Randomised controlled trials in general practice

Are preferable to observational studies

EDITOR,—Mike Pringle and Richard Churchill rightly emphasise that a randomised controlled trial should be used in general practice only when it is the appropriate method for the research question that is being posed.¹ However, they refer to the potential biases in randomised controlled trials without paying due regard to the advantages of such trials over observational methods.

Observational studies do not provide definitive answers to questions about therapeutic effectiveness.² This is because bias and confounding are much harder to control for with observational methods than with experimental designs. Without randomisation, decisions about treatment will depend on patients' characteristics, and thus treatment and control groups will differ in ways other than the treatment they receive. Differences in outcome may then be due to these other factors rather than to the treatment.² Even in experimental studies the adequacy of randomisation has an important bearing on the assessment of a treatment effect.³ For this reason, when appropriate and when possible, randomised controlled trials should be performed in preference to observational studies.

Failure to recruit all eligible patients in a randomised controlled trial does not imperil that trial's subsequent generalisability as much as the authors suggest. Once effectiveness has been established by a randomised controlled trial the application of the results to individual patients is not limited by the eligibility criteria of that trial.⁴ Extrapolation to individual patients relies on the assessment of their likely risk. Each patient's risk and benefit are calculated from large cohort studies, from which the outcome of multiple risks in a population can be seen and applied. Guidelines on the treatment of hypertension have taken this approach, basing the assessment of individual risk and benefit on data from the Framingham study and the results of randomised controlled trials.⁵

There is a paucity of evidence from randomised controlled trials and systematic reviews of such trials in general practice; by contrast, an entire database is devoted to such trials in pregnancy and childbirth. Without randomised controlled trials in general practice we will not be able to distinguish harmful from beneficial treatment. Such trials should continue to be performed in general practice for the same reason as in any other clinical setting—that is, when doubt exists about the efficacy of a treatment.

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Internal validity of trials is more important than generalisability

EDITOR,—Mike Pringle and Richard Churchill raise important issues relating to the practicalities of performing and interpreting the results of randomised controlled trials in general practice.¹ They suggest that observational studies are acceptable when a randomised study is too difficult to

perform or when its results will be clinically meaningless, reminding us of the complementary (rather than competing) roles that experimental and observational methods should have in the evaluation of health care interventions.² We are concerned, however, that they overstate the problems of conducting randomised controlled trials in general practice. By so doing they may discourage practitioners from participating in research that can provide important evidence that can be used to inform clinical decision making.

Firstly, many of the methodological problems that the authors raise apply to randomised controlled trials in general, not just to those in primary care settings. Patients should never be treated as experimental animals. It is important in any trial that patients' autonomy is respected, that patients are not coerced into taking part, that confidentiality is maintained, and that the potential risks and benefits of the treatments are explained. It is one of the shortcomings of modern medicine that more attention is paid to obtaining informed consent in most randomised controlled trials than in everyday clinical practice.³

Secondly, we disagree with the assertion that failure to recruit consecutive patients (which is bound to occur if genuine informed consent is obtained) introduces selection bias. Selection bias occurs when allocation to treatment is influenced by factors that might affect outcome. This is an inevitable consequence of non-random allocation of treatment, as occurs in any observational design; it is eliminated by randomisation. Pringle and Churchill raise the issue of generalisability. This is always a potential problem with randomised controlled trials but is more so when studies are performed in secondary care and then results are applied to primary care.⁴ The solution to problems such as this is to perform more trials in primary care settings, not fewer.

It is a basic principle of epidemiology that the internal validity of a study is always more important than its generalisability, since it is never appropriate to generalise an invalid finding.⁵ This principle should not be forgotten when the practical difficulties of carrying out randomised trials in primary care settings are being considered.

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General practice research framework carries out such trials

EDITOR,—Allowing that "randomised controlled trials are not impossible to perform in general practice," Mike Pringle and Richard Churchill ask if they are really the gold standard long advocated by the *BMJ* or fool's gold.¹ They conclude that "it would be wrong to stick blindly to a gold standard which is likely to produce the wrong findings—methodologically pure but clinically meaningless."

They seem to have overlooked the Medical Research Council's general practice research framework.² This now includes almost a tenth of the British population; in addition, about

400 general practitioners attend its annual meetings to discuss the opportunities presented by high quality networked randomised controlled trials as well as the authors' long list of problems and obstacles, which all of us know only too well. Since it was set up in 1977 for the Medical Research Council's study of treatment for mild hypertension³ the general practice research framework has published studies on many clinical topics, involving many millions of person years of observation. All were methodologically sound, and I cannot recall one that was clinically meaningless.

Instead of giving up before we try, why not pay some attention to ways in which these obstacles to good work have been overcome?

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Neonatal circumcision does not protect against penile cancer

EDITOR,—Although Morten Frisch and colleagues have made a valuable contribution to the study of penile cancer, they mistakenly repeat the myth that neonatal circumcision renders the subject immune to penile cancer.¹ The reference given for this statement is not an epidemiological study but an opinion article by the American circumciser Abraham L Wolbarst in 1932.² Wolbarst invented this myth and was directly responsible for its proliferation; he based it on unverifiable anecdotes, ethnocentric stereotypes, a faulty understanding of human anatomy and physiology, a misunderstanding of the distinction between association and cause, and an unbridled missionary zeal. It was not based on valid scientific and epidemiological research.

All subsequent repetitions of this myth are traceable to Wolbarst's article, though Wolbarst himself advocated universal neonatal circumcision principally as a preventive for epilepsy, paralysis, and masturbation. Circumcisionists such as Wolbarst do not seem to have promoted the myth because they have a genuine interest in reducing the rate of penile cancer; they have used it instead as a scare tactic to increase the rate of neonatal circumcision. It is surprising that sober scientists such as Frisch and colleagues could have relied on such a reference in their research.

Epidemiological studies disproved Wolbarst's myth long ago. In North America the rate of penile cancer has been estimated to be 1 in 100 000³—somewhat higher than the rate of 0.82 per 100 000 found by Frisch and colleagues. Maden *et al* reported penile cancer among a fifth of elderly patients from rural areas who had been circumcised neonatally and had been born at a time when the rate of neonatal circumcision was about 20% in rural populations.⁴ Their study also shows that the rate of penile cancer among men circumcised neonatally has risen in the United States relative to the rise in the rate of neonatal circumcision.

Science must look beyond normal human anatomy to discover the true risk factors for penile cancer. Current investigations into risks posed by infection with human papillomavirus (circumcised males have been shown to have an increased risk of such infection) and use of tobacco have been instructive.⁵ Frisch and colleagues have otherwise injected a welcome note of scientific rationalism into the debate over circumcision, which, despite the active participation of medical staff, is in