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Why don't we initiate more large simple randomized controlled trials?

James M. Wright

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When new drugs come to market and are prescribed by physicians to real-world patients, their costs and effectiveness may vary considerably from those measured in carefully controlled randomized controlled trials (RCTs). Physicians, patients and provincial governments that fund pharmacare programs must base their prescribing and funding (coverage) decisions on the very limited information available from RCTs. In the real world, such drugs are prescribed not only for the relatively healthy and usually younger patients who enter RCTs, but also for patients with comorbidities and for older patients. As well, serious but less common side effects might not be detected in clinical trials; if any are detected, their frequency may not be precisely determined. Thus the real-world cost-effectiveness may not mirror that shown in RCTs.

In this issue, Laupacis and colleagues (see page 1167),¹ build on previous work² in proposing a model for drug evaluation in Canada that might reduce the uncertainty. A good example of this type of problem is the recent introduction of a new class of drugs for the treatment of arthritis, the COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs). Laupacis and colleagues² have previously documented the rapid uptake of COX-2 selective NSAIDs in Ontario and the cost of this to the Ontario Drug Benefit Program. One of the surprising findings is that, despite approval for payment for these NSAIDs as limited-use products, the availability of the COX-2 selective NSAIDs not

only led to a shift away from nonselective NSAIDs, but also created a large new cohort of anti-inflammatory drug users.

The widespread use of COX-2 selective NSAIDs has created a familiar dilemma. What do we do when the evidence for a widely prescribed class of drugs is insufficient to know whether the benefits outweigh the harms as compared to those of the standard therapy? The concern about harm in this example comes from the results of 2 large RCTs^{3,4} designed to look at the incidence of complicated peptic ulcers in patients with arthritis, treated either with COX-2 selective NSAIDs or with nonselective NSAIDs. For this serious adverse-event outcome, rofecoxib showed a significant benefit³ and celecoxib showed a trend toward a benefit.^{4,5} However, a more comprehensive analysis of these trials suggests that, rather than being safer than nonselective NSAIDs, rofecoxib and celecoxib are more harmful; the number of patients with at least one serious adverse event of any kind was higher with the COX-2 selective NSAIDs than with the nonselective NSAIDs.^{6,7}

The authors⁸ acknowledge that the controversy is unresolved and propose a model for drug evaluation in Canada that might prevent such dilemmas. The component of their model that I believe has the most chance of providing a solution is the mandated conduct of a large simple RCT after marketing.^{1,9}

In this particular example the optimal opportunity for initiating the RCT would have been immediately after the COX-2 selective drugs were first marketed in Canada. At

that time the Therapeutics Products Directorate could have identified that these drugs had unproven risk-benefit evaluations and, in cooperation with the provinces, mandated the conduct of a large simple RCT. If that had happened, we would now most likely have the answer.

If such a trial were done, it could ask this simple question: "Do COX-2 selective NSAIDs cause fewer deaths and nonelective hospitalizations than nonselective NSAIDs during 1 year of therapy?"⁹ In view of the controversy and unknowns about this subclass of drugs, knowing this composite safety outcome is essential, as opposed to, for example, knowing simply the gastrointestinal safety outcomes. Randomization could be done by telephone and could document a limited amount of baseline information, as was done in the ALLHAT study.¹⁰ Monitoring and analysis could be done by an independent committee and use intention-to-treat principles. Costs would be low because randomization is inexpensive, and death and hospitalization data are already captured. The size of the RCT required to detect a 15% difference would be 10 000 to 20 000 patients.⁹ The utilization data for Ontario seniors suggests that these numbers could likely be achieved in Ontario alone.¹

There are 3 possible findings of such a trial: (1) COX-2 selective inhibitors cause more nonelective hospitalizations and deaths than nonselective NSAIDs; (2) COX-2 selective inhibitors cause fewer nonelective hospitalizations and deaths than nonselective NSAIDs; or (3) no significant difference between the 2 drug subclasses for these outcome is detected. Any of these 3 findings would substantially resolve the present controversy and provide the information that physicians and policy-makers need to make rational prescribing and funding decisions.

The prescription of COX-2 selective inhibitors for a large new cohort of seniors in Ontario who have not recently received an NSAID¹ suggests that a large simple RCT could also test the common belief that acetaminophen is safer than NSAIDs. People with chronic arthritis who have not received an NSAID for the previous year could ethically be randomly assigned to 1 of 3 arms of the trial: acetaminophen, a COX-2 selective NSAID or a nonselective NSAID.

The fact that the best opportunity to conduct these trials has passed should not deter clinical investigators and regulators from initiating a trial as soon as possible. If it is not done we risk repeating the mistake demonstrated by the Women's Health Initiative RCT.¹¹ Likewise, if the large simple antihypertensive trial (ALLHAT)¹⁰ had been initiated and completed earlier, perhaps the drain on scarce health care resources caused by the decline in the use of first-line thiazides for hypertension could have been avoided.

I look forward to the day when Canada establishes an infrastructure to support large simple RCTs. When that happens many new drugs could be given a notice of compliance with conditions. The required conditions would be the completion of a large simple RCT comparing the new drug with the best-established effective therapy. I envisage that most Canadian patients receiving the new drug would be included in such an RCT. With such a mechanism in place, clinicians and patients could have the satisfaction of knowing that new information about the benefits and harms of the new drug would soon be available.

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