Publication Bias

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It is widely believed that there is a bias against publishing "negative" studies. Researchers think that editors are more likely to reject trials that do not show a positive effect of some intervention, or that a purported risk for a disorder, is, in fact, not a risk factor. Yet, research looking to support findings of clinical publications have often shown a failure to confirm the original report. The reasons for this unreliability are manifold. All clinical research on living specimens is biased by the sample chosen. Even large data "mining" operations, for example, looking at a Medicare database involving hundreds of thousands of people, obviously reflect only those who have Medicare insurance. In research, as in everything else, there are "the known knowns, the known unknowns and the unknown unknowns." Lack of publishing results is one of the unknown unknowns.

Clinical research publications follow a format, most of which is on a template formulated by the journal or recommended by some organization. In the discussion section, which follows the research data presentation, there is a summary of the important findings, both negative and positive and their implications. In the next to last paragraph the authors usually summarize the weaknesses of their study. They address the possible biases of their study, then explain why their results should be believed, albeit with certain cautions, and conclude with the final sentence noting that the results need to be confirmed. This is sound advice, but there is always the lurking problem of the unknown unknowns.

In this issue of RIMJ, Khatri et al[1] reviewed English language studies of two common eye disorders in diabetics. They found that only 20% were published. This was a surprise to me, having never thought of the problem and would have guessed that maybe 20% or less were not published. I learned that this is a common problem and similar rates of non-publication span the spectrum of medical studies. There are many potential reasons for not publishing. For example, I knew of a clinical study that tested a European antipsychotic drug in patients with psychotic symptoms associated with Parkinson's disease. A small open label trial was very suggestive of significant benefit so that a double blind placebo trial was sponsored by the drug company. I thought this was a great idea, but I was not directly involved in the study. The study was completed but with a negative result. The drug was ineffective. I waited for the publication and learned that there would be none. No one explained to me why this was to be the case. Most researchers like to see their names in print and these investigators were not bound to hide their results by virtue of being employees of the company. Presumably, and understandably, the drug company thought that negative results would reflect poorly on the drug. There was little to be gained by proving themselves good corporate citizens. I don't know why the investigators didn't publish. The results were readily available, however, in ClinicalTrials.Gov, so I got to publish in one of the easiest papers in history.[2] Of course, anyone could have looked up the results that way, but few people knew of the trial, and most papers are identified via topic searches in PubMed. Except for active researchers, few scan ClinicalTrials.Gov for study results.

Many clinical trials fail to meet their recruitment goals, which means that their careful planning for how many subjects they needed in order to obtain a statistically significant outcome was for nought and that the study was unable to obtain useable data. Since the estimate for how many subjects are needed is something of a guess, the study may have recruited too few to draw reliable conclusions. Some projects faltered because investigators did not adequately oversee their portion of the study, recruiting subjects who should not have meet inclusion criteria, or who dropped out prematurely, lacking sufficient commitment ("garbage in, garbage out"). A study may produce results that mystify the researchers, expecting one outcome, anticipating a possible failure, but not expecting a surprise that they cannot explain.

Studies are often abandoned mid-stream, possibly because of worrisome side effects or unwanted trends. Occasional studies are halted due to business decisions. A company purchases a new drug that will compete with the one being studied. And the acceptance rate for manuscripts submitted to many journals may be small.

A likely major contributor to non-publication is repeated rejections. Peer review requires independent experts in the field to read a paper, make suggestions for improvement and grade it. Most journals have two anonymous reviewers, but some may have four or five. The quality of the reviews vary, and since reviewers do not see the other reviewers' comments until after their own has been submitted, their opinions may vary enormously. In addition, one may wait

several months to get a review back, make suggested changes and have it then rejected. After five or six submissions, the authors may give up.

Most likely there are other reasons for failure to publish as well, but the implications of this failure are more difficult to assess. Non-publication does not mean the outcome was negative, although that would be the likely implication, but literature searches won't turn up studies that were not reported. We don't know what we don't know. Maybe a study I want to do has been done before? Maybe I think a treatment is a great and innovative idea, not knowing that it's failed in five different studies. Or the opposite: a treatment was successful in a small trial, which would bolster your chance of getting funded for a larger trial.

We owe it to our subjects to try to publish what we find. Institutional review boards (IRBs) will ask about publications when a study officially ends, but they may not require a justification for failure to publish. They should. ❖

References

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