EVIDENCE-BASED MEDICINE

Issues in the Design and Conduct of Randomized Trials in Surgery

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ABSTRACT

Although surgeons may perceive that evidence-based medicine mandates a strict adherence to randomized trials, it more accurately involves informed and effective use of all types of evidence (from meta-analysis of randomized trials to individual case series and case reports), with particular emphasis on evidence from the medical and surgical literature, in patient care. With the escalating amount of available information, surgeons must consider a shift in paradigm from traditional practice to one that involves question formulation, validity assessment of available studies and appropriate application of research evidence to individual patients. Surgical investigators must endeavor to conduct methodologically rigorous trials, whenever possible, and be explicit and transparent in their reporting of methods and data. Herein, an overview of the issues involved in the design and conduct of surgical trials with an emphasis on randomization, concealment of allocation, blinding, type I and II errors and intention to treat analysis, is provided.

SURGEONS AS EVIDENCE-BASED PRACTITIONERS

The term evidence-based medicine (EBM), coined by Dr. Gordon Guyatt, first appeared in 1990 in a document for applicants to the internal medicine residency program at McMaster University; Guyatt (1990) described EBM as an attitude of enlightened skepticism toward the application of diagnostic, therapeutic, and prognostic technologies. The practice of evidence-based medicine has evolved, and the terminology become entrenched in the vocabulary of most clinicians over the past several years. Sackett et al. (1997) further elaborated the definition to “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” The practice of EBM means integrating individual clinical expertise with the best available evidence from systematic research.

The User’s Guide to the Medical Literature, which has appeared in the Journal of the American Medical Association and subsequently as a definitive text (The Users’ Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. Guyatt G and Rennie D, eds. AMA publications, 2002), in addition to the User’s Guide to the Orthopaedic Literature in the Journal of Bone & Joint Surgery provide surgeons with the tools to critically appraise the methodological quality of individual studies and apply the evidence.

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Meta-analysis of RCTs

Single RCT

Cohort Studies

Case-Control Studies

Case Series

Expert Opinion

Figure 1. Hierarchy of Evidence. See text for details.

HIERARCHY OF RESEARCH DESIGN

In the hierarchy of research designs, randomized controlled trials (RCTs) represent the highest level of evidence (Figure 1). Randomization is the only method for controlling for known and unknown prognostic factors between two comparison groups; lack of randomization predisposes a study to potentially important imbalances in baseline characteristics between two study groups. The role of nonrandomized (observational) studies in evaluating treat-
ments is an area of continued debate: deliberate choice of the treatment for each patient implies that observed outcomes may be caused by differences among people being given the two treatments, rather than the treatments alone. Unrecognized confounding factors can interfere with attempts to correct for identified differences between groups. Nonrandomized trials have been reported to either overestimate or underestimate treatment effects when compared to results from RCTs. These considerations have supported a hierarchy of evidence, with randomized controlled trials representing the highest echelon of available evidence, followed by controlled observational studies, and finally, uncontrolled studies.

Table 1. Checklist for Assessing Quality of Reporting

<table>
<thead>
<tr>
<th>Randomization</th>
<th>1 Yes</th>
<th>2 Yes</th>
<th>1 Partly</th>
<th>0 No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the patients assigned randomly?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization adequately described?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was treatment group concealed to investigator?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description of outcome measurement adequate?</td>
<td>1 Yes</td>
<td></td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Outcome measurements objective?</td>
<td>2 Yes</td>
<td></td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Were the assessors blind to treatment?</td>
<td>1 Yes</td>
<td></td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Total/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were inclusion/exclusion criteria well defined?</td>
<td>2 Yes</td>
<td>1 Partly</td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Number of patients excluded and reason?</td>
<td>2 Yes</td>
<td>1 Partly</td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Total/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the therapy fully described for the treatment group?</td>
<td>2 Yes</td>
<td>1 Partly</td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Was the therapy fully described for the controls?</td>
<td>2 Yes</td>
<td>1 Partly</td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Total/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Was the test stated and was there a p value?</td>
<td>1 Yes</td>
<td></td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Was the statistical analysis appropriate?</td>
<td>2 Yes</td>
<td>1 Partial</td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>If the trial was negative, were confidence intervals of post hoc power calculations performed?</td>
<td>1 Yes</td>
<td></td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Sample size calculation before the study?</td>
<td>1 Yes</td>
<td></td>
<td>0 No</td>
<td></td>
</tr>
<tr>
<td>Total/4 (if positive trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total/5 (negative trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score:</td>
<td>20 points (if positive trial)</td>
<td>21 points (if negative trial)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


WHY SHOULD RANDOMIZED TRIALS BE UNDERTAKEN?

Surgeons want to know if their procedures are effective, and although clinical observations provide important insights, they may be limited by lack of objectivity. This results from difficulties in integrating observations (e.g. taking into account variations in the natural history of a disorder), placebo effect, subtle but important effects of patient selection for one procedure versus another, a patient’s desire to please, and an expectation that more aggressive interventions are better interventions, and drawing inferences from them. As a result of these limitations, surgeons commonly rely on research evidence from a range of studies, including RCTs, to guide their clinical practice.

Observational studies populate the surgical literature; in contrast, RCTs are a much rarer find. When available, however, RCTs provide many advantages over an observational study, due mainly to the process of randomization which eliminates biases in the choice of treatment, facilitates blinding, and finally, represents our only means to control for unknown prognostic factors. Although cases exist in which observational studies have been shown to have effect estimates similar to those of RCTs, there are many cases where observational studies yield disparate results to those reported in RCTs. For example, an observational study of extracranial to intracranial bypass surgery suggested a “dramatic improvement in the symptomatology of virtually all patients” undergoing the procedure. However, a subse-
quent large RCT demonstrated a 14% relative increase in the risk of fatal and nonfatal stroke in patients undergoing this procedure as compared to medical management. Given that most published interventions report moderate as opposed to large treatment effects, surgeons need to design, run and participate in RCTs, and when available, use these studies to guide clinical practice.

**ASSESSING THE VALIDITY OF SURGICAL TRIALS?**

One might propose that prior to applying the results of surgical trials to clinical practice, surgeons should be convinced that the results in these trials are valid. To provide an answer for orthopaedic surgery, a systematic review of published randomized trials in the Journal of Bone and Joint Surgery from 1988-2000 was performed. Two investigators independently conducted hand searches of the Journal of Bone and Joint Surgery over a twelve year period between 1988 and 2000. Randomized trials were identified by review of the methods sections of each of the studies. Discrepancies in identification were resolved by a consensus of the two reviewers. To further ensure that all randomized trials during the 12 year period were identified, an advanced PubMed search was performed using a journal search engine (Journal of Bone and Joint Surgery) and Year of publication. The Detsky quality index was utilized to score the methodology (Table 1). Briefly, this 14 item index contains questions which fall into the following categories: (1) randomization; (2) outcome measures; (3) eligibility criteria and reasons for patient inclusion (withdrawal/dropout); (4) interventions; and (5) statistical issues. Each of the 5 broad categories was given equal weight (4 points each). The final section on statistical analysis contains an extra question for negative or non-statistically significant trials. Thus, the total possible score for positive trial and negative trials is 20 and 21, respectively.

Of 2468 studies identified, 72 (2.9%) studies met all eligibility criteria. Two investigators each assessed study quality under blinded conditions and abstracted relevant data. A well-reported checklist was used to guide the assessment of study quality14 (Table 1). The mean transformed score for overall study quality for the seventy-two studies was 68.1 ± 1.6%. Sixty percent (43/72) of the randomized trials scored less than 75%. Drug trials had significantly greater mean quality scores than surgical trials (72.8% vs. 63.9%, P<0.05). It was encouraging to note that the sample of trials illustrated an increased interest in the conduct of randomized trials in orthopaedics over the past decade. The limitations in study design identified in the sample of trials could be addressed in future orthopaedic trials, if surgeons endeavor to (1) randomize patients with arbitrarily generated treatment schedules (computers); (2) use centralized computer randomization; (3) blind all those who can be blinded in a trial (i.e., patients, outcome assessors, data analysts, and caregivers); (4) limit the numbers of those lost to follow-up, and clearly document both losses to follow up and study withdrawals; and finally, avoid the risk of a Type II error (described below) by conducting an *a priori* sample size calculation to plan the number of patients that will be required for the study.

**IS THE TRIAL RANDOMIZED?**

While it may seem elementary to define what is meant by “randomization”, many clinicians remain unfamiliar with the rationale for random allocation of patients in a trial. Orthopaedic treatment studies attempt to determine the impact of an intervention on events such as nonunion, infection, or death - target outcomes or target events. Patient age, fracture severity, comorbid conditions, health habits, and a host of other factors typically determine the frequency with which a trial’s target outcome occurs (prognostic factors or determinants of outcome). If prognostic factors (both known and unknown) prove unbalanced between a trial’s treatment and control groups, the study’s outcome will be biased, either under- or overestimating the effect of treatment. Thus, through randomization, surgeons can achieve a balance between known and unknown prognostic factors between treatment groups.

**WAS RANDOMIZATION CONCEALED?**

Equally important is the concept of “concealment”, not to be confused with *blinding*, discussed below. Concealed randomization ensures that surgeons are unable to predict the treatment arm into which their next patient will be allocated. The most effective way to accomplish this is via remote, 24-hour telephone randomization service. Historically, treatment allocations in surgical trials have been placed in envelopes. While *technically* concealed, envelopes are easily tampered with; the following example illustrates this point.

In 1995, Hensen et al.(1996) undertook a randomized trial comparing open versus laparoscopic appendectomy. Logistically, the trial ran smoothly during the day, however, at night the attending surgeon’s presence was required for laparoscopic but not open procedures; in addition, the limited operating room availability rendered the longer laparoscopic procedure a nuisance. Reluctant to call in the consultant, and particularly reluctant with certain senior colleagues, the residents sometimes adopted a practical solution: when an eligible patient arrived, the residents ascertained which attending staff was on, in addition to the length of wait to access an operating room; then, depending on the situation, held the translucent envelopes up to the light. Once an envelope was found that dictated an open procedure, that envelope was opened. The first eligible patient in the morning would then be allocated to a laparoscopic appendectomy according to the passed-over envelope. If patients who present at night are sicker, the residents’ behavior would bias the results against the open procedure.

While an overwhelming proportion of orthopaedic surgical trials (97.5%) are described as randomized, less than half of these report concealed randomization (40.5%). In other
words, there is the possibility that investigators in the majority of trials (59.5%) could identify the treatment to which their next patient would be allocated.

Figure 2. Can Surgeons be blinded?
Photo used with permission, courtesy M. Bhandari.

WHO WAS BLINDED?

Surgical trials cannot be completely blinded due to the relative impossibility of blinding surgeons (Figure 2); Devereaux et al. (2003) identified significant ambiguity when investigators use the term “double-blinding”: in a survey of 91 internists and researchers, 17 unique definitions of “double-blinding” were obtained. Moreover, hand searches of 200 randomized trials in five high profile medical journals (New England Journal of Medicine, The Lancet, BMJ, Annals of Internal Medicine and JAMA) revealed that authors using the term “double-blind” typically did not state which groups they blinded. Possible relevant targets of blinding in a randomized trial include physicians, patients, outcome assessors, and data analysts. Surgical trials can always blind the data analyst, almost always blind the outcome assessor, occasionally blind the patient, and never blind the surgeon. In our review of orthopaedic trials, outcome assessors were blinded only 44% of the time and data analysts were never blinded. However, at least two thirds of surgical trials could have the outcome assessors, patients, or data analysts blinded.

WAS AN “INTENTION TO TREAT” ANALYSIS CONDUCTED?

Surgeons can also influence randomization by systematically omitting from the results those patients who do not receive their assigned treatment. Readers might, on first glance, agree that such patients who never actually received their assigned treatment should be excluded from the results. Some patients randomized to surgery never have the operation because they are too sick, or suffer the outcome of interest (such as stroke, deep venous thrombosis or myocardial infarction) before they get to the operating room. If investigators include such patients, who are destined to do badly, in the control arm but not in the surgical arm of a trial, even a useless surgical therapy will appear to be effective; the apparent effectiveness of surgery, however, will come not from a benefit to those who have surgery, but from the systematic exclusion of those with the poorest prognosis from the surgical group. More commonly, patients randomized to one surgical treatment arm do not receive the assigned treatment for technical reasons. Again, these patients are likely destined to have poorer outcomes. As a result, investigators exclude these patients from the analysis thereby losing the balance of prognostic factors achieved through randomization.

The principle of attributing all patients to the group to which they were randomized represents the “intention-to-treat” principle (Figure 3). This strategy preserves the value of randomization, in that both known and unknown prognostic factors will be, on average, equally distributed in the two groups, thus the observed effect will be that due solely to the treatment assigned. When reviewing a report of a randomized trial, one should look for evidence that the investigators analyzed all patients in the groups to which they were randomized.

Some suggest that an intention to treat approach is too conservative and more susceptible to type II error due to increased biologic variability. The argument is that an intention-to-treat analysis is less likely to show a positive treatment effect, especially for those studies that randomized patients who had little or no chance of benefiting from the intervention. These critics argue that an efficacy approach to an analysis is more important than an effectiveness approach.

Figure 3. Intention to Treat
Assume 15 patients are assigned to have their radial fracture supplemented with bone cement, and they have circumstances that make the injection of bone cement technically impossible. Excluding these patients and analyzing only those who actually received the treatment is so-called per protocol analysis, which leads to an imbalance in baseline prognostic factors between groups, diminishing the effect of randomization. Intention to treat analysis analyzes results for all patients allocated to a particular treatment thereby preserving the balance of prognostic factors from randomization.

R = Randomized.
ENSURING COMPREHENSIVE FOLLOW-UP

Ideally, at a trial’s conclusion, the investigators will be well-aware of the status of each patient with respect to the target outcome. Patients whose status is unknown are often referred to as being “lost to follow-up”. The greater the number of patients who are lost to follow-up, the more a study’s validity is potentially compromised; the reason for this being that patients who are lost often have different prognoses from those who are retained, and may disappear because they suffer adverse outcomes (including death) or because they are doing well and did not return to clinic for follow-up assessment.

When does loss to follow-up seriously threaten validity? The rules in this respect are misleading. Consider an hypothetical randomized trial in which 1,000 patients are entered into both treatment and control groups, and of whom 200 (20%) are lost to follow-up (100 in the treatment group and 100 in the control group). Treated patients have adverse outcomes at half the rate of the control group (200 versus 400), a reduction in relative risk of 50%. To what extent does the loss to follow-up potentially threaten our inference that treatment reduces the complication rate in half? If we assume the worst, that all treated patients lost to follow-up had the most unfortunate outcome, the number of adverse outcomes in the treatment group would be 300 (30%). If there were no adverse outcomes among the control patients who were lost to follow-up, our best estimate of the effect of treatment in reducing the risk of complications drops from 50% (1-200/400) to 25% (1-300/400). Thus, assuming the worst does change the estimate of the magnitude of the treatment effect. If assuming a worst case scenario does not change the inferences arising from study results then loss to follow-up is not a problem. If such an assumption significantly alters the results (as shown above), validity is compromised.

MINIMIZING ERRORS (ALPHA AND BETA ERRORS)

Trials of small sample size are subject to beta errors (Type II errors, mentioned above), in which the probability of concluding that no difference between treatment groups exists, when, in fact, there is a difference (Figure 4). Typically, investigators will accept a beta error rate of 20% (β=0.20), which corresponds with a study power (i.e., the ability of a study to conclude a difference when a real difference exists) of 80%. Most investigators agree that beta error rates greater than 20% (study power less than 80%) are subject to unacceptably high risks of false negative results.

In an effort to quantify the extent to which orthopaedic trauma trials were under-powered, 620 potentially relevant citations from Medline were reviewed, only 196 of which were randomized trials that focused upon adult fracture care.19 Application of the eligibility criteria to the complete manuscripts eliminated 79 studies. Thus, a total of 117 randomized trials in orthopaedic trauma were included for the power analysis, in which 19,942 patients were randomized. Moreover, study sample sizes ranged from 10 to 662 patients (mean=95 patients, standard deviation = 79). The majority of trials involved treatment of hip fractures (34.2%). The mean overall study power among the 117 trials was 24.65% (range 2%-99%), and the Type II error rate for primary outcomes was 91%.

The power of a study represents the probability of concluding that there is a difference between two treatments when one actually exists.19 Power (1-β) is simply the complement of the Type II error (β). Thus, if we accept a 20% chance of an incorrect study conclusion (β=0.20), we are also accepting that the correct conclusion will be obtained 80% of the time. Study power can be used before the start of a clinical trial to assist with sample size determination.19 The power of a statistical test, typically, is a function of the magnitude of both the treatment effect (the designated Type I error rate, α), and the sample size (N).19 When designing a trial, investigators choose the desired study power (1-β) and calculate the necessary sample size to achieve this goal.

Most surgeons are less familiar with the concept of concluding that the results of a particular study are true when they are in reality due to chance (or random sampling error); this erroneous false positive conclusion represents a Type I or α-error (Figure 4). By convention, most studies in orthopaedics adopt an α-error rate of 0.05, thus, investigators can expect a false positive error about 5% of the time. Ideally, the rate of Type I error is based on one comparison between alternative treatment groups, usually designated as the primary outcome measure. In situations where no primary outcome variable has been determined, there is a risk of conducting multiple tests of significance on multiple outcomes measures. This form of data-dredging by investigators risks spurious false positive findings. Several techniques are available to adjust for multiple comparisons, such as the Bonferroni correction.20

<table>
<thead>
<tr>
<th>TRUTH</th>
<th>DIFFERENCE</th>
<th>NO DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESULTS</td>
<td>DIFFERENCE</td>
<td>CORRECT CONCLUSION (1-β)</td>
</tr>
<tr>
<td>OF THE</td>
<td>NO DIFFERENCE</td>
<td>FALSE NEGATIVE (β error or Type II error)</td>
</tr>
</tbody>
</table>

Figure 4. Errors in Hypothesis Testing. See text for details.

Most readers are intuitively skeptical when one in a list of 20 outcomes measured by an investigator is significant (p < 0.05) between two treatment groups. This situation typically occurs when investigators are not sure what they are looking for and therefore test several hypotheses hoping that one may be true. It is therefore argued that studies generating a large number of measures of association have markedly greater probability of generating some false-
positive results due to random error than does the stated alpha level for individual comparisons.\textsuperscript{21,22}

We conducted a review of randomized trials published within the last two years in order to determine the risk of Type I errors occurring among surgical trials in which the primary outcome was not explicitly stated;\textsuperscript{20} as such, we hand-searched four orthopaedic journals, six general surgery journals, and five medical journals to identify such trials. Information on outcomes and statistical adjustment for multiple outcomes was recorded for each study, and the risk of a Type I error was calculated for each study that did not explicitly state a primary outcome measure for the main statistical comparison. A total of 159 studies met the inclusion criteria for the study: 60 from orthopaedic journals, 49 from non-orthopaedic surgical journals, and 50 from medical journals. Of those trials that did not state a primary outcome measure, the risk of Type I errors (false positive results) in orthopaedic and non-orthopaedic surgery journals (mean: 37.3\%±13.3\% and 37.6\%±10.5\%, respectively) was significantly greater than medical journals (10.1\%±1.9\%) (P<0.05).\textsuperscript{20}

**HOW PRECISE WAS THE ESTIMATE OF TREATMENT EFFECT?**

The true risk reduction can never be known; all that is known is the estimate provided by rigorous controlled trials, and the best estimate of the true treatment effect is that observed in the trial. This estimate is called a "point estimate", a term that implies that although the true value lies somewhere close to it, it is unlikely to be precisely correct; investigators give the range within which the true effect likely lies by the statistical strategy of calculating confidence intervals.\textsuperscript{4}

The 95\% confidence interval (CI) is traditionally, albeit arbitrarily, used; it is defined as that range which includes the true relative risk reduction 95\% of the time. The true RRR will seldomly be found toward the extremes of this interval, and the true RRR will lie beyond these extremes only 5\% of the time - a property of the confidence interval that relates closely to the conventional level of "statistical significance" of p < 0.05.\textsuperscript{20}

**REPORTING ALL THE FACTS: CONSOLIDATED STANDARDS OF REPORTING TRIALS (CONSORT)**

In a recent effort to improve the reporting of RCTs, a group of methodologists and journal editors developed the consolidated standard of reporting trials (CONSORT) statement which was first published in *JAMA* in 1996 (25). CONSORT provides a checklist and flow diagram to guide authors in preparing RCT reports. The CONSORT checklist consists of 21 items that pertain mainly to the methods, results and discussion of a RCT report and identify key pieces of information necessary to evaluate the internal and external validity of the report.

The true benefit of a well-conducted randomized trial in surgery can only be realized when it has been reported in a clear and comprehensive manner. It has been shown herein that most reports of randomized trials in orthopedic trauma fail to provide the information necessary to judge study validity and to effectively apply the results to patient care.\textsuperscript{26} Over 70\% of published trials met less than half of the CONSORT criteria. Even more striking is that less than 5\% of studies present a summary measure of the magnitude of effect, such as a relative risk reduction or odds ratio, and less than 10\% provide an estimate of precision, such as the confidence interval.

A well-designed, and well-reported, surgical trial should be able to answer each question asked in the CONSORT criteria. Adequate reporting of trials will only enhance readers’ understanding of what was actually accomplished, rather than what readers assume was done. Given the dramatic increase in randomized trials over the past decade, a well-reported study will enable investigators to adequately assess the validity, or believability, of published trials before deciding whether to apply their results to clinical practice. Moreover, when multiple trials on a similar topic exist, adequate reporting will enhance investigators’ abilities to decide whether statistical techniques to pool results across multiple studies (meta-analysis) might be appropriate.

**CONCLUSION**

Although surgeons, as other physicians, may perceive that evidence-based medicine mandates a strict adherence to randomized trials, it more accurately involves informed and effective use of all types of evidence (from meta-analysis of randomized trials to individual case series and case reports), with particular emphasis on the evidence from the medical and surgical literature, in patient care. With the escalating amount of available information, surgeons must consider a shift in paradigm from traditional practice to one that involves question formulation, validity assessment of available studies and appropriate application of research evidence to individual patients.

Surgical investigators must endeavor to conduct methodologically rigorous trials, whenever possible, and be explicit and transparent in their reporting of methods and data. Currently, the field of surgery is experiencing an exciting period of growth and innovation, fueled largely by a renewed enthusiasm for conducting high quality trials. The limitations of the surgical trials in the recent past will be effortlessly overcome by future investigators who endeavor to answer clinically important questions while respecting the need for scientific methodology in their quest for answers.

**AUTHOR BIOGRAPHIES**

Dr. Bhandari and Dr. Devereaux are both from the Department of Clinical Epidemiology and Biostatistics, McMaster University in Hamilton, Ontario. Dr. Bhandari’s salary was provided, in part, by a Detweiler Fellowship Award, Royal College of Physicians and Surgeons of Canada. Dr. Devereaux was funded by a Canadian Institutes of Health Research/Heart and Stroke Foundation scholarship.
REFERENCES