Prescribing doctors are, increasingly, using clinical trial data as a major source of information for evidence-based medicine for the treatment of infectious diseases, as in other clinical disciplines. However, it may be difficult to extract from these data the information that is needed for the management of the individual patient. At the same time, clinical trial data have been used, apparently satisfactorily, in the process of drug registration, and the pharmaceutical industry has spent increasingly large sums of money to satisfy the needs of this process. This paradox—more money spent, but an outcome of limited usefulness to the prescriber—was the subject of the report of a group with expertise in all aspects of antibiotic clinical trials, meeting as the Witley Park Symposium.1 Their objective was to identify the strengths and weaknesses of the current antibiotic clinical trial procedure for all its potential users, and to suggest means that would improve the utility of the results for doctors and their individual patients.

The group identified current users of clinical trial data as: the pharmaceutical company developing, promoting and marketing the drug; the regulatory agencies responsible for drug registration for marketing; a group, defined as politicians, responsible for the well-being of the public; prescribers; and patients, who are taking an increasingly vociferous interest in the way in which their illnesses are managed. From this list alone it is clear that the needs are diverse, and that not all data are of value to all users.

The established validity of the comparative, randomized, blinded, prospective clinical trial, with its means of avoiding bias and its statistically valid outcome, was fully recognized. It was also recognized that its full potential was not always realized in practice. A major disadvantage of such trials was identified as their reliance on historical results that established the efficacy of what is usually referred to as the comparator drug: this drug may never have been satisfactorily demonstrated to be effective in comparison with placebo, and may, furthermore, have lost efficacy because of an increasing incidence of acquired resistance. As a result of the common requirement for the demonstration of equivalent efficacy, patients infected with bacteria that are resistant in vitro are often excluded from clinical trials, so that the clinician will have no guidance on how to manage such infections, and the microbiologist no guidance on the clinical importance of the antimicrobial resistance that he recognizes in the laboratory. There is an added problem that antibiotics have to be prescribed for serious infection before the specific pathogen has been identified: even in the best designed clinical trial, patients are treated for, e.g., community-acquired pneumonia, rather than for pneumococcal pneumonia, let alone penicillin-resistant pneumococcal pneumonia. At the very least this will result in randomization problems when subsets of patients are eventually analysed. The conclusion of the Witley Park group was that these and other factors result in failures in external validity—that is, the results cannot be applied to individual patients who rarely correspond to the ‘average’ patient for whom results are necessarily presented in such trials. This is the nub of the problem for the would-be rational antibiotic prescriber.

The problem was not left there. The group recognized that rare, adverse effects on the individual patient would not necessarily be recognized, even in the large clinical trials that appear to have become the norm. Furthermore, the effects of prescribing a given drug on the environment and on society at large, whether this is an increase in antibiotic resistance or the cost burden, are scarcely considered at all in clinical trials. Finally, little use is made of the extensive databases of medically relevant data that are becoming generally available.2

In the face of all these problems, changes in the way antibiotic clinical trials are designed and performed are clearly necessary, although this must not tip the balance so far as to render them less useful for those who currently derive greatest benefit from them. In coming up with sug-

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gestions for the future, the group recognized that much more study is required before action is taken. Their most radical suggestions were that, after Phase I studies undertaken essentially as now, Phase II studies should include *in vitro* and animal models in which human pharmacokinetics are mimicked. There should then be intensive open studies on small numbers of infected patients, with increased attention to pharmacokinetic and pharmacodynamic parameters in relation to improved measures of clinical response, and to effects on the normal flora and on pathogens. Results from these studies might then be generalized to other types of patients and to infections at different sites but with similar parameters. This could be followed by small intensive randomized controlled trials.

Successful completion of this programme might lead to provisional limited registration, which could be followed by well-conducted larger prospective trials to establish efficacy (and even superior efficacy) and safety. Only after successful completion of this stage would full registration be granted, but during widespread clinical use there would still be a requirement to monitor for rarer adverse events, for the onset and effects of acquired resistance, and for true costs and benefits, using health-related databases. This is an ambitious list of changes, and clearly many of the users of information derived from clinical trials will have views. Whatever the outcome, it is to be hoped that the individual clinician prescribing for an individual patient will have a better evidence base for their decisions on antibiotic therapy, and that both short- and long-term effects of treatment are quantified.

**References**