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# *Reporting the Results of a Study That Did Not Go According to Plan*

IN this issue of ANESTHESIOLOGY, Dr. Subramaniam *et al.*[1] report the results of their interesting trial titled "Continuous Perioperative Insulin Infusion Decreases Major Cardiovascular Events in Patients Undergoing Vascular Surgery: A Prospective, Randomized Trial." In this report, the potential benefits in reducing major adverse cardiac events by using a continuous insulin infusion *versus* a standard intermittent insulin bolus was evaluated in patients undergoing peripheral vascular bypass surgery, abdominal aortic aneurysm surgery, or below- or above-knee amputation. In respect to its goals and research design, this study is similar to other studies published by the Journal. However, this study is remarkable in that its conduct did not go according to the authors' original plan, for despite a lengthy enrollment period, the original recruitment goals were not achieved.

That a reader can discern that the actual enrollment did not match the target enrollment is made possible by the laudable reporting efforts of these authors. These efforts can be seen in several important ways. First, the trial was registered on the National Library of Medicine clinical trials database. Because of their efforts, an interested reader can refer to ClinicalTrials.gov (Identifier NCT00328094) to examine several elements of the elegant pretrial planning done by Subramaniam *et al.* Registering clinical trials before their initiation has favorably become a more common practice, and preregistering a clinical trial is highly recommended for those trials that will be submitted to ANESTHESIOLOGY.

A second commendable reporting element of the article is the clearly presented statistical power analysis that fully discloses the large number of patients thought to be needed for an adequate balance between type I and type II errors. In this case, the authors were forthcoming in respect to the fact that they had successfully recruited only 54% (242 of 452) of their interim sample (which was itself only a fraction of the total proposed sample size). This disclosure stands in stark contrast to a less desirable reporting practice, sometimes used, in that the authors avoided the temptation of adjusting their calculations to report a *post hoc* power calculation (often called *observed power*). Such *post hoc* power calculations rely on dubious logic and should be avoided[2]; the practice of Subramaniam *et al.* was exemplary in doing so.

The ultimate effort made in fully reporting their trial, however, was achieved when these authors made their raw data available to this author. There is simply no greater disclosure than making data publicly available for further scrutiny, and in this regard Subramaniam *et al.* have demonstrated a commitment to fully disseminating their work. Because of their laudable reporting efforts, their trial can be thoroughly evaluated, and in so doing, several interesting methodologic issues can be raised.

Interpreting a clinical trial can be challenging under the best of circumstances, but in the current case, the well-reported recruiting challenges faced by the authors makes interpreting their trial even more daunting. For example, to what level of statistical significance should this trial be held? It is prudent to adjust interim analyses for the multiple comparisons that they usually represent (*e.g.*, using group sequential methods), but in this case the timing of the interim analysis was unexpected (and final) and any adjustment certainly effects the already tenuous balance of possible inferential errors. The authors have chosen to leave their significance judgments unadjusted, and this is clearly stated to an interested reader.

Further, although the randomization procedures used in the trial result in an expectation that the treatment groups will be equivalent in all conceivable dimensions, randomization does not guarantee that groups will be equivalent. Perhaps somewhat because of a lower-than-intended sample size (and bad luck), there is evidence that the continuous insulin infusion and intermittent insulin bolus groups may have differed meaningfully in several respects. This can be seen in table 1, where the continuous infusion group (67 ± 10 yr old) was younger than the intermittent bolus group (71 ± 11 yr) ($P$ = 0.02), with subtly (though not statistically) different disease characteristics. Because the authors allowed their data to be further analyzed, a *post hoc* adjustment was able to be calculated using the patient characteristics in tables 1 and 2.

Using propensity score methods not proposed in the original analytical plan, the probability that a patient would be randomized to the continuous insulin infusion group could be calculated. The resulting probability was then used as a covariate with group status to better isolate the unique effect of the treatment condition on major adverse cardiac events (*i.e.*, controlling for the measured imbalances between the groups). The results were interesting in that group assignment could be suc-

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cessfully predicted using the patient characteristics (implying a subtle randomization imbalance), with a C index of 0.66 ($P < 0.001$). When these imbalances were accounted for, the beneficial effect size of the continuous infusion intervention was only somewhat attenuated from the reported odds ratio of 0.29 (95% confidence interval, 0.10–0.83) to an adjusted odds ratio of 0.37 (95% confidence interval, 0.11–1.20). It is of great note that the *post hoc* nature of this analysis, combined with the 6.8% of missing data in one or more of the considered covariates, reduces the value of this approach (*i.e.*, readers should focus on the effect sizes rather than statistical significance judgments), but is nevertheless an interesting exercise made possible by the authors' openness.

The work of Dr. Subramaniam *et al.* is exceptional in its candid reporting of the tribulations encountered when conducting this trial. The resulting report will be interesting to our readers, and perhaps controversial to some, for the study presents several interpretation difficulties that result when a trial does not proceed according to plan. Indeed, readers will have to balance their usual considerations with the notion that the conducted study consisted of far fewer participants than thought necessary to fully address the research question. However, because of the very forthcoming disclosures of the authors' original intentions, the article can be thoroughly evaluated with a focus on the valuable data. Deviations in research plans will certainly be encountered by future researchers, and severe deviations will present insurmountable problems in most circumstances. However, Dr. Subramaniam *et al.* have set a great precedence for honorable conduct in their reporting of their study.

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