

Medical Oncology Group of Australia Cancer Achievement Award

R John Simes
NHMRC Clinical Trials Centre, University of Sydney, New South Wales.
Email: john@ctc.usyd.edu.au

Inspirations and influences for a life in clinical trials

Thank you to Medical Oncology Group of Australia (MOGA) and Novartis, and thank you to those people who nominated me for this award. It is a privilege and an honour to receive it, and I appreciate this opportunity to speak on my last 20 years in clinical trials research. I would like to reflect on how some early experiences and my mentors have shaped my research; on how the work in establishing the Clinical Trials Centre and the clinical trials research has involved such a large number of people working collaboratively, and what has motivated me and several others in clinical trials research in trying to change clinical practice for the better.

Professor Marvin Zelen, Director of Biostatistics at the Dana Farber Cancer Institute and Harvard School of Public Health in Boston, was my fellowship supervisor at Harvard and a major influence on the career path I have taken. Other colleagues at Harvard include Rich Gelber, Steve Lagakos and Milton Weinstein.

At Harvard, Marvin Zelen encouraged me to undertake clinical decision analysis. This led to a project looking at the value of single-agent versus combination chemotherapy and the trade-offs between toxicity and survival in advanced ovarian cancer.[1] The decision analysis included estimating the effects of treatments on cancer outcomes, as well as assigning values to various outcomes, based on interviews with Dana Farber staff. The recommendation from the analysis was that combination chemotherapy was the preferred treatment provided there were at least moderate survival gains associated with it, but if there were not, then the additional toxicity would not justify this therapy. So the decision really depended on the survival estimates from randomised trials, but also depended on patient preferences concerning the toxicity-survival trade-off. So this study stimulated other questions. One was how to combine effects on survival with quality of life. Rich Gelber and others were doing research in this area using the outcome, TWIST (Time Without Symptoms and Toxicity). We also included time with toxicity and time after progressive disease, but assigned lower values or weights to these periods. Depending on the weights assigned, combination chemotherapy was either preferred or not preferred to single agent therapy, in a so-called threshold utility analysis.[2] With Paul Glasziou, we then applied these approaches more broadly in quality adjusted survival analses or Q-TWIST.[3,4] This work also stimulated a series of patient preference studies, initially looking at the trade-off of toxicity from adjuvant therapy for breast cancer compared with the additional survival benefit.[5] This work and subsequent studies by Martin Stockler, Andrew Martin, Peter Grimison, Vlatka Duric and others have demonstrated that the survival gains from adjuvant therapy can be relatively small relative to side-effects, but these preferences are also important in that they vary from one person to another.[5–7] What this example illustrates is that what first seemed a problem in assessing trade-offs, became an opportunity for further research and has led to many important results by a larger group of researchers over the years.

My next example also arose from this same problem and related to false-positive results from published trials. Are published trials representative of all trials or do unpublished trials have different results? When we compared them in our ovarian cancer study, the published trials showed a significant survival benefit for combination chemotherapy over single-agent chemotherapy, whereas for the trials listed on a trials register (but not necessarily published), there was no significant difference.[1] In the context of the decision analysis, if you believed the evidence from the published trials you would recommend the combination chemotherapy, but if you believed the information sourced from the registered trials, there was insufficient evidence to recommend it. What we advocated was that rather than basing a review of the evidence just on the published trials, we should be prospectively registering all trials to provide unbiased estimates of treatment effects.[8]

Twenty years later, prospective registration of all clinical trials is now required by all leading medical journals and many regulatory authorities. As a result, most clinical trials are now registered in advance, and systematic

reviews of the trial evidence are much less likely to be prone to publication bias. In Australia, we now have over 4300 trials registered on the Australian New Zealand Clinical Trials Registry (ANZCTR, set up with a National Health Medical Research Council Enabling Grant). Not only are they linked internationally through the World Health Organisation's platform to ensure that all studies can be identified worldwide, but they are also linked to specialised registries, such as in cancer, so that patients can see which trials are ongoing, potentially boosting patient participation.

A third example of another problem occurred in relation to an Australian trial I undertook with Martin Tattersall, Alan Coates and others comparing two approaches to informed consent.[9] In the individual approach, patients were given all information the clinician considered was important. 'Total disclosure' involved a one page informed-consent form, including all possible side-effects of therapy (compared with up to a 25 page consent form for some studies today). Our trial showed that patients who received more detailed information were more knowledgeable about their treatment, but also more anxious and less willing to take part in trials. Rather than saying that one approach was right or wrong, this illustrated that there were trade-offs involved.

An interesting problem arose in interpreting the results from this trial, which had multiple outcomes that were correlated with each other. These outcomes appeared significant if considered individually – with P values less than 0.05. However, if you adjusted each result for multiple comparisons using the Bonferroni adjustment, you would have regarded most of the results as non-significant. The problem was that this appeared not appropriate for correlated outcomes, and it motivated me to look further into the Bonferroni procedure, which in this case was too conservative. So I did some work on a modified Bonferroni procedure, now called the 'Simes test'. The procedure ranked all the P values from 1 to k and then compared the jth P value with the level j/k times the significance level, and then declared the test significant if any P value was less than that level. In this analysis, I tried to prove a theorem, which was that when all the tests were independent, this procedure would have a type I error probability exactly equal to the alpha significance level. The reason for mentioning this here is not to get into the mathematics of it, but to say that I spent several months and lots of mathematical calculations to prove this theorem. I submitted a paper to Biometrika with three pages to demonstrate the proof. One of the referees said it was a nice paper, but you can actually do the proof in three lines rather than in three pages, provided a nice little proof, and didn't want to be referred to by name, so all I could do was acknowledge the very helpful support from my referee.[10] I also included a conjecture that when tests were not independent, this result would be normally (but not always) conservative, and did some simulation studies to show that it was the case. But I then left a conjecture in the paper asking whether a proof would work for most families of tests. That generated a whole lot of interest, leading to, now, about 500 citations, as various people use the concept to solve fairly complex mathematical problems. Journal editors used to send me these papers to referee because I wrote the original one, but many years ago I called a halt because it was all getting far too complex. It is interesting where things can take you. Since then, this has led to other statistical procedures which are now used in the Hochberg procedure, which you will see in clinical trial protocols. Another implication from these discussions of multiple comparisons is that researchers will often need to seek independent confirmation of their findings in other trials — yet another rationale for systematic reviews of all the relevant evidence.

What are some of my thoughts from this early experience at Harvard? First, when you are faced with a problem, see it as an opportunity for developing new methods or for leading to further research. I think many practical problems we face in clinical research today, be it in biostatistics or in molecular biology or whatever, can benefit from that same philosophy.

After my time in Boston, Professor Zelen encouraged me to take on a significant role in doing the kinds of things that we had been doing in the US in terms of clinical trials, and he gave me confidence to pursue that endeavour. And I think these are useful lessons for me, and others. When I came back to Australia, I worked at the Ludwig Institute at the University of Sydney. My career has been enormously influenced by Martin Tattersall and others, including Alan Coates, Dick Fox and Paul Glasziou at the Ludwig. I was encouraged to write a position paper for the National Health Medical Research Council on the need for a national clinical trials centre. When expressions of interest were sought, people persuaded me to apply for the same centre that I was advocating, which led to its establishment in 1988. That centre has grown over the years to about 150 staff collaborating with hospitals and other trial sites, through many of the major cancer cooperative trial groups in Australia and other groups. It is based at the University of Sydney over two campuses, with clinical trials research teams led by several people including Tony Keech, Val Gebski, Wendy Hague, Burcu Vachan, Deborah Schofield, Lisa Askie and Martin Stockler.

Our mission at the Clinical Trials Centre is to improve health outcomes, practice and policy, using clinical trials research. We have a range of programs, including undertaking trials, evaluating evidence, career development, education and training activities for clinical trials, strategies for translating research into practice, quality-assurance programs, and clinical trial methodology, including biostatistics, quality of life and health economics assessments. Collectively, our trials have recruited over 60,000 patients, in cardiovascular disease, cancer and neonatal disorders, as well as other smaller trials in other areas. Our trials are part of international collaborations whose studies have recruited over 170,000 patients. Cardiovascular disease trials research tends to involve large numbers of patients and a smaller numbers of trials. In cancer, there are more trials, but with small to moderate numbers

of patients. The role of the Clinical Trials Centre is to work collaboratively as either a coordinating centre or a statistical centre with many other players.

In relation to cancer trials, I want to acknowledge that this is an enormous collaborative effort. It involves people who set up and are managing each of the cancer cooperative groups, people within the team at the Clinical Trials Centre, clinical investigators and site coordinators, international collaborative groups, and the patients and participants. There are 13 cancer cooperative trial groups in Australia and the Clinical Trials Centre has worked closely with eight of these. I have been actively involved with the ANZ Breast Cancer Trials Group, whose research was one of the first activities of the Clinical Trials Centre. Many people there, including John Forbes, Alan Coates, members of the Board and others, do great work. Likewise, I've had a major role in the Australian Gastro-Intestinal Trials Group, and I must acknowledge everybody in that group, particularly the chair, John Zalcberg.

An important theme for us at the Clinical Trials Centre is to see how we can translate the evidence of clinical trials into better practice. We want to evaluate the evidence in terms of undertaking clinical trials, look at ways of combining the evidence in systematic reviews, and see that evidence translated into guidelines and protocols and, ultimately, improvements in health.

Some recent examples of studies we have been privileged to be part of include: the MAX trial, which showed improvements in progression-free survival for bevacizumab in addition to chemotherapy for patients with colorectal cancer;[11] the CO.17 trial of molecular targeted therapy for colorectal cancer;[12] and the CALYPSO trial of the international gynaecological groups with the Clinical Trials Centre as the statistical centre.[13] The germ-cell trial (with the ANZ Germ-Cell Trial Group and now the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)), recently published by Peter Grimison and others, showed ongoing survival advantages of the chemotherapy regimen developed in the US.[14] The Sentinel Node versus Axillary Clearance breast cancer surgical trial of over 1000 patients, led by the Royal Australasian College of Surgeons, showed significantly less lymphoedema and better quality of life for sentinel-node-based management, and also led to changes in practice by integrating the procedures for surgical training in the trial protocol.[15] Less toxic capecitabine treatment was shown to lead to longer survival in a trial of the ANZ Breast Cancer Trials Group.[16] A trial involving both Australasian Gastro-Intestinal Trials Group and the Trans-Tasman Radiation Oncology Group, showed possibly better progression-free survival associated with preoperative chemoradiotherapy for some oesophageal tumours;[17] then a systematic review confirmed the advantage of chemoradiotherapy,[18] which is now one of the standard treatments.

The talents of many people will be required to address future challenges and to continue to champion this research. I have been privileged to work with and continue to work with many research fellows, PhD students and study coordinators, and I am very much looking forward to following their careers.

Finally, to come back to my reflections from my time at Harvard. First, in terms of problems that you might be faced with in research or practice, see these as an opportunity for developing new methods or new approaches. Second, for the mentor, don't underestimate the importance of giving encouragement and inspiring confidence; this was a huge influence on my career.

References

1. Simes RJ. Treatment selection for cancer patients: application of statistical decision theory to the treatment of advanced ovarian cancer. J Chronic Dis 1985; 38(2): 171–186.
2. Simes RJ. Application of statistical decision theory to treatment choices: implications for the design and analysis of clinical trials. Stat Med 1986; 5(5): 411–420.
3. Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. Stat Med 1990; 9(11): 1259–1276.
4. Goldhirsch A, Gelber RD, Simes RJ, et al. Costs and benefits of adjuvant therapy in breast cancer: a quality-adjusted survival analysis. J Clin Oncol 1989; 7(1): 36–44.
5. Simes RJ, Coates AS. Patient preferences for adjuvant chemotherapy of early breast cancer: how much benefit is needed? Natl Cancer Inst Monog 2001; 30: 146–152.
6. Duric V, Stockler M. Patients' preferences for adjuvant chemotherapy in early breast cancer: a review of what makes it worthwhile? Lancet Oncol 2001; 2: 691-697.
7. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? Ann Oncol 2005; 16(11): 1786–1794.
8. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol 1986; 4(10): 1529–1541.
9. Simes RJ, Tattersall MH, Coates AS, et al. Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment for cancer. Br Med J 1986; 293(6554): 1065–1068.
10. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986; 73(3): 751–754.
11. Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, bevacizumab and mitomycin C in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group randomised phase III MAX study. J Clin Oncol 2010; 28(19): 3191–3198.
12. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. New Engl J Med 2008; 359(17): 1757–1765.
13. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010; 28(20): 3323–3329.
14. Grimison P, Stockler M, Thomson D, et al. Comparing two BEP regimens for good-prognosis germ-cell tumours: long-term analysis of a randomised trial. J Natl Cancer Inst 2010; 102(16): 1253–1262.
15. Gill PG, Wetzig N, Gebski V, Stockler M, Ung O, Campbell I, Simes J, and the SNAC Trial Group. Sentinel-lymph-node-based management or routine axillary clearance? One-year outcomes of sentinel node biopsy versus axillary clearance (SNAC): a randomized controlled surgical trial. Ann Surg Oncol 2009; 16: 266–275.
16. Stockler MR, Sourjina T, Harvey V, et al. A randomized trial of capecitabine given intermittently versus continuously versus classical CMF as first line chemotherapy for women with advanced breast cancer unsuited to more intensive treatment. 29th Annual San Antonio Breast Cancer Symposium; 14–17 Dec 2006; San Antonio, Breast Cancer Research and Treatment 2006; 100 (suppl 1): S278-S278.
17. Burmeister BH , Smithers BM , Gebski V, et al; for the Trans-Tasman Radiation Oncology Group (TROG) and the Australasian Gastro-Intestinal Trials Group (AGITG) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005; 6(9): 659-668
18. Gebski V, Burmeister B, Smithers MB, et al. Meta-analysis of the survival benefits from preoperative chemoradiation therapy and chemotherapy in oesophageal carcinoma. Lancet Oncol 2007; 8: 226–234.