New Law May Be Having Some Effect on Publication Bias

By Rabiya S. Tuma

Positive trials get reported more often than negative trials, according to many studies. And despite efforts in the past decade to combat publication bias, it remains a substantial problem, according to two articles published last fall. One found that results had been published from fewer than half of the trials registered in the federal database, clinicaltrials.gov. The second article found that approximately one-third of the trials eventually published in journals changed the trial endpoint prior to publication.

Despite the disconcerting results, experts are cautiously optimistic that a federal law may be having an effect. The law requires not only registration of trials but also that researchers enter results into the database. Journal policies had previously encouraged trial registration, but the new law adds clout. “The only way trial registration was going to have an effect was if someone was going to enforce it, and this is the enforcement that is needed. I think it could well address publication bias,” said Virginia Barbour, M.D., chief editor of the open-access journal PLoS Medicine, in the Public Library of Science in London.

Although experts look forward to evaluating the influence of the law, no one—including Barbour—expects that it can entirely cure the problem. Other efforts are needed, experts say, including increased scrutiny of trial protocols and registration information during the peer-review process.

Extensive Problem

To combat publication bias, the research community has already taken key steps. In 2000, the National Institutes of Health established clinicaltrials.gov, a publicly accessible database of trials. And in 2005, the International Committee of Medical Journal Editors began requiring that trials be registered in a public database prior to enrolling the first patient, in order to be considered for publication. Then Congress passed the law requiring registration and that results be reported in clinicaltrials.gov, beginning in 2007. Although it is too early to know how the 2007 law will affect publication bias, the first two measures have been in place several years, and researchers can now use data from clinicaltrials.gov and the National Library of Medicine to get a more concrete assessment of just how big the problem really is.

In one of last fall’s articles, Joseph Ross, M.D., of the Mount Sinai School of Medicine in New York, and colleagues systematically assessed the completeness of registration for all 7,515 trials entered in the database and completed before 2006, excluding phase I trials. They reported in PLoS Medicine that nearly all the trials included the required data elements, such as intervention, condition to be addressed, sponsor, and trial design. However, the proportion of trial records that contained optional data elements was much lower. For example, only 53% of the records included a trial end date, 66% included a primary outcome measure, and 56% included secondary outcome measures.

To determine what proportion of these trials reported results in a journal publication, Ross’s team looked at a 10% sub-sample that was randomly selected. They were able to identify publications from just 46% of the trials. Only 31% of the clinicaltrials.gov records included a citation for the publication of the results.

In the second study, published in the Journal of the American Medical Association, Philippe Ravaud, M.D., Ph.D., of the Hôpital Bichat-Claude Bernard in Paris, and colleagues compared the primary outcome reported in journal publications with the endpoints originally listed in clinicaltrials.gov. For the analysis, they identified 323 randomized, controlled trials in cardiovascular disease, rheumatology, and gastroenterology that were published in 10 high-impact journals in 2008. Of those, 147 (45.5%) were registered in clinicaltrials.gov prior to completing enrollment and had a primary outcome clearly specified; 45 (13.9%) were registered after trial completion; 39 (12%) had no clear primary outcome; three (0.9%) were registered after completion and had no clear primary outcome measure; and 89 (27.6%) were not registered at all.

When Ravaud and colleagues compared the endpoints reported in the journal article with those listed in the registry, they found a discrepancy in 46 (31%) of the trials that had been properly registered prior to completing enrollment. And in nearly all cases in which the endpoints were not the same, the reported outcome was positive, suggesting that researchers were searching for something in their trial data that they could highlight.

“By doing these sort of shenanigans, like testing lots of hypotheses and reporting only those that look positive, they are not acting in the subjects’ best interest.”

Something should change.”
New Requirements
Like PLoS Medicine’s Barbour, Ross is hopeful that the new federal regulations might be the change that is needed. The Food and Drug Administration Amendments Act of 2007 mandates that trial sponsors or primary investigators register a trial within 21 days of enrolling the first patient and that they enter basic results into the expanded clinicaltrials.gov database within 12 months of the last patient’s receiving the trial intervention or being evaluated in the study. Investigators who do not comply can be fined as much as $10,000 per day or have federal research funds withheld or recovered. Trialists can apply for an extension if their investigational drug or device is under regulatory review.

The law, commonly referred to as FDAAA, went into effect in September 2007 and covers trials that were ongoing at that time and to be completed after December 26, 2007, or initiated after September 2007. Thus far, results for more than 1300 trials have been entered into the database. “So it is just a matter of time to have a critical enough mass for people to start picking up the data when they do these studies [on publication bias],” said Deborah Zarin, M.D., director of clinicaltrials.gov at the National Library of Medicine, within the National Institutes of Health. “They are not the Department of Justice. They are not the NIH actually pulling funding. So it is tricky.” However, FDAAA at least allows the community to call attention to trials that are not reporting outcomes, Ross said. “And if the law needs to be strengthened, we will have given it the opportunity to show that the actors are not playing well on their own and maybe we need people to provide oversight.”

Increasing Scrutiny
None of the experts interviewed expect that FDAAA can eradicate publication bias on its own. Ravaud, whose team authored the report showing that many researchers were changing endpoints, said that study authors, journal editors, and trial sponsors share the responsibility for FDAAA’s limited effect.

“Mandatory trials registration was a crucial step to improve transparency. However, the full potential of registration is not used,” he wrote in an e-mail. In his view, journal editors should require the registration record and compare that with any manuscript submission. Such scrutiny may not reduce all publication bias, but it would reduce the chance that a researcher could alter the aim of the trial.

Berry makes a similar suggestion, but rather than relying on the trial registration information, he suggests that journals require submission of the original trial protocol—or at least the statistical analysis portion—so that the editors can see what the original goals and planned analyses were. Such documents would also show any substantial changes that were made to the protocol. In some instances, he said, there are valid reasons to change endpoints during a trial, such as results coming out from a separate study, but that investigators need to make the changes and the reasons for the changes clear—and they need to be made prior to data analysis. “Bias arises when you change it based on what you see,” he said.

Some journals already require these extra documents with clinical trial manuscript submissions. For example, although the editor of the New England Journal of Medicine declined to be interviewed, a spokesperson said that the journal requires the trial registration information with submission and often asks for the study protocol or statistical plan.

Barbour said that both PLoS Medicine and PLoS One not only require the trial protocol for the review process but also publish it with the article. “It is routine practice at our journal that when a manuscript comes in we will always look at the registry record, we will always look at the protocol, we will look at any associated documents,” she said. “Although we can’t pick up everything, we can pick up the obvious big holes that are there.”

One barrier to enforcing FDAAA is that there is no standardized way of reporting a trial or putting it into a database and thus no easy way to spot violations. “If there were better tools for that it would help enormously,” Barbour said. “Then you could imagine a system with automatic flagging if the protocol said you have four primary outcomes but you are reporting only two. Right now it requires somebody to go through it line by line, and that is really time consuming.”

Occasionally a trial sponsor says that the protocol is confidential and refuses to make it available for publication. Barbour said that the PLoS journals reject such submissions straightaway. In her view the trial is a long narrative, of which a journal article can only report a small portion. To evaluate it completely, reviewers and readers need to be able to see the whole narrative.

But even when a journal does have access to the original trial protocol, problems can arise, according to Berry. Recently, he and several coauthors submitted a clinical trial manuscript to a high-impact journal. The editors were interested but wanted to publish the paper only if the authors...
changed the statistical analysis used to test the value of the experimental therapy. “We, the authors, had to work to keep the journal editors on the straight and narrow,” he said. “They did not like the protocol-defined primary analysis of the primary endpoint and wanted us to use a different analysis, one not mentioned in the protocol or in the statistical analysis plan.” He said that the statistical analysis the editors didn’t like was one that the U.S. Food and Drug Administration had approved before the trial began.

Berry, Barbour, and others agree that the recent reports highlight one piece of good news: With clinicaltrials.gov, the medical research community can begin to understand the magnitude of the publication bias problem. Expanding the database to include results will probably make it even more valuable. “What that means is that we are going to be able to go to one source, see which trials are being done, and even see some of the more straightforward results being found from the trials, to compare that with the published literature to know what is going on,” Ross said.