Title

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Journal

International Journal of Radiation Oncology • Biology • Physics, 90(4)

ISSN

0360-3016

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Publication Date

2014-11-01

DOI

10.1016/j.ijrobp.2014.07.052

Peer reviewed

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

EDITORIAL

Introducing Prospective Manuscript Review to Address Publication Bias

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Received May 19, 2014, and in revised form Jul 21, 2014. Accepted for publication Jul 31, 2014.

Publication bias: Then and now

Publication bias occurs when a study's results influence its probability of publication (1). This form of bias has long been acknowledged as a problem, resulting in a body of literature that is not a representative sample of all scientific investigations (1-4). In particular, it has been observed that published academic literature tends to be skewed toward "positive" studies, that is, those that reject the null hypothesis (1-6).

Seminal works by Sterling (1) and by Bozarth and Roberts (2) found that more than 90% of studies that they sampled reported statistically significant results supporting the primary hypothesis(es). Multiple subsequent studies have documented the following: (*1*) Positive studies are more likely to be published in journals with higher impact factors, and to be rated as more important by other investigators (7); (*2*) Trials supporting the use of a novel therapy are more likely to be published (8); (*3*) Published trials are more likely than unpublished to report statistically significant results, distorting literature-based meta-analysis (9); (*4*) Results published in high-impact journals can improperly influence clinical practice, even after contradictory results have been published in less influential journals (3); (*5*) Peer reviewers are strongly influenced by the size and direction of observed effect sizes (10); and (*6*) Authors are less likely to submit (and editors less likely to publish) evidence that does not support the investigators' primary hypothesis (11).

The net impact of these phenomena is that both type I error (the probability of rejecting the null hypothesis given that it is true) and type II error (the probability of failing to reject the null hypothesis given that it is false) will differ for the scientist and the reader (4).

Modern literature suggests that, despite recognition of the problem, we are no better at addressing it. When Sterling et al repeated the original experiment 40 years later, to determine the proportion of published studies that were "positive," they found that it was essentially unchanged (96%) (4). Moreover, "positive" studies were nearly as prevalent in prestigious journals (85%). Such analysis, of course, presumes that the authors' primary hypothesis(es) can be identified, which is not always true, even for randomized trials (12). More recently, a 2009 meta-analysis estimated that positive studies were nearly twice as likely as negative studies to be published, and were published faster (5). A separate meta-analysis concluded that strong evidence exists supporting an association between statistically significant results and probability of publication (6). In addition, statistically significant outcomes are more likely to be reported, and the outcomes selected for reporting are frequently inconsistent with the initial protocol.

Although some studies have reported no difference in publication practices between manuscripts with positive and negative results (13, 14), these generally considered only prospective clinical trials. Clinical trials, particularly randomized trials, tend to have greater care expended in

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Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 90, No. 4, pp. 729–732, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.07.052

their initial planning and design, and to have aims publicized in advance of their conclusion. Publication bias is likely to be a greater problem with unregistered and retrospective studies, where the hypotheses being tested may not be publicly declared in advance. For example, Easterbrook et al found that publication bias was a greater problem for observational and laboratory studies than for randomized trials (7). Irrespective of study design, however, simple awareness of the problem has been insufficient to effect change, and active steps to mitigate publication bias across the academic literature are needed.

Causes of publication bias

To some degree, publication bias might be considered natural, or even desirable. Some editors have even expressed skepticism as to the degree to which publication bias exists or is a concern (15). Small studies may be underpowered to detect effects or outcomes of interest, or may have other methodologic concerns that could bias the study toward the null hypothesis. Repetitious negative studies may rightfully be perceived as having diminished scientific impact or producing minimal innovation. Furthermore, on the whole, we might hope and expect the set of scientific investigations to yield more positive than negative findings, as investigators presumably conduct experiments that they deem likely to succeed, where "success" is normally equated with a positive outcome. Indeed, positive trials may represent the consummation of years of diligent, groundbreaking science aimed at improving therapy, a laudable clinical and scientific goal.

That said, we would be wise to contemplate the incentives and pressures that scientists face to produce "positive" research. First, academic advancement, such as decisions about admission, hiring, or promotion frequently depend on both the number and impact of an individual's scholarly papers, which in turn depend on the nature (positive or negative) of one's results. Regulatory approval of novel therapies, their sales, and use also are clearly conditional on positive findings. Academic recognition in the form of speaking engagements, invited lectures, honoraria, grants, and other forms of remuneration typically ensue for investigators who report positive findings, particularly in high-impact journals.

Second, the academic community and media place a high value on what we might call "deterministic" or discovery-based science, as opposed to "stochastic" or estimation-based science. The Nobel Prize, as one example, is given "to the *person* who shall have made the most important *discovery* within the domain of physiology or medicine" [emphasis added] (16). It is easier to venerate an individual who discovers a planet, gene, fossil, cure, or x-ray than a collection of investigators who concludes that a therapy lacks clinical effectiveness.

Third, the labor and expense associated with conducting medical science generates a tacit pressure to have something to show for it. A single randomized trial may provide the lone unbiased estimate of a treatment's effect. The existence of one positive trial can affect the conduct of would-be confirmatory (or contradictory) studies. Individuals frequently ascribe undue importance to a single investigation, reflected in authors' purporting to "show," "determine," or "demonstrate" effects, rather than to "observe," "find," or "estimate" them. Yet a critical property of all science is reproducibility, which derives not from one study but from the collective verification and validation on the part of the scientific community.

We want positive studies. In medicine, we need positive studies. Yet this need invites varying degrees of academic misconduct, ranging from peccadillos (Texas sharpshooter fallacy) (17), to misdemeanors (*P* value gerrymandering), to felonies (suppressing incongruous evidence), to capital crimes (fabricating data). Most investigators are presumably motivated by good intentions, but we are all subject to these forces, and likely subconsciously or consciously guilty of producing results that are misleading, because what we want or hypothesize to be true is often untrue. More imperatively than positive studies, we need reliable studies. Although these pressures will probably never disappear, we can take action at the editorial level to ensure that a study's findings are reliable, to save us from ourselves, as it were. If investigators could be assured that the positivity or negativity of their study would not influence acceptance, they might choose to submit different ones for publication, and to write in such a way that others could theoretically reproduce the same results.

Reducing publication bias

Most journals are curated at the level of the polished manuscript. In addition to its scientific merits, a study's fashionableness can weigh on its chances of acceptance, akin to a magazine. For an academic journal, however, editors ought to be able to determine an article's suitability for acceptance based on less information.

In 1989, Begg and Berlin (3) called for restructuring of the process by which study results are disseminated, changing editorial policies, and altering the methods of statistical analysis, to address publication bias. This led, among other things, to the helpful development of trial registries. Despite this advance, problems such as changing primary endpoints post hoc and failing to report data still exist (18). Furthermore, registries do not help for the large body of science that is not generated from a clinical trial.

Decades ago, Newcombe proposed a concept for prospective manuscript review to address publication bias (19). In principle, the scientific importance, interest to the intended audience, and methodological soundness of a study should be identifiable *a priori*, and the results of a study should be regarded as independent of its scientific merits. The most common editorial process used by leading journals, however, is retrospective review, that is, evaluating a manuscript for publication after the study has been completed.

Recently, the journal *Cortex* implemented a process in which a manuscript is submitted for publication in stages, and is evaluated on the proposed design, before disclosure of its results and discussion (20) To our knowledge, however, prospective review has not been tested in any leading oncology journals. We hypothesize that prospective review will reduce publication bias, and we therefore propose to conduct an experiment.

Proposed prospective review process for the Red Journal

We, at the Red Journal, have a strong commitment to improving the ethical and scientific basis of the work that we publish. To this end, this coming year, we propose to initiate a study to assess the impact of a 2-stage prospective manuscript review process (Supplemental Material). In particular, we will concentrate on projects performed by young investigators who have the most to gain in both the short-term (because their projects will be prescreened for quality) and the long-term (from a "cultural change" perspective). Submitted manuscripts could be associated with either completed projects (which will be randomly assigned to prospective vs standard review) or a planned research project (ie, a concept, which will be assigned to prospective review) (Fig. 1). Corresponding authors will be asked to participate in a brief questionnaire when they log on to submit the manuscript. In stage 1, authors will submit their introduction and methods sections, along with a specific description of their hypothesis, analysis plan, and which results will be presented and how. After peer review, if the manuscript is approved in stage 1, authors will be invited to submit the entire manuscript in stage 2. In stage 1, reviewers will be coached to prioritize and evaluate the significance of the scientific question, suitability of the subject matter for the Red Journal readership, and soundness of the methods to test the question and plan to present them. Stage 2 will emphasize the execution of the study, fidelity to the original proposal, and balance and quality of discussion. At this point, an editorial decision will be made as to whether to reject, accept, or revise the manuscript.

The primary hypothesis that we will test is whether prospective review reduces the proportion of original clinical investigations that are classified as "positive" (ie, reject the null hypothesis) or "indeterminate." We will also assess reviewer/author satisfaction with the process, impact on overall review time, and factors associated with acceptance and publication bias. At the conclusion of the study, we will decide whether this process is likely to reduce bias and should be continued.

An unavoidable limitation of this process is that we cannot know information about studies that are "upstream" of the process, that is, not submitted for publication. However, by attempting to remove the nature of results from the publication decision, we may lower the threshold to submit high-quality negative studies.

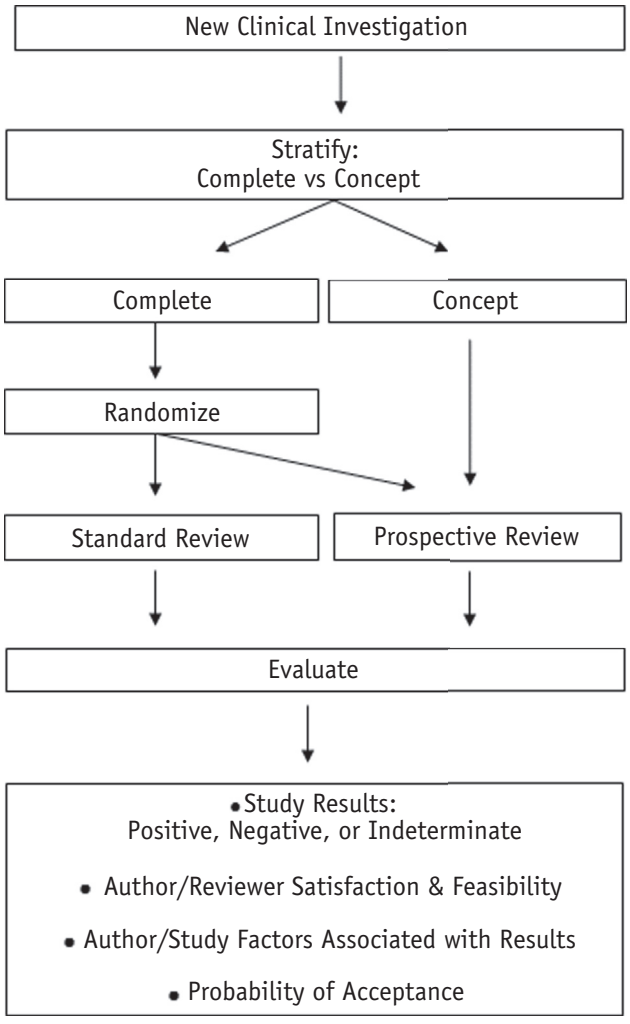

Fig. 1. Trial schema.

Conclusion

At least as much as authors, editors are critical to controlling publication bias. Retrospective review is vulnerable to bias in the same fashion as retrospective study designs. Dickersin et al asserted that "journal editors should formalize editorial policy stating that the decision to publish will be based on issues of quality and logical reasoning by the authors and not the direction and strength of study results" (21). A straightforward way to ensure commitment to this policy is to blind the results. In this manner, we can shift the emphasis of our literature toward answering questions, rather than supporting hypotheses.

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