Journal of Clinical Epidemiology 79 (2016) 130−139

Randomized trials are frequently fragmented in multiple secondary publications

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Accepted 6 May 2016; Published online 5 July 2016

Abstract

Objective: To assess the frequency and features of secondary publications of randomized controlled trials (RCTs).

Study Design and Setting: For 191 RCTs published in high-impact journals in 2009, we searched for secondary publications coauthored by at least one same author of the primary trial publication. We evaluated the probability of having secondary publications, characteristics of the primary trial publication that predict having secondary publications, types of secondary analyses conducted, and statistical significance of those analyses.

Results: Of 191 primary trials, 88 (46%) had a total of 475 secondary publications by 2/2014. Eight trials had >10 (up to 51) secondary publications each. In multivariable modeling, the risk of having subsequent secondary publications increased 1.32-fold (95% CI 1.05−1.68) per 10-fold increase in sample size, and 1.71-fold (95% CI 1.19−2.45) in the presence of a design article. In a sample of 197 secondary publications examined in depth, 193 tested different hypotheses than the primary publication. Of the 193, 43 tested differences between subgroups, 85 assessed predictive factors associated with an outcome of interest, 118 evaluated different outcomes than the original article, 71 had differences in eligibility criteria, and 21 assessed different durations of follow-up; 176 (91%) presented at least one analysis with statistically significant results.

Conclusions: Approximately half of randomized trials in high-impact journals have secondary publications published with a few trials followed by numerous secondary publications. Almost all of these publications report some statistically significant results. © 2016 Elsevier Inc. All rights reserved.

Keywords: Secondary publications; Randomized controlled trial; Clinical trial; Individual patient data; Multiplicity; Secondary findings

Funding: There were no sponsors for this study. S.E. was supported by postdoctoral awards from MITACS Elevate and SickKids Restracomp, Z.N.S. by a doctoral award from the Canadian Diabetes Association and the Ontario Graduate Scholarship, and S.B. by a doctoral award from the Social Sciences and Humanities Research Council. The Meta-Research Innovation Center at Stanford (METRICS) is funded by a grant from the Laura and John Arnold Foundation. Sponsors providing individual financial support to authors did not have a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

Conflict of interest: None.

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http://dx.doi.org/10.1016/j.jclinepi.2016.05.016
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1. Background

Randomized controlled trials (RCTs) are the gold standard for determining the effectiveness of treatments [1]. RCTs are a challenging endeavor given the rigor in designing and conducting trials, resources required [2], and the time taken to complete them [3]. Many researchers may find leading RCTs unattractive for their career, as RCTs typically result in a single published report and they are called anecdotally the deathbed of the assistant professor. However, with the pressure of publishing in academia, the paradigm of only one publication stemming from an RCT may be changing with authors performing secondary analyses on their trial data to publish additional articles.

Data sets from RCTs can be rich sources for secondary analyses [4]. Some organizations, such as the National Institutes of Health, have policies that encourage data sharing, specifically to support secondary analyses [5]. The vast majority of secondary analyses are however performed by the original authors of each trial [6,7]. Even when authors share data with other investigators, some original authors remain as coauthors in the resulting publications [4]. Secondary analyses can offer additional insights beyond the primary publication of the trial results. They can also provide to scientists, physicians, and the public more complete information about interventions [8]. However, there are also criticisms of secondary analyses: they may lack statistical power for new hypotheses [9], and multiple post hoc analyses (e.g., subgroups) can generate spurious misleading findings [8]. There are also issues with fragmenting results with ''salami publications'' [10,11], and even duplicate publication of RCTs has been described [12,13]. Fragmentation of the evidence across multiple articles may confuse readers, clinicians, and systematic reviewers.

To our knowledge, there has been no empirical evaluation of the frequency and features of secondary publications of individual RCTs. Here, we aim to assess the phenomenon and its implications at large scale, using a sample of RCTs published in high-impact journals. Specifically, we aim to assess how many secondary publications of RCTs are published by the authors of the primary publication; how soon they appear; what types of trials lead to more secondary publications; what are the reasons for completing secondary publications; and whether these secondary analyses claim statistically significant research findings.

2. Methods

2.1. Eligibility criteria

Using a previously constructed database of a random sample of 200 RCTs reporting on a primary outcome in high-impact journals in 2009 [14], eligible studies for our current evaluation include all published secondary publications coauthored by at least one of the same author(s) of the original primary trial publication and using individual-level data from the original trial.

2.2. Primary trials

Primary trials have been previously identified and used in a project assessing the prevalence and impact of adjustments in results of RCTs [14]. In brief, searches were made in PubMed for study type = randomized controlled trial for the 25 biomedical journals with highest impact factor (Journal Citation Reports 2009) that are also likely to publish RCTs: BMJ, American Journal of Psychiatry, American Journal of Respiratory Critical Care Medicine, Annals of Internal Medicine, Annals of Neurology, Archives of General Psychiatry, Archives of Internal Medicine, Blood, Brain, Circulation, European Heart Journal, Gastroenterology, Gut, Hepatology, Journal of Allergy and Clinical Immunity, Journal of the American College of Cardiology, Journal of Clinical Oncology, Journal of the National Cancer Institute, JAMA, Lancet, Lancet Infectious Diseases, Lancet Neurology, Lancet Oncology, New England Journal of Medicine, and PLoS Medicine. We included studies involving human participants and published in 2009. As previously stated [14], these 200 trials were randomly chosen with random numbers from a total of 684 articles of trials published in these journals in 2009.

In our previous evaluation [14], we had already excluded three articles that did not analyze primary outcomes between the study arms. For the current project, we also excluded articles that did present some analyses of primary trial outcomes but had already been preceded by an earlier publication of other primary outcomes; conversely, we did not exclude trials with preceding publications that did not present any primary analyses (e.g., design articles, baseline data reports, early results, other secondary analyses). We thus checked the cited references of each article and identified citations to previous relevant publications of the same trial. This process eliminated another eight articles. Two articles each reported the results from two separate trials and were considered separately. Thus, 191 trials were finally selected for evaluation (Appendix A at www.jclinepi.com).

2.3. Selection of secondary publications

We used the Thomson Reuters ISI Web of Science database to identify secondary publications for the 191 original primary trials. It would be extremely unlikely for a secondary publication not to cite the primary trial. We identified and recorded the total citations of each primary trial publication until February 2014. We refined the ''times cited'' results to include only articles that include as an author any of the original trial authors. We recorded the number of citations by articles that use individual-level data from the original trial and included as an author any of the authors of the original trial. For articles considered to potentially reflect secondary publications, the full text was examined to confirm eligibility.

To identify secondary publications published before the primary publication of the primary outcome, we reviewed

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