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Systematic Reviews Published in Emergency Medicine Journals Do Not Routinely Search Clinical Trials Registries: A Cross-sectional Analysis

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Abstract

Study objective—Publication bias compromises the validity of systematic reviews. This problem can be addressed in part through searching clinical trials registries to identify unpublished studies. This study aims to determine how often systematic reviews published in emergency medicine journals include clinical trials registry searches.

Methods—We identified all systematic reviews published in the 6 highest-impact emergency medicine journals between January 1 and December 31, 2013. Systematic reviews that assessed the effects of an intervention were further examined to determine whether the authors described searching a clinical trials registry and whether this search identified relevant unpublished studies.

Results—Of 191 articles identified through PubMed search, 80 were confirmed to be systematic reviews. Our sample consisted of 41 systematic reviews that assessed a specific intervention. Eight of these 41 (20%) searched a clinical trials registry. For 4 of these 8 reviews, the registry search identified at least 1 relevant unpublished study.

Conclusion—Systematic reviews published in emergency medicine journals do not routinely include searches of clinical trials registries. By helping authors identify unpublished trial data, the addition of registry searches may improve the validity of systematic reviews.

INTRODUCTION

Systematic reviews and meta-analyses have the potential to provide clinicians with a methodologically rigorous synthesis of all the available evidence on a particular topic. These methods are of particular importance to emergency physicians, who routinely encounter a breadth of clinical questions with limited time to find answers. These factors make it

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difficult to either memorize best practices or review all published studies during the course of clinical care. Because of the ongoing rapid expansion in emergency care research and because there are neither clinical guidelines nor a well-defined standard of care for many of the conditions that emergency physicians must manage, systematic reviews and meta-analyses often serve as the most appropriate source of information to guide decision making.

Although systematic reviews are often informative, they are susceptible to bias. In particular, publication bias occurs because of the nonpublication of negative, nonsignificant, or otherwise unfavorable results and is a major threat to the validity of systematic reviews. Several methods of assessing for publication bias are commonly used: contacting leading investigators in the field; reviewing conference proceedings, published abstracts, and bibliographies of included articles; constructing funnel plots; and analyzing with statistical techniques such as Egger's test. Each of these methods, however, suffers from substantial limitations. For example, nonresponse limits the utility of contacting investigators, conference proceedings cannot identify data that have not yet been presented in poster or abstract format, and the risk of false-positive results and a lack of power for detecting bias in reviews with few included studies limits funnel plot utility.[1–3] Clinical trials registries, on the other hand, were developed in part to address the problem of publication bias and may provide a more consistent method of identifying unpublished trials. However, the extent to which registry searches are used by emergency medicine researchers is unknown. Our objective was to determine how frequently systematic reviews published in emergency medicine journals assess for publication bias through the use of clinical trials registry searches.

MATERIALS AND METHODS

Study Design

We identified systematic reviews published between January 1, 2013, and December 31, 2013, in the 6 highest-impact-factor emergency medicine journals: *Annals of Emergency Medicine*, *Academic Emergency Medicine*, *American Journal of Emergency Medicine*, *Injury*, *Journal of Trauma and Acute Care Surgery*, and *Resuscitation*. Systematic reviews were identified by searching MEDLINE through PubMed, using the following search terms: (Meta-analysis[Publication Type] OR meta-analysis[Title/ Abstract] OR meta-analysis[MeSH Terms] OR review [Publication Type] OR search*[Title/Abstract]). This search strategy has been shown to be sensitive for the identification of systematic reviews published in general medical journals.[4] We used the advanced search feature of PubMed to restrict the search to articles with print or online publication dates between January 1, 2013, and December 31, 2013, in the 6 aforementioned journals. One author (C.W.J.) subsequently reviewed the tables of contents from all issues published in 2013 for these 6 journals to identify systematic reviews missed by the PubMed search.

Two study authors (L.G.K. and C.W.J.) independently reviewed the full text of each article retrieved by the search strategy to determine whether it described results from a systematic review. We classified articles as systematic reviews according to previously developed criteria: the article included a clear statement identifying the topic of the review, authors provided a detailed description of the methods and data-sources used to identify evidence

included in the review, the article included explicit inclusion and exclusion criteria, and the results included at least 1 study that met these inclusion criteria.[4] We limited this analysis to systematic reviews that assessed interventions in humans to focus on reviews for which clinical trials registry searches should be most useful.

Outcome Measures

The main outcome of interest was whether each review included a search of at least 1 clinical trials registry. This outcome was independently assessed by 2 authors (L.G.K. and C.W.J.) for each included study. Acceptable registries included clinicaltrials.gov and other clinical trials registries meeting the World Health Organization Registry Criteria, version 2.1.[5] When registry searches had been performed, we reviewed the text to determine whether the searches identified any relevant ongoing or completed but unpublished trials. If the results of the registry search were unavailable or ambiguous, we attempted to contact the corresponding author by e-mail for clarification of search results. We also determined whether review authors provided detailed search terms to allow replication of the clinical trials registry search. Other data points included funding source(s), stated compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement,[6] and the number of studies included in each review. Discrepancies between authors about review classifications or the inclusion of clinical trials registry searches were resolved by consensus.

Primary Data Analysis

Interrater agreement for the primary outcome was calculated with Cohen's κ. Statistical analyses were performed with PASW (version 18.0; IBM, Armonk, NY).

RESULTS

Our PubMed search retrieved 191 results, of which 111 were deemed not systematic reviews. Of the 80 remaining systematic reviews, 40 were determined to be interventional. The table of contents search identified 1 additional interventional review, yielding a final sample of 41 reviews (Appendix E1, available online at http://www.annemergmed.com). The majority of included reviews were published in *Annals of Emergency Medicine*, *Resuscitation*, and *Injury* (Table). A clinical trials registry search was performed for 8 (20%) of the interventional reviews. Four of these 8 (50%) identified 1 or more relevant unpublished trials as a result of the registry search. Of these 4, 2 reviews identified completed, unpublished studies through the trials registry search, and 3 reviews identified relevant ongoing studies. For 2 reviews, the specific terms used to perform the clinical trials registry search were provided. Of the 16 reviews that reported compliance with PRISMA, 2 included a registry search. Six of 25 reviews not reporting PRISMA compliance performed registry searches.

Cohen's κ coefficient for interrater reliability with respect to whether systematic reviews included clinical trials registry searches was 0.93, indicating excellent agreement.

LIMITATIONS

Our study has several limitations. It is possible that authors conducted a clinical trials registry search but did not describe this in the article if it was perceived to be unhelpful. We examined systematic reviews published in emergency medicine journals. Little is known about the use of clinical trials registries for systematic reviews published in other medical specialties or in general medical journals. Additionally, we limited this analysis to reviews published in 2013; recently conducted systematic reviews are more likely to benefit from including registry searches because the consistent registration of clinical trials only began in 2005. Registry use by authors of systematic reviews has almost certainly increased during the past decade and is likely to continue to increase.

DISCUSSION

Among systematic reviews of interventions published in emergency medicine journals in 2013, publication bias was not routinely addressed with clinical trials registry searches. For authors who did search clinical trial registries, approximately half identified relevant unpublished studies, indicating the potential benefit of this approach.

Clinical trials registry searches provide systematic review authors with the ability to directly identify relevant ongoing or completed but unpublished studies. The use of this technique offers several significant advantages compared with traditional methods of assessing for unpublished data. First, registry searches allow the identification of specific relevant studies compared with funnel plots and statistical methods of assessing for publication bias, which can provide insight only about the statistical likelihood that unpublished data may exist. Funnel plots may be unhelpful when reviews have few included studies; however, this limitation does not apply to clinical trials registry searches.[7] Additionally, funnel plot asymmetry can occur for reasons other than publication bias, such as heterogeneity across studies of varying sample size (eg, smaller studies may study only sicker patients).[8] Furthermore, even experts often disagree when interpreting funnel plots.[3] Registry searches also have an advantage over reviewing reference lists from included studies or conference abstracts because these sources are likely subject to the same reporting biases as published articles.

Another important feature of registry use is that registry searches are particularly well suited to identifying large unpublished trials. Unfortunately, approximately 30% of large randomized trials are not published.[9] Funnel plots are inherently unable to identify the presence of unpublished trials that are large relative to published studies. This is particularly concerning because the presence of large unpublished studies can significantly alter the interpretation of the effect estimate from available studies.[10] Conversely, large trials, which are almost always intended for publication, are the most likely to be registered, thereby allowing clinical trials registries to address this important limitation of funnel plots.

Finally, clinical trials registry searches have the potential not only to help identify the existence of unpublished trials but also to facilitate access to results from these trials. Results are available in clinicaltrials.gov for an estimated 22% of large unpublished trials.[9]

Even for trials for which results are not available, registry entries typically include information about study size. Knowing the sample size of unpublished trials allows the authors of systematic reviews to more accurately estimate the potential influence of unpublished trials on the effect estimate from the published trials.

Incomplete or missing registry entries still constrain the utility of registries to serve as a comprehensive resource for identifying unpublished data. However, registration of clinical trials has increased rapidly during the past decade, and the amount and quality of information available in trials registries will likely continue to improve, rendering this concern less important over time.

Among interventional systematic reviews published recently in emergency medicine journals, clinical trials registry searches were not routinely used to assess for publication bias. However, when registry searches were performed they often provided additional information about the presence of unpublished data. The routine use of trials registry searches by systematic review authors may help to limit or define the presence of publication bias, thereby improving the validity of systematic reviews.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Editor's Capsule Summary

What is already known on this topic

Publication bias remains a major threat to the validity of systematic reviews and meta-analyses.

What question this study addressed

Whether authors of systematic reviews in emergency medicine reported that they checked trial registries for relevant unpublished trials.

What this study adds to our knowledge

Trial registries were checked in only 20% of the 41 reviews published in 2013.

How this is relevant to clinical practice

This finding should sensitize journal editors and reviewers to the importance of ensuring that systematic reviews have checked the appropriate registries for unpublished articles.

Table

Characteristics of systematic reviews published in 6 emergency medicine journals from January 2013 through December 2013.

Review Characteristics	Interventional Reviews (n=41)
Journal, n	
Academic Emergency Medicine	3
American Journal of Emergency Medicine	3
Annals of Emergency Medicine	8
Injury	11
Journal of Trauma and Acute Care Surgery	3
Resuscitation	13
Funding source, n*	
Industry	1
NIH/government	6
Other	3
None	32
Number of studies included in review, median (range)†	16 (3–182)

NIH, National Institutes of Health.

*One review was performed with both NIH and industry support.

†n=39. Two reviews did not report the total number of included studies.