

# Randomized, Controlled Trials

## *Is There a Role for Them in Surgery?*

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During the 1960s and 1970s, the first randomized controlled trials in surgery were performed. Prior to this, surgical advances were largely made by physiologic experimentation in the laboratory and careful observation of series of patients. By relying on these types of studies, there was no doubt that appendectomy for acute appendicitis, surgery for toxic megacolon, and antibiotic treatment of surgical infections resulted in improved patient outcomes and survival. However, as surgery advanced, it was less obvious that treatments, such as highly selective vagotomy was superior to truncal vagotomy and pyloroplasty, a splenorenal shunt was superior to a portocaval shunt, or that lumpectomy was as effective as modified radical mastectomy. It was difficult to know for certain whether the superior outcomes that were reported were indeed due to the newer treatment or due to differences in patient selection, perioperative care and follow-up, or even individual surgical expertise. Thus came the need for randomized controlled trials which, by having a concurrent control group, random allocation of patients, standardized ancillary care and follow-up, and well defined outcomes, one could be confident that if a treatment difference were observed, it was due to the treatment itself; and one could easily make a conclusion about which treatment was more effective. The randomized controlled trial became accepted as the optimal design for determining treatment effectiveness. Indeed, randomized controlled trials have become so accepted that regulatory agencies demand evidence from clinical trials before granting approval for new drugs.

There are a number of examples where results from rigorously performed trials have had a great impact on clinical practice. These include the lumpectomy versus mastectomy trials, the carotid endarterectomy trials, and ECIC bypass trials. Unfortunately, there are also many examples of poorly performed trials where the validity of the result is questioned. These studies tend to be underpowered, single-institution trials. Trials designed to detect small differences between treatments or to show that 2 treatments are equivalent are particularly at risk for making incorrect conclusions unless they are methodologically rigorous. Additionally, it has been recognized that randomized controlled trials may be more difficult to perform in surgery. Problems cited are difficulties with standardization of the procedures, blinding, and lack of acceptance by patients and surgeons. Rapid changes in technology and trials designed to detect minimal differences and hence requiring large sample sizes have hindered the performance of surgical trials and also have limited their generalizability. There is also evidence that industry sponsorship may lead to biased results.

In this issue of *Annals*, there are 3 articles that address various aspects of surgical clinical trials. The article by Jacquier and colleagues<sup>1</sup> addresses the issue of reporting of clinical trials. These authors have been part of the CONSORT group, which has developed standards for the reporting of clinical trials. While there is no direct proof that standardized reporting leads to improved conduct of trials, intuitively it would seem that, if the standard for reporting trials is high, then the standard for performing the trial would also be improved. Nonetheless, there are some important reasons for standardizing reporting. First, it should increase the ability to combine trial results and perform meta-analyses.

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Second, and perhaps most importantly with respect to surgical trials, it allows the reader to determine not only whether the results of the trial are valid but also whether they are applicable to one's own practice. These authors reviewed a random sample of 158 articles reporting randomized controlled trials assessing surgical procedures. Unfortunately, overall the reporting of surgical trials tended to be inadequate. Among their findings, they found that the setting was reported in only 7%, volume of the provider in only 3%, and selection criteria for care providers in 41%. While this information may not be important with regard to some procedures, given that there is a definite volume outcome relationship with many surgical procedures, this information would seem extremely relevant to both evaluate the results of some trials and determine their generalizability. The CONSORT group has extended their statements beyond pharmacologic trials, and a modified statement for the reporting of surgical trials would also seem to be worthwhile. The article by Balasubramanian and colleagues<sup>2</sup> supports the recommendations made by Jacquier and colleagues. They reviewed 69 randomized controlled trials published in general surgical and general medical journals in the year 2003. The Jadad score, which is used to assess the quality of trials, was low in a large proportion of trials. Furthermore, trials reported in surgical journals tended to have lower scores compared with those published in medical journals. What is most disconcerting about these findings is that past studies<sup>3</sup> have found similar findings. This suggests that, despite more acceptance of the randomized controlled trial design to assess surgical interventions, the message is not getting out about the need for improved quality and rigorousness of trials.

Finally, the article by Shikata and colleagues<sup>4</sup> addresses the question put forward by nay sayers of evidence-based medicine and that is: do we really need to perform randomized controlled trials? Isn't evidence from a case series of 1000+ patients, or using administrative data, 100,000 patients, just as good or better than evidence from a randomized controlled trial? Shikata and colleagues performed a rather difficult study where they compared the results of meta-analyses of randomized controlled trials on topics in digestive surgery to results from observational studies. For the latter, they either found meta-analyses of

observational studies or performed a meta-analysis using accepted methodology for both the search and analysis. In total, they compared 18 topics covering a spectrum of topics from management of anal fissure to laparoscopic versus open appendectomy to extended versus limited lymph node dissection for adenocarcinoma of the stomach. They found that only one fourth of observational studies gave different results from randomized controlled trials, although between-study heterogeneity was more common in observational studies. So, what can be concluded by these findings? One interpretation would be that generally the results from observational studies correlate with those of randomized controlled trials, suggesting that randomized controlled trials are unnecessary. Another interpretation might be that the standard of randomized controlled trials is low; therefore, the risk of making erroneous conclusions is great despite the study purportedly being a randomized controlled trial. Likely, there is truth in both statements. Careful observation of series of patients may lead to correct conclusions about the effectiveness of a treatment in many instances. However, in situations where one wishes to detect a *small but clinically important difference*, a randomized controlled trial is mandatory. However, unless the trial is performed rigorously and, of course, reported with a high standard, then the results may be biased and lead to erroneous conclusions.

Thus, these 3 publications point out, not the limitations of the randomized controlled trial design in assessing surgery, but the tendency of surgical trials to be performed and reported with inadequate rigorousness. Raising the awareness of these issues is important and hopefully will lead to improvements.

## REFERENCES

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