

Letter from the editor

Evidence gets personal

Report from a James Lind Alliance/Lancet conference: “How can clinical trialists better meet the needs of clinicians and patients?”

When Paul Glasziou's 2-year-old son developed an acute otitis media over a weekend, his father was faced with a dilemma. Should he trust the findings of his own systematic review on the treatment of otitis media, which suggested a 'watch and wait' approach,[1] or would parental concern lead him down the conventional route of antibiotics? To his credit, he chose the former route and continued to administer analgesics only. His son made a rapid recovery.

This story exemplifies the difficulty clinicians have in implementing research evidence from population studies, in the world of individual patients each with their own personal circumstances, expectations, and preferences.

Glasziou was speaking at a conference organised jointly by the James Lind Alliance and the Lancet at the Royal Society of Medicine, London, co-chaired by Iain Chalmers and Richard Horton in June 2007. The objectives of the conference were to explore the ways in which clinical trials can better meet the needs of clinicians and patients, and to discuss ways of drawing conclusions from research for individual patients. A stimulus for the conference was the imminent publication of Professor of Clinical Neurology and BMJ Clinical Evidence contributor Peter Rothwell's book *Treating Individuals*, which builds on a series of papers published in the Lancet in 2006.[2]

The starting point for ensuring that research meets the needs of patients and clinicians is to ensure that trials are planned, conducted, and reported with the needs of patients uppermost. This requires that researchers overcome what Professor Stephen Holgate described as the “communication gap” between healthcare professionals and the public. To date, as Dr Sandy Oliver reported, little research has been done to compare the different perceptions of researchers, clinicians, and patients. One exception to this is a study that found a mismatch between patients' priorities and those of investigators conducting research into osteoarthritis: while the patients in the study valued research into surgical approaches and education, the bulk of published research explored pharmacotherapy.[3]

Even where studies investigate interventions of interest, the outcomes measured must include those important and relevant to patients. Hence the importance of research aimed at determining which outcomes are most important to the public. The problem of external validity (the extent to which conclusions reached in a clinical trial can be translated into groups different from those studied) was a major theme of the conference, and is extensively explored in *Treating Individuals*. Professor Holgate described a study of people with asthma in Australia, which found that a mere 5% of patients in an average practice met typical eligibility criteria for a randomised trial.[4] The extent to which the patients included in clinical trials are representative of patients in broader settings can have important consequences for the implementation of research findings in practice. Holgate described how the practice of excluding smokers from asthma trials delayed the realisation that inhaled steroids are less effective in asthmatic patients who smoke.[5] As a substantial minority of people with asthma continue to smoke, this has undoubtedly led to both a waste of resources and sub-optimal care, as other agents, notably leukotriene antagonists, are effective.

It is tempting, therefore, to call for more pragmatically conducted trials with broader patient representation, but this can itself lead to variability in effect among subgroups that may be hidden behind a “net” treatment effect. One example of this was highlighted by Holgate, who described how a negative Cochrane review contributed to the virtual withdrawal of inhaled sodium cromoglycate as a treatment for childhood asthma.[6] Subsequent work has criticised the review for pooling results across diverse populations, and concluded that this may have obscured a treatment benefit in specific groups.[7]

Subgroup analysis is one vehicle for improving the ability to make individual evidence-based treatment decisions. This implies moving beyond the assumption that a “net” effect found in a mixed population can be presumed to be true across different patient groups. For example, Rothwell and colleagues have shown that, although the relative risk reduction of stroke with carotid endarterectomy in symptomatic carotid stenosis may be lower in elderly patients compared with younger people, the increased baseline stroke rate in untreated elderly patients can lead to an increase in the absolute treatment benefit in this elderly age group.[8] Similarly, novel techniques have been used to test which individual patients may gain or lose from specific interventions. Following the observation that tissue plasminogen activator (tPA) was more effective than streptokinase in acute coronary syndrome[9], but recognising that the mortality risk difference varied 16-fold among patients, Kent and colleagues used modelling techniques to show that the benefit of tPA was only true for high-risk patients and that, in the lowest risk group, tPA might, paradoxically, increase overall risk.[10] The group has now used similar models to predict outcomes for other related clinical contexts.[11]

A key requirement of these attempts to target individual care is the use of complete data sets from trials to create individual patient meta-analyses. Despite encouragement from influential bodies such as the National Institutes of Health and Medical Research Council, another speaker at the conference, Doug Altman, claimed that there continues to be resistance to this from some research groups, perhaps on the grounds of protecting confidentiality.

Ensuring that trials cover interventions, comparisons, and outcomes that matter to patients, increasing patient involvement in the planning and conduct of trials, and attempting to ensure that the populations within trials mimic those in normal practice, are all important stepping stones towards improving the applicability of research. Promising results using subgroup analysis, individual patient meta-analysis, and innovative modelling techniques show that individualising treatments from clinical trials is feasible. Technology is increasingly providing the potential to deliver knowledge within clinical systems. The increasing capability to refine that knowledge and make inferences based on known patient characteristics (e.g. age, comorbidity, risk factors), means that individually targeted evidence-based care should become the reality rather than mere aspiration.

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