vertising of prescription drugs. These changes are badly needed and would go a long way toward preventing similar future harm. Canada is of course not the only country in which drug regulation needs a radical overhaul: regulatory agencies in Europe and the United States also fail to adequately consider the public interest.[4]

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[Dr. Garland responds:]

Mark Voysey has summarized the challenge facing physicians who treat depressed children. Two additional and more detailed critiques of the published and unpublished evidence[1,2] are now available, and these reports underscore the fact that our evidence base has been distorted by selective publication and interpretation of data. However, as Voysey points out, a practical approach is required, and this may include judicious prescription of medication in individual cases, particularly in the presence of anxiety disorders, with appropriate monitoring.[3] However, evidence-based psychological treatments such as cognitive behavioural therapy and interpersonal therapy[4] need to be made more available.

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The best type of trial

James Wright[1] asks why we do not do more large simple randomized controlled trials (RCTs) in Canada. To support his point, Wright alludes to the differing results in observational studies on hormone replacement therapy and the results obtained in the Women's Health Initiative (WHI) clinical trial.[2] However, as pointed out in a recent article by Garbe and Suissa,[3] there were some serious methodological concerns with the WHI trial. In particular, the high rate of unblinding of gynecologists in the study introduced the potential for detection bias.

Clinical trials are important and have their place. However, we should not neglect the power of observational studies in determining drug outcomes. There is longstanding evidence that the results of careful observational research are very close to those obtained in clinical trials.[4] The power of a clinical trial is its ability to control for unknown confounders through randomization. But randomization is not a guarantee — it merely means that on average the unknown confounders will be balanced.

In an era of limited resources for health research, we must realize that not every study can be a clinical trial and that observational studies can provide accurate answers to questions much faster than RCTs. This can be important for conditions that require lengthy periods of follow-up. The key is to ask the right question and then use the appropriate type of study to answer it.

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James Wright[1] is mistaken in thinking that postmarketing conduct of a large simple RCT is the best way to resolve controversies associated with the introduction of new drugs. Such trials add more to the controversy than they resolve, as was the case with the ALLHAT study.[2]

Wright has missed fundamental deficiencies in megatrial methodology. The real-world RCT that he advocates would recruit a large and heterogeneous population, with few inclusion and exclusion criteria. The required simplicity is typically accomplished by not collecting clinical data that would allow analysis of important subgroups. The only outcome variable that can be better assessed in these heterogeneous conditions is eventual mortality, which may be low in some patient groups and of limited relevance in others.

Prior knowledge from both RCT

and observational studies is required to select appropriate subjects and to create a protocol that controls for confounding variables. Megatrials should therefore be conducted only at the end of a long process of therapeutic development.[3] Paradoxically, megatrials may be superfluous once a significant treatment effect is evident from meta-analysis of existing trials,[4] as indicated by studies demonstrating agreement of statistical conclusions among megatrials.[5]

Observational studies can recruit a broader range of patients and are often cheaper, quicker and less difficult to carry out than RCTs. Moreover, high-quality observational studies and RCTs usually produce similar results.[6] Hence, observational studies may be preferable for identifying rare side effects and when RCTs would be impractical.[7]

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[The author responds:]

Chris Delaney and Michal Pijak and associates argue that observational studies are preferable to the large simple RCTs recommended in my commentary[1] because they sometimes yield the same results as RCTs. That is true, but the problem is that often they do not. Therefore, without confirmatory RCT data, we risk making serious mistakes if we advise or prescribe solely on the basis of observational studies. Because of the Women's Health Initiative RCT, we can advise women that the harms of long-term estrogen–progesterone combination therapy outweigh the benefits,[2] but on the basis of observational data, physicians were advising the opposite. The details of this debate are well covered in 2 recent articles.[3,4]

I agree with Delaney that the key to research is to ask the right question, find out if the question has been answered and, if not, use the appropriate study to answer it. Because of the inability to draw conclusions from observational data alone, the appropriate study is almost always an RCT. Unfortunately, this type of study is too infrequently conducted. The ALLHAT trial[5] is an exception to this general pattern. As a result of that trial, we can advise patients, with a high degree of certainty, that chlorthalidone, a thiazide-like diuretic, is preferable to amlodipine, a calcium-channel blocker (CCB), as first-line therapy for hypertension; for every 61 patients treated, using a thiazide rather than a CCB prevents one death or hospital admission for heart failure. This finding would not have been discovered from observational data.

Barton,[6] in the editorial cited by Pijak and associates, stated that "If high quality randomized trials exist for a clinical question then they trump any number of observational studies." We need to appreciate that well-designed, large, simple RCTs are not that difficult or expensive to conduct and are highly preferable to widespread empiri-