Time to put the Canadian Institute for Health Research on trial

David L. Sackett, MD

The Canadian Institute for Health Research (which replaces the Medical Research Council and certain other agencies) is charged with the task of reorganizing health research to better serve the health of Canadians. I suggest that it will fail to do so unless it dramatically increases support for randomised clinical trials (RCTs) and those who design and conduct them. Here is some evidence on these issues, and the conclusions to which that evidence has led me.

Thirty years ago Canadians with a history of transient ischemic attack who participated in an RCT conducted in 26 centres stretching from St. John's to Victoria were the first patients in the world to reliably avoid stroke and death with aspirin therapy costing pennies a day.[1] A decade later, Montrealers with unstable angina pectoris who took part in an RCT of aspirin and heparin therapy were the first in the world to reliably avoid myocardial infarction and death with this simple regimen.[2] More recently, Canadian women with post-term pregnancies who participated in a Canadian multicentre RCT of induction (v. monitoring) were the first in the world to reliably avoid cesarean section for this condition.[3] Still more recently, Canadian newborns with severe respiratory distress enrolled in a multicentre Canadian RCT of nitric oxide were the first in the world to reliably avoid risky extracorporeal membrane oxygenation with this far less expensive regimen.[4] Other landmark Canadian trials have shown us how to prevent gastrointestinal bleeding in patients requiring mechanical ventilation.[5] and demonstrated that a less expensive, conservative transfusion policy was as good or better than a more expensive, liberal policy in saving the lives of critically ill patients.[6] These facts lead to my first conclusion: Canadian lives have been and are being saved by Canadian RCTs.

A recent report in *Nature* documented the impact (with respect to quality, not quantity) of research carried out in various categories by researchers in several countries. Under the heading of "clinical medicine," which includes RCTs, Canada is second only to the US in its international impact — ahead of the England, France, Germany, Australia and Japan.[7] Canada leads the world in research in clinical dentistry and is above average in pharmacology and pharmacy, but is progressively below average in biochemistry, biological sciences, preclinical studies and anatomy. This brings me to a second conclusion: Canadian trialists, though small in number, are world-class scientists.

Millions of dollars' worth of bench research that appeared to show a reduction in atherosclerosis-related oxidative stress with vitamin E therapy was recently tested in an RCT that asked the vital question: Does the vitamin E therapy endorsed by this research really help prevent heart disease? The answer was a resounding "No."[8] Similarly, the monoclonal antibodies that perform so well at the bench have been shown not to benefit critically ill infected patients.[9] Finally, the CAST trial[10] has shown that advice from experts about how we ought to treat our patients may raise, rather than lower, mortality (more Americans were killed by encainide and flecainide than by the Viet Cong[11]). None of these treatments was discovered to be useless or harmful in non-RCT studies. Hence, conclusion 3: RCTs limit harm to Canadians from useless or harmful treatments. (By contrast, a full understanding of the mechanism of action of a compound is not a prerequisite for testing that compound in an RCT; indeed, RCT results often nurture basic research by generating exciting hypotheses to be tested at the bench.)

The actions of reverse transcriptase are the same in Turin, Tokyo, Toledo or Toronto, and the same holds for the vast majority of bench research techniques and conclusions. By sharp contrast, and despite the worldwide applicability of many explanatory RCTs testing the efficacy of drugs, the results of a significant proportion of pragmatic RCTs are country specific and not transferable. Whenever there are regional variations that affect the impact of the experimental manoeuvre, whether they be differences between patients (e.g., with respect to compliance, values or treatment preferences) or between practitioners (e.g., who provides the treatment, with how much competency, with what concurrent interventions and at what expense), the results of an RCT may be impossible to extrapolate from one country to another, especially given the increasing emphasis on the need to integrate locally-relevant economic analyses into RCTs. Conclusion 4: Whereas the results of bench research can be imported into Canada from abroad, the results of RCTs often cannot.

I am informed that the Medical Research Council devotes less than 3% of its budget to RCTs, in glaring con-

© 1999 Canadian Medical Association or its licensors

trast to its counterpart in the US, the National Institutes of Health, which devotes 12%. (Dr. Salim Yusuf, former Acting Chief of the Clinical Trials Branch of the National Heart, Lung and Blood Institute of the US National Institutes of health: personal communication; 1999). On a per capita basis the US spends 100 times as much as Canada on RCTs. Furthermore, although the Medical Research Council has never cancelled a bench research competition, it did cancel one for RCTs. (After vigorous protests, it was later treated as "postponed.") Finally, in its last 2 competitions the Medical Research Council, protecting its preference for reductionist bench research, has turned down 40% of the RCT applications judged scientifically sound by its own committee. If funded, these RCTs would now be testing treatments to reduce the suffering of patients with chronic lung disease, peripheral vascular disease and hip fracture, and would be testing a new strategy for reducing the death rate of premature babies. Conclusion 5: The opportunity cost of the refusal of the Medical Research Council to fund scientifically sound RCTs includes the disability and untimely death of Canadians.

Parenthetically, using companies that manufacture pharmaceuticals or medical devices as the primary source of financial support for RCTs is thrice wrong. First, by definition it allows private profit, rather than public health, to determine the research agenda in the face of ample evidence that most pharmaceutically-funded research ignores the young and the poor and seeks approval of "me-too" drugs.[10] Ironically, as this editorial was being written, 5 international drug companies pleaded guilty and paid $88 million in fines for fixing the prices of a number of drugs in Canada, including the one found useless in the RCT of vitamin E therapy.[8,11] Second, pharmaceutical firms almost never fund RCTs of surgical operations, head-to-head comparisons of competing drugs, or strategies for maintaining clinical competency (e.g., reducing overprescribing). Finally, the tax relief given to this for-profit research takes millions of dollars of public money away from better uses such as the support of patient-oriented, investigator-led, peer-reviewed research. Conclusion 6: It is irrational to give pharmaceutical firms huge "for-profit" research tax write-offs when those funds could better be spent supporting investigator- and patient-initiated RCTs that promote the health of Canadians.

Will the Canadian Institute for Health Research, top-heavy with the attitudes and senior members of the MRC, redress this imbalance? I doubt it.

Surely it is time for Canadians — both patients and those who care for them — to place the Institute on trial and demand to know when it is going to raise the support of Canadian RCTs to at least 12% of its total budget for grants and awards, coupled with parallel increases in support for young investigators and for RCT centres[12] whose efforts are of direct and immediate benefit to the health of Canadians.

Dr. Sackett is Former Director of the Centre for Evidence-Based Medicine at Oxford and is Professor Emeritus at Oxford University, McMaster University and the University of Ottawa.

Competing interests: None declared.

References

1. Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978;299:53-9.
2. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
3. Hannah ME, Hannah WJ, Hellmann J, Hewson S, Milner R, Willan A, for the Canadian Multicenter Post-term Pregnancy Trial Group. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. A randomized controlled trial. *N Engl J Med* 1992;326:1587-92.
4. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med* 1997;336(9):597-604.
5. Cook D, Guyatt G, Marshall J, Lesea D, Fuller H, Hall R, et al, for the Canadian Critical Care Trials Group. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998;388:791-7.
6. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al, and the Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340(6):409-17.
7. Adams J. Benchmarking international research. *Nature* 1998;396:815-8.
8. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardiaco. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447-55.
9. McCloskey RV, Straube RC Sanders C, Smith SM, Smith CR, for the CHESS Trial Study Group. Treatment of septic shock with human monoclonal antibody HA-1A: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1994;121(1):1-5.
10. Cardiac Arrythmia Suppression Trial (CAST) investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321(6):406-12.
11. Moore T. *Deadly medicine*. New York: Simon & Schuster; 1995.
12. Balms for the poor. *Economist* 1999;352(8132[Aug 14-20]):63-5.
13. Demont P. Drug companies fined $88M for price-fixing. *Natl Post* [Toronto] 1999 Sept 23;Sect A:5.
14. Gluud C, Sorensen TIA. Organisation of a clinical trial unit: a proposal. *Fundam Clin Pharmacol* 1998;12:298-305.

Correspondence to: *Dr. D.L. Sackett, Trout Research and Education Centre at Irish Lake, R.R. 1, Markdale ON N0C 1H0; sackett@bmts.com*