Reporting of Randomized Clinical Trials Remains Far from Optimal

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Clinical trials are a cornerstone of therapeutic innovation. It is therefore extremely important that they are designed appropriately, conducted meticulously, analyzed correctly, and, in the specific context of this Editorial, reported accurately and fully (“the truth, the whole truth, and nothing but the truth”), and interpreted in a clinically meaningful manner.

The published results of individual trials serve 2 important functions. First, they are available to be used by physicians practicing evidence-based medicine, “the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients,”¹ to decide if the treatment discussed is an appropriate one for his or her patients on a case-by-case basis. To facilitate the optimal practice of evidence-based medicine, these physicians must be given transparent, accurate, and complete data addressing both efficacy and safety (harms).

The second function of individual study reports is to contribute to the creation of treatment guidelines. Groups of experts representing professional societies and learned bodies frequently write treatment guidelines based on their review of all relevant study reports. These guidelines, whose validity and applicability is predicated on the accuracy and completeness of data presented in the original study reports, can then be used by physicians for whom intensive daily clinical duties preclude the reading and personal synthesis of multiple individual reports. Based on both forms of utilization, a question of great import is this: How good are reports of individual clinical trials? The question has been asked for several decades, and the answer remains disconcerting.

Concerns expressed by a considerable number of researchers and journal editors in the early 1990s led to several meetings that generated the Consolidated Standards of Reporting Trials (CONSORT) Statement.² CONSORT is a set of reporting recommendations, not a statement on how clinical trials should be conducted: its key message is that whatever is done should be fully and accurately reported. It is also a work in progress. The first statement was published in 1996,³ the first revision in 2001,⁴ and another revision in 2010.⁵ The latest information on CONSORT and also various extension statements (including one published in 2004 addressing better reporting of harms⁶), can be found on its web site.²

Imperfections in Reports of Randomized Clinical Trials

In 2010, Moher and colleagues⁵ observed that “overwhelming evidence shows the quality of reporting of randomized

controlled trials (RCTs) is not optimal.” More recent papers continue to paint a similar picture.⁷⁻¹² For example, Magin and colleagues⁸ investigated how completely socioeconomic data were presented in studies reporting trials of stroke or transient ischemic attack published in 12 major journals subsequent to the release of the revised CONSORT statement: socioeconomic status is associated with access to care, and with poststroke outcomes including mortality, functional outcome, recurrent stroke, and hospital readmission. Only 12% of the studies included in the authors’ review reported any measure of socioeconomic status. As they concluded, “Improving reporting of [socioeconomic status] could enhance clinicians’ ability to evaluate RCT findings and apply them to their patients.”⁸

As a second example, Maggi and colleagues⁹ evaluated the degree to which reports of randomized clinical trials published in the *New England Journal of Medicine*, *Lancet*, the *Journal of the American Medical Association*, and the *British Medical Journal* adhered to CONSORT recommendations with regard to reporting adverse events. Using the Medline search engine, reports of 122 randomized clinical trials published in 2009, 5 years after the 2004 publication of the CONSORT extension statement on harms, were identified. The most frequently met CONSORT recommendation was mention of harms in the paper’s title or abstract (72.1% of the papers analyzed). The recommendation met most infrequently was the reporting of how harms information was collected (10.7%).

Public Registration and Reporting of Clinical Trials

In a 2004 Perspective article published in the *New England Journal of Medicine*, Steinbrook¹³ commented as follows:

For many years, the registration in a public data bank of all clinical trials—from start to completion and reporting of results—has seemed a quixotic quest of some academic researchers, medical-journal editors, and librarians. Within the past two months, however, a constellation of events and developments has broadened this effort and captured the attention of the medical profession, the news media, and government officials. . . . Although uncertainties are ahead, there is a growing realization that the public registration of clinical trials is an idea whose time has come. In the long term, no one benefits from the selective release of information about trials and the selective reporting of results.

Registration and reporting of trials in this manner is now routine practice. ClinicalTrials.gov¹⁴ is “a database of privately

and publicly funded clinical studies conducted around the world” that continues to grow: at the time of writing this Editorial, it listed 264,949 research studies in all 50 states in the US and in 203 countries. Given that study results are typically presented on ClinicalTrials.gov and in journal publications, one would expect the presented results to be identical in both places. However, this expectation is not always met. Consider these examples addressing the reporting of adverse events. Riveros and colleagues¹⁵ observed that “trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article.” Hartung and colleagues¹⁶ observed as follows: “Reporting discrepancies between the ClinicalTrials.gov results database and matching publications are common. Which source contains the more accurate account of results is unclear, although ClinicalTrials.gov may provide a more comprehensive description of adverse events than the publication.” Tang and colleagues¹⁷ compared the consistency between serious adverse events posted at ClinicalTrials.gov and those published in corresponding journals. They concluded that many trials with serious adverse events posted at ClinicalTrials.gov omit the reporting of these events in corresponding publications, or report a discrepant number as compared with ClinicalTrials.gov, commenting that “these results underline the need to consult ClinicalTrials.gov for more information on serious harms.”

Evidence-Based Medicine and the Challenge of Generalizability

It was noted earlier that published results of individual trials can be used by physicians practicing evidence-based medicine to help decide if the treatment discussed will likely be useful for a specific patient under his or her care, where “useful” can be operationally defined as having a favorable benefit-risk balance. Imagine that a particular randomized clinical trial has been perfectly reported. Physicians still have to consider this question: Can the information presented in the paper, that is, information generated from the specific set of participants employed in the trial, be generalized to a given patient? One of my favorite quotes, from physician-scientist David Katz, addresses this topic as follows¹⁸:

The inapplicability of some evidence to some patients is self-evident. Studies of prostate cancer are irrelevant to our female patients; studies of cervical cancer are irrelevant to our male patients. Yet beyond the obvious exclusions is a vast sea of gray. If our patient is older than, younger than, sicker than, healthier than, ethnically different from, taller, shorter, simply different from the subjects of a study, do the results pertain?

These sentiments make it clear that even given perfectly reported information from a trial, physicians have to use clinical judgment to arrive at their best estimation of the benefit-risk balance for each individual patient. A lack of completeness in reported information compounds physicians’ difficulty in

determining the generalizability of information provided in study reports to their patients. As for a trial’s study design, conduct, and analysis, its reporting and interpretation must be of optimal quality.

Recent Thoughts From Two Fellow Editors-in-Chief

I recently read with interest articles by the Editors-in-Chief of the *Journal of the American Medical Association*, Dr Howard Bauchner,¹⁹ and the *Journal of the American College of Cardiology*, Dr Valentin Fuster.²⁰ To place their thoughts in context, they first commented on the fast-paced culture in which many of us now live, and 24-hour instantaneous access to electronic communication via email and social media. They then discussed an increasing trend in clinical publishing—the desire of clinical trial investigators to publish papers simultaneously with the results’ presentation at a scientific meeting (an example of this occurrence was discussed in my November 2017 Editorial²¹). Bauchner¹⁹ commented as follows: “Funders, authors, societies, and journals need to move more deliberately; ensure appropriate rigorous external peer review and internal scientific and editorial scrutiny; redouble efforts to ensure that shortening the time to publication does not adversely affect scientific quality and accuracy; and perhaps, of necessity in some cases, slow the process of scientific publication. . . . Timely assessment and dissemination of medical research findings is certainly important, but for most articles, rushing to publication in days or weeks will not improve health outcomes.” Fuster²⁰ observed, “it is my impression that papers that are rushed through the peer review process for the purpose of simultaneous publication with major medical meetings often contain the most errors.”

Very interesting thoughts.

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