Clinical trials research in the new millennium: the International Clinical Trials Symposium, Sydney, 21–23 October 2002

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THE INTERNATIONAL CLINICAL TRIALS SYMPOSIUM, held in Sydney in October 2002, brought together over 700 people to explore the issues and future directions for clinical trials. The support from government as well as industry and the diversity of people attending the symposium indicated the importance of clinical trials research in Australia.

Established principles and new challenges

After about 50 years of developing and refining the design and conduct of clinical trials, researchers have established the fundamentals. Randomisation, blinding, informed consent, adequate sample size and a prospectively stated study design are well accepted as means of producing unbiased evidence of the effectiveness of therapies. However, the symposium brought to light various issues that continue to challenge clinical trials researchers. Prominent among these were:

- how to make the conduct of trials more relevant to clinical practice (and, conversely, how to draw more of "real-world" care into the context of trials);
- the importance of consumers participating (not just as patients, but by voicing research questions);
- how to ensure that trials research concentrates on the clinical questions most needing answers (rather than on, for example, comparable products jostling for market share); and
- how success in these areas can practicably be achieved (not least by using technology to run trials efficiently).

Some of these themes have been aired in the Journal.[1]

Bridging the gap between researchers and practitioners and patients

Stephen Blamey (*Chairman, Medical Services Advisory Committee, Commonwealth Department of Health and Ageing, Canberra*) set the agenda in his opening address by stressing the importance of evidence-based medicine in allocating government funding.

On behalf of the users of trial evidence, David Henry (*Professor of Pharmacology, University of Newcastle*) recommended that purchasers of services be represented when trials are being designed (and possibly share the cost of trials). Sue Lockwood (*Chair, Breast Cancer Action Group, Melbourne*), using the example of the Australian Sentinel Node Biopsy Trial (Royal Australasian College of Surgeons),[2] showed that involving consumers ensures that recruitment is fast and that the outcome is evidence that matters to patients. Bob Temple (*Director, Office of Medical Policy, US Food and Drug Administration, Rockville, Md, USA*) raised the issue of the need for regulatory bodies to have a say in trial design to ensure that trials meet their objectives for rigour and new indications.

Researchers can reach out to consumers by publicising the results of trials. Although journals have traditionally been the providers of this information, Richard Horton (*Editor,* Lancet) thought that promoting the results of research in other ways, such as communications aimed directly at consumers, is what really changes practice. Evidence may become known only from discussion in other journals and the mass media. As noted by Sally Redman (*Chief Executive Officer, Institute for Health Research, University of Sydney*), results published in specialised journals are often translated into practice by way of guidelines.

"I carry a card that says, '*Invite me to participate in all randomized controlled trials for which I am potentially eligible*'," said Iain Chalmers (*Founder of the UK Cochrane Centre*). He added that participation in controlled trials should become a widely available treatment option within routine healthcare. It was pointed out early in the symposium by Paul Glasziou (*Professor of Evidence-based Practice, School of Population Health, University of Queensland*), and others, that patients participating in clinical trials appear to do better than those receiving standard care outside of trials.[3]

Refinements in trial design, such as recruitment of clusters of patients rather than individuals (Judy Simpson, *Associate Professor, Department of Public Health and Community Medicine, University of Sydney*), and more control of confounders to widen entry criteria, can mean that more patients will be able to take advantage of participating in a trial. When commercial confidentiality is not an issue, trials can be advertised on web sites or public trials registers so that patients themselves can take the initiative in enlisting.

Which diseases and treatments need evidence?

Various speakers identified the many areas where more trials research is needed. Richard Horton championed an international perspective and the need for trials research in developing countries, focusing on diseases affecting people in these regions.

In terms of the numbers of trials and the numbers of patients recruited, cardiovascular disease and cancer are way ahead. This is partly because of the large number of people with these diseases and the number of new treatments being developed. A challenge for researchers is to diversify to other areas.

An innovative afternoon session comprised 12 concurrent forums in different clinical specialties. The objective was to identify current research priorities for particular clinical

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areas, and to develop new trial proposals or address concerns about trial methodology, such as measurement of outcomes, methods of randomisation and recruitment of patients. Besides cardiovascular disease and cancer, the forums embraced complementary medicine, diabetes, general practice, HIV medicine, perinatal medicine, reproductive and gynaecological medicine, rheumatology and surgery, as well as health technology assessment and information technology in research.

The symposium also included speakers whose work focused on laboratory rather than human research. Some urged that the need for increased support of clinical studies should not compromise basic science research.

A vision of the possibility of selecting the right drug for an individual patient is becoming a driving force in drug development (Peter Shaw, *Director, Human Genetics and Pharmacogenomics, Bristol-Myers Squibb, Pennington, NJ, USA*), particularly in oncology, where some drugs are especially effective for patients with certain genetic profiles. In HIV research, characterisation of viral gene sequences is affecting all aspects of trial design and analysis, adding to their complexity (Victor DeGruttola, *Professor of Biostatistics, Harvard School of Public Health, Boston, Mass, USA*).

Systems for conducting trials more efficiently

Mike Conlon (*Chief Information Officer, University of Florida Health Science Center, Gainesville, Fla, USA*) related that internet-based systems can reduce overall operational costs by a factor of three and significantly reduce workloads. Several groups in Australia are also working toward eliminating paper in the day-to-day running of trials. In view of the need for more and better trials in more areas of healthcare, these efficiencies will be essential.

The necessity for an Australian trials registry

Performing trials is an expensive business. Researchers need to know about every trial in their field so as not to duplicate what is already being done (John Simes, *Director, NHMRC Clinical Trials Centre, University of Sydney*). Most of the trials in Australia are still unregistered (Paul Glasziou). Patients and their doctors want to know which trials are available and suitable. Ensuring that everyone can find out which trials are under way requires central coordination. The way forward would be an Australian register of clinical trials. A national register is essential for planning, for maximising patient participation, and for identifying relevant randomised trials for studies compiling the available evidence. Tony Keech (*Deputy Director, NHMRC Clinical Trials Centre, University of Sydney*) stressed that such a register would also facilitate meta-analyses, which ideally should be planned prospectively.

Panel sessions — debates and hypotheticals

Whether (subject to consent and safety) every patient should be in a clinical trial was savagely contested by Richard Horton and Harvey White (*Director, Coronary Care and Cardiovascular Research, Green Lane Hospital, Auckland*) and David Celermajer (*Professor of Cardiology, University of Sydney*) and Martin Tattersall (*Professor of Cancer Medicine, University of Sydney*). Horton and White asserted that the key to better patient recruitment lay with doctors — they must offer more trial opportunities to their patients. And simpler inclusion criteria would allow typical patients with multiple morbidities to participate. Celermajer and Tattersall insisted that proof-of-concept trials do not require typical patients and that entry criteria do not require broadening.

A hypothetical, moderated by David Celermajer, took a make-believe hospital ethics committee through an evolving scenario. The committee members agreed on the principles of justice, equity and non-maleficence, and that the trial research must be of adequate quality and not harmful to patients. However, when trials researchers want to extend the protocol to reuse data and analyse blood samples, a green light from the ethics committee may come only after strong debate. If blood analysis reveals a risk of disease, should the risk be disclosed to individual patients? If so, should it also be disclosed to their relatives? Some of the ethical dilemmas showed how closely the conduct of trials reflects usual medical practice, in that many ethical issues are the same.

The ultimate panel session was moderated by Norman Swan (*Producer and Presenter of the* Health Report, *Australian Broadcasting Corporation, Sydney*), who examined the main themes emerging from the symposium with a broad-based panel. The panel recommended the following areas of action.

- More trials, especially prospectively designed trials in resource-poor countries; AIDS and malaria should have priority.
- Registration of trials.
- Trials in everyday practice.
- Development of funding mechanisms for trials.
- Guidelines as a means of translating trial evidence into practice.
- Trials of treatments (other than drugs) and technologies, to build on the work done by the pharmaceutical industry.
- Advancing alliances of triallists and government, particularly the NHMRC.

Conclusion

Clinical trials have come of age. Researchers are now critically evaluating their methods to improve the precision of trial results and reduce bias. At the same time, a widening of inclusion criteria for patients entering trials is allowing more patients to take part. Therefore, the trial environment is becoming more like standard clinical practice; indeed, the next step may take us toward integrating trials with medical care so that research is part of the healthcare system.

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