Interpreting the results of small trials

The randomized controlled trial of preventive home nursing visits for frail elderly people reported by Dawn Dalby and colleagues[1] raised several key issues regarding the design, interpretation and reporting of trials testing the efficacy of interventions in the elderly population.

With the testing of complicated interventions and the chronic shortage of resources in this area, clinical trials may be conducted with inadequate numbers of patients to reliably demonstrate positive effects. Dalby and colleagues enrolled 142 patients, giving the trial a prestudy power of 50%. Inadequate sample size will likely result in findings that have high statistical variability (low precision). Consequently, the 95% confidence intervals around the point estimates of the primary outcome for the control and intervention groups will be imprecise and are likely to overlap and result in statistically insignificant results. As the number of patients in the trial increases, the 95% confidence intervals become more precise with less overlap (if there is a positive treatment effect) and the results may become statistically significant. For these reasons, the study by Dalby and colleagues does not demonstrate that nursing visits are ineffective. In fact, no firm conclusions can be drawn from its results.

The authors cited their lack of adequate power as a possible explanation for their lack of statistically significant results. From a methodological and theoretical perspective, Goodman and Berlin[2] have argued against the use of post hoc power to explain negative trials. Once a trial is completed, they argue, the use of confidence intervals, rather the post hoc power, is the proper way to interpret trials with results that do not reach statistical significance.

The danger inherent in conducting small, inadequately powered trials is that potentially effective interventions will be judged as ineffective simply because of the inability to detect statistically significant and clinically important benefits. Consequently, caution must be exercised when embarking on small trials and interpreting the results.

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Does the urea breath test tell us what we need to know?

The Feb. 8th issue of *CMAJ* had an interesting article by Carlo Fallone and colleagues concerning the urea breath test for *Helicobacter pylori* infection,[1] interesting not only for what the test will detect but for what tests it may push to the sidelines. There is certainly talk of the urea breath test lessening the need for gastroscopy, something that is welcomed as a means to cut costs and decrease patient discomfort and morbidity. But it does mean fewer chances to pick up premalignant lesions or early frank carcinoma. Protocols surrounding the urea test recommend scoping only when alarm signs appear, but clinical signs and symptoms are often the herald of higher stage disease. As a pathologist, all too often I see carcinoma cases from all parts of the GI tract presenting on the cutting table as advanced, node-positive disease.

It seems to me that at present we are not scanning, scoping or poking enough to detect the early, treatable malignancies. If our present diagnostic modalities are too expensive or risky for this more rigorous hunting, then surely more resources must be devoted to some sort of revolution in diagnostic imaging or direct visualization technology. Tasting and smelling for disease are no substitute for looking.

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[The authors respond:]

The point Julius Wroblewski has brought up is a good one. We would certainly like to detect lesions early, rather than at a point when they are no longer treatable. However, we

must recognize that a definitive diagnosis is not necessarily required for adequate treatment and that serious diagnoses are rare in patients who present with gastrointestinal symptoms. We would also like to point out that the context for using the urea breath test in the "test and treat" approach for adult patients with dyspepsia is primary care.

Dyspepsia is extremely common, affecting 7% of patients presenting to a general practitioner's office, and it occurs with moderate severity in approximately 29% of Canadians.[1,2] It is obviously not feasible nor necessary for close to 30% of the Canadian population to undergo endoscopy. We should try to perform this procedure in the patients who would most benefit. In fact, if all patients with dyspepsia who present to a primary care physician were to have a gastroscopic examination the waiting list for this procedure would become enormous, potentially resulting in a delay in diagnosis for those patients with symptoms suggesting more significant pathology. Hence, we have to find ways to determine which patients may have significant pathology. Alarm features (vomiting, bleeding, anemia, abdominal mass, dysphagia and weight loss) and advanced age suggest a higher risk of pathology. Performing endoscopy on these individuals and simply performing a test for and treating *Helicobacter pylori* infection in those that do not have these risk factors may reduce the waiting lists for endoscopy and hence potentially increase the detection of early lesions.

Furthermore, once the urea breath test becomes more widely available, testing for and treating *H. pylori* infection would not result in a significant delay for further investigation if the patient were not to respond to treatment. A urea breath test result can be faxed within 24–48 hours and the course of treatment is only 1 week. In addition, a Canadian randomized controlled trial recently showed significant improvement in symptoms with the "test and treat" approach compared with placebo[3] and another study found this strategy to be significantly more cost-effective, without detrimental outcome, than a strategy using endoscopy first.[4]

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Distorted spending priorities in Canada

I was intrigued by a recent news item in *CMAJ* entitled "Detecting hep C for $1.5 million a case."[1] The title implies concern about the cost of a new program to identify donors infected with hepatitis C by nucleic acid amplification testing. I am concerned about any inference that the decision of the Canadian Blood Services to implement this program was cost-ineffective. I believe it would have been morally and fiscally irresponsible to decide otherwise.

If screening for hepatitis C were not introduced, all of the carriers detected would be denied vital personal information and possible treatment. Some could donate again and infect additional blood recipients. People who received the contaminated, unscreened blood products could potentially infect others. The lives of up to 13 Canadians every year could be ruined, with far-reaching effects on their family, friends and associates. The treatment, lost productivity, early disability and death of these 13 people would actually prove to be even more costly than the screening program.

Rather than focusing solely on the short-term cost-effectiveness of our underfunded health care system, let's look at the Canadian Blood Services' decision relative to the distorted priorities of our federal government. Consider, for example, the $30 million aid package recently offered to professional hockey franchises, the $3 million Ottawa spends on fireworks every Canada Day, the $2.4 billion of the $3 billion federal job creation program that our Auditor General says was wasted and the $5 billion spent on fruitless, politically motivated attempts to bail out defunct and poorly managed industries.[2]