgroup analyses, and per protocol analyses, rather than in intention to treat analyses, as well as with other analyses. Three types of selective reporting of outcomes exist: the selective reporting of some of the set of study outcomes, when not all analyzed outcomes are reported; the selective reporting of a specific outcome—for example, when an outcome is measured and analyzed at several time points but not all results are reported; and incomplete reporting of a specific outcome—for example, when the difference in means between treatments is reported for an outcome but no standard error is given. A specific form of bias arising from the selective reporting of the set of study outcomes is outcome reporting bias, which is defined as the selection for publication of a subset of the original recorded outcome variables on the basis of the results.(88)

Term	Definition
Place of publication bias	Place of publication bias is defined as occurring when the place of publication is associated with the direction or strength of the study findings. For example, studies with positive results may be more likely to be published in widely circulated journals than studies with negative results. The term was originally used to describe the tendency for a journal to be more enthusiastic towards publishing articles about a given hypothesis than other journals, for reasons of editorial policy or readers' preference.(2) Furthermore, clinical trial results may be publically available (for example as PDFs via company or public web pages); however they may not be indexed in any databases and therefore practically difficult to locate.
Positive-outcome bias	Preference (of journals) for (publishing) trials showing significant results.(89)
Publication bias	Occurs when the publication of research results depends on the nature and direction of the results. Because of publication bias, the results of published studies may be systematically different from those of unpublished studies.(2) The non-publication of clinical trials might mean that the results are entirely unavailable/inaccessible, that the results are submitted to a regulatory agency but are unavailable to other researchers, systematic reviewers, or other stakeholders, or that some of the results remain unavailable (see selective outcome reporting bias).
Time lag bias	Occurs when the speed of publication depends on the direction and strength of the trial results. For example, studies with significant results may be published earlier than those with non-significant results.(2)