

DIAGNOSING DYING

Most of us value good experiences: good times, good friends, and a good life. And, as our society ages, of increasing concern is a good death.

In the year 2000, close to 130 000 Australians died. More than 70% were aged 65 years or older, most succumbing to cancer and cardiovascular disease. Most died in hospital.

It is likely that many did not have a good death. In hospitals the pervasive ethos of healing and curing is not conducive to confronting death. Investigations and invasive procedures continue when palliative care is actually long overdue, and technology stubbornly defies death. When death is imminent, feelings of helplessness, guilt or failure are allayed by hiding reality behind closed curtains or abandoning the dying patient to a side room.

Why should this be?

Explanations include the notion that death must be defeated at all costs, or that clinical training focuses more on when to begin treatment than when to stop. But of more immediate concern is a deficiency in diagnosing dying, and the resultant failure to “change gear” from *curing* the living to *caring* for the dying.

In *Care of the dying patient: the last hours or days of life*, UK physicians John Ellershaw and Chris Ward stress that diagnosing dying is a complex process, and barriers to its realisation include “disagreement about the patient’s condition, no definitive diagnosis, failure to recognise key symptoms and signs, a poor ability to communicate with the patient or family and medico-legal issues”. They note that increased clinical confidence in the diagnosis of dying requires changes in attitudes to research into and education about the process of dying.

With the ageing of our society, this is long overdue.

Martin B Van Der Weyden

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Emergence of hetero-vancomycin-intermediate *Staphylococcus aureus* (hVISA) in Sydney

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TO THE EDITOR: Methicillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to glycopeptides (vancomycin-intermediate *S. aureus*, or VISA) was initially described in Japan,¹ then the United States,² and subsequently other regions of the world. Recently, Ward and colleagues reported the initial Australian isolate — a hetero-resistant VISA (hVISA) strain — in Melbourne, Victoria.³ We report the first isolation of hVISA in Sydney, New South Wales.

A 79-year-old man underwent mitral valve annuloplasty in April 2002. Post-operative complications included MRSA bacteraemia, which resolved. He was discharged at the end of July 2002, but 12 days later was admitted to a second hospital with endocarditis caused by *Streptococcus viridans*. A month later, he developed a third episode of septicaemia, and MRSA was isolated from blood cultures. Despite two weeks' treatment with intravenous vancomycin, blood cultures again yielded MRSA. A transoesophageal echocardiogram confirmed endocarditis. Resistance screening of the MRSA

isolate by E test (AB Biodisk, Solna, Sweden)⁴ gave minimum inhibitory concentrations of 16 mg/L for vancomycin and 32 mg/L for teicoplanin, suggesting resistance to glycopeptides. The patient was then treated with intravenous linezolid and underwent vegetectomy. Subsequent blood cultures were negative for MRSA, but the patient died seven days after surgery from nosocomial pneumonia caused by *Escherichia coli*. Population analysis of the MRSA isolate showed that it was heterogeneously resistant to vancomycin (hVISA).

The emergence of hVISA in Sydney is a sentinel event, with ramifications for clinicians, laboratories and infection control. Routine susceptibility testing will not detect this resistance. Hence, clinicians and laboratories should consider VISA and hVISA if a patient with a proven MRSA infection fails to respond to vancomycin or teicoplanin, or has had several courses of vancomycin/teicoplanin and continuing positive cultures. If alerted that specimens could contain VISA or hVISA, the laboratory should perform glycopeptide resistance screening using E tests or other methods. Isolates that screen positive should be confirmed with population analysis profile testing.⁴

Treatment of hVISA and VISA infections, particularly bacteraemia and endocarditis, with vancomycin and/or teicoplanin is likely to fail. Alternative antibiotics include linezolid and quinupristin-dalfopristin, which are both very expensive. There is limited information on the success or otherwise of these agents in treating serious staphylococcal infections, especially bacteraemia and endocarditis.⁵

As a number of outbreaks of VISA and hVISA infection have already been described in other countries, we must ensure that these organisms do not

become established in Australian institutions.

- Strict attention to infection control must be observed, particularly hand-washing and use of alcohol hand rubs before and after patient contact.
- Attention to rational prescribing of antibiotics is required, avoiding broad-spectrum agents whenever possible.
- Vancomycin and teicoplanin should be used only when necessary: when there is resistance to other agents, and only when infection is present. Colonisation is not an indication to use glycopeptides, nor is minor allergy to β -lactams.

1. Hiramatsu K, Hanaki H, Ino T, et al. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 1997; 40: 135-136.
2. Tenover FC, Biddle JW, Lancaster MV. Increasing resistance to vancomycin and other glycopeptides in *Staphylococcus aureus*. *Emerg Infect Dis* 2001; 7: 327-332.
3. Ward PB, Johnson PD, Grabsch EA, et al. Treatment failure due to methicillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to vancomycin. *Med J Aust* 2001; 175: 480-483.
4. Walsh TR, Bolmstrom A, Qvarnstrom A, et al. Evaluation of current methods for detection of staphylococci with reduced susceptibility to glycopeptides. *J Clin Microbiol* 2001; 39: 2439-2444.
5. Chambers HF. Clinical role of linezolid and quinupristin-dalfopristin in treatment of staphylococcal infections. Abstracts of the 10th International Symposium on Staphylococci and Staphylococcal Infections; 2002 16-19 Oct; Tsukuba, Japan, 2002. ISSSI-351-Abstract-03. □

Clinicians' attitudes to clinical practice guidelines

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TO THE EDITOR: In their systematic review of clinicians' attitudes to clinical practice guidelines, Farquhar et al¹ found that, although healthcare providers reported high satisfaction with guidelines, a significant number also expressed concerns about their practicality, their role in cost-cutting and their potential for increasing litigation. The review, however, did not address other potentially significant concerns of clinicians regarding the perceived validity of guidelines and the influence of external agencies (such as the pharmaceutical industry) on treatment recommendations.

In April 2002, I conducted a survey of 155 full-time nephrologists and renal medicine trainees practising in Australia and New Zealand about their attitudes to the Caring for Australians with Renal Insufficiency (CARI) clinical practice

Correspondents

We prefer to receive letters by email (editorial@ampco.com.au). Letters must be no longer than 400 words and must include a word count. All letters are subject to editing. Proofs will not normally be supplied. There should be no more than 4 authors per letter. Each author should provide current qualifications and position and full details of postal address, telephone and facsimile numbers.

There should be no more than 5 references. The reference list should not include anything that has not been published or accepted for publication. Reference details must be complete, including: names and initials for up to 4 authors, or 3 authors et al if there are more than 4 (see mja.com.au/public/information/uniform.html#refs for how to cite references other than journal articles).

guidelines (www.kidney.org.au/cari). The response rate was high (90.3%), with the majority (89%) of doctors agreeing or strongly agreeing that CARI provided a useful evidence summary. However, only 39% indicated that their practice had been significantly influenced by these guidelines, and just 14% felt that patient outcomes were improved as a result of CARI. While a minority expressed concern about the applicability of guidelines to individual patients (16%) and the potential for augmenting litigation (44%), the most significant worry was that 49% did not agree that the treatment recommendations matched the available evidence. Of those who felt that the recommendations were not justified, most believed that erroneous conclusions had been drawn from the evidence and that working parties had been affected by external influences, principally the pharmaceutical industry (74%). This view was significantly more common among nephrologists who were guideline authors (odds ratio, 3.6; 95% CI, 1.5–8.5; $P < 0.01$).

Choudhry et al² similarly reported that guideline authors frequently felt that their coauthors' recommendations were influenced by financial relationships with the pharmaceutical industry, despite the fact that only 7% believed that their own recommendations had been influenced by such factors, and that conflicts of interest were disclosed in only a minority (<5%) of instances. In fact, 47 (59%) of the 80 guideline authors surveyed had financial relationships with companies whose drugs were considered in the guideline they authored.

Other studies have further demonstrated that most clinical practice guidelines published in the peer-reviewed literature in the past decade did not adhere well to established methodological standards of identifying, evaluating and synthesising scientific evidence.^{3,4} Any review or survey of clinicians' attitudes to clinical practice guidelines should therefore include an assessment of their opinion as to the quality of those guidelines and the extent to which outside agencies (such as drug companies) may have influenced them.

1. Farquhar CM, Kofa EW, Slutsky JR. Clinicians' attitudes to clinical practice guidelines: a systematic review. *Med J Aust* 2002; 177: 502-506.
2. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA* 2002; 287: 612-617.
3. Steudel WI, Schwerdtfeger K. Guidelines for guidelines. *Acta Neurochir* 2001; 78: 217-223.
4. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are guidelines following guidelines? The methodological quality of clinical practice guidelines in the peer-reviewed medical literature. *JAMA* 1999; 281: 1900-1905. □

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IN REPLY: Johnson's letter raises an important point about the influence of external agencies such as pharmaceutical companies in the development of clinical practice guidelines. Although our systematic review¹ of 30 studies of clinician attitudes to clinical practice guidelines did not identify this issue as a major barrier, it is possible that the surveys used overlooked this concern. Conflict-of-interest statements and the source of funding for clinical practice guidelines and their development teams are not always published. In the AGREE² questionnaire (a measurement instrument developed for clinical practice guidelines), reporting conflict of interest and source of funding is encouraged. The New Zealand Guideline Group has a policy of declaring conflicts of interest, and pharmaceutical industry representatives are not included in guideline development teams.³

Choudhry et al⁴ reported that 59% of guideline authors had financial relationships with companies whose drugs were considered in the guideline they authored. Although these figures are not surprising given the role of the industry in research and educational activities, they do present a challenge to guideline development teams. The New Zealand Guideline Group approach (apart from declaring conflicts of interest and not including industry representatives on guideline development teams) is to take an evidence-based strategy. This involves considering all available evidence, publishing search strategies, linking evidence tables to evidence statements and recommendations, developing the recommendations by using a "considered judgement form" (which takes into account evidence, cost, generalisability and applicability),

and drawing on representatives from a broad range of stakeholders (including consumer and allied health groups). By taking such an approach, it is hoped that the influence of external agencies can be minimised.

1. Farquhar CM, Kofa EW, Slutsky JR. Clinicians' attitudes to clinical practice guidelines: a systematic review. *Med J Aust* 2002; 177: 502-506.
2. The AGREE collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Available at: <http://www.agreecollaboration.org> (accessed Feb 2003).
3. The New Zealand Guidelines Group. Available at: http://www.nzgg.org.nz/development/documents/nzgg_guideline_handbook.pdf (accessed Feb 2003).
4. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA* 2002; 287: 612-617. □

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IN REPLY: The fundamental purpose of clinical practice guidelines is to improve patient outcomes. Thus, as members of the CARI (Caring for Australians with Renal Insufficiency) Guidelines Steering Committee, we welcome Johnson's letter, which gives us reassurance and renewed enthusiasm to move forward with improving and refining the CARI clinical practice guideline process. The most gratifying revelation in Johnson's survey was the near-90% endorsement of the CARI guidelines as a document providing a useful evidence summary — clearly very reassuring in those areas in which that evidence relates to treatment interventions for patients with renal disease. Of additional interest was the range of responses to questions about matching the recommendations with available evidence. This seems to reflect both an awareness among renal medicine health workers of the importance of evidence-based medicine and a maturing understanding of the need for the evidence to be of high quality.

The CARI guideline process has a relatively short history (just over three years), and before Johnson's survey the CARI Steering Committee had adopted a number of strategies that anticipated some of the issues his survey raises. These strategies included:

- establishing a formal link with the Renal Cochrane Organisation (to produce the best possible search outcomes of all the available evidence);

■ adopting the National Health and Medical Research Council (NHMRC) evidence levels I (systematic reviews) and II (randomised controlled trials) as the minimum requirement to justify definitive guidelines (to assess the quality of evidence available and match appropriate guidelines with that evidence);

■ adopting a peer-review process to evaluate draft guidelines to complement newly revised requirements for guideline writers' conflict-of-interest declarations (to assess perceptions of guideline validity and the influence of external agencies);

■ broadening the multidisciplinary nature of guideline working parties.

In addition, the Australian Kidney Foundation has moved to further disseminate the guidelines, and the CARI guideline process has been reformed with the aim of meeting the standards required to achieve NHMRC endorsement. Furthermore, feedback obtained from legal advisers suggests that the CARI guidelines and the process of establishing them are far more likely to *obviate* litigation than to *promote* it. The next important phase for the CARI guidelines will be the development of an implementation process.

As the acceptance of evidence-based medicine increases and the knowledge base among healthcare workers of the nature, quality and relevance of evidence in patient care expands, the CARI guideline process is likely to be enhanced. The results of future surveys of the type carried out by Johnson will be keenly anticipated. □

Australian health policy research and development

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TO THE EDITOR: In concluding that health policy research in Australia is a virtual desert,¹ Van Der Weyden failed to acknowledge several recent developments.

The Health Services Research Association of Australia and New Zealand, formed in late 2001 (www.chere.uts.edu.au/hsraanz/), and its biennial con-

ferences (the next to be held in Melbourne in November 2003), are evidence of good quality research across a range of topics. Particularly Australian contributions include economic evaluation as a basis for funding decisions in both pharmaceuticals and medical services; the Coordinated Care Trials; and the adaptation of casemix funding to Australian cost structures and payment mechanisms.

Health policy development around the world borrows freely from other countries, but, unlike the generalisability of biomedical and clinical research, health services research can only be transferred after taking into account the characteristics of each country's unique system.

Nonetheless, health services and policy research are underfunded and underdeveloped in Australia. Is the answer an internationally acclaimed Australian Institute for Health Policy? Not entirely. A well-funded institute would overcome some of the lack of security of tenure faced by health services researchers — and would certainly be a welcome advance over the usual Australian practice of spreading the available funds so that a paltry amount goes to each State or Territory. However, according to the Wills Review,² Australia requires not one but several research centres with the necessary critical mass.

We need a multifaceted strategy that goes beyond the organisational base. Funding is needed for investigator-initiated long term research to address underlying theory and methods, as well as contemporary policy issues. Researchers need to be able to build sustained inquiry into a specific area, instead of moving rapidly from topic to topic just to maintain their funding. Recognised avenues for training, education and further professional development are needed to build a critical mass of researchers. Only then will the success rate of National Health and Medical Research Council (NHMRC) project grants for health services research move from its current 5% or less to the success rate for public health of around 20%, or even the overall success rate of 25%–30%.

Finally, the US-based Harkness Fellowships in Health Policy and Practice

are important,³ but support only two Fellows each year. This program needs to be complemented by an Australian-based program of training and international exchange on a similar scale to the various public health training programs.

1. Van Der Weyden M. Australian health policy research and development: where is it? *Med J Aust* 2002;177: 586.
2. Health and Medical Research Strategic Review (Chair: Peter Wills): Enabling the Virtuous Cycle, Implementation Committee Report. Commonwealth Department of Health and Aged Care, September 2000. Available at: <http://www.health.gov.au/nhmrc/wills/contents.htm> (accessed February 2003).
3. The Commonwealth Fund Harkness Fellowships in Health Care Policy. Information available at: <http://www.cmfw.org/fellowships/harkness.asp?link=3> (accessed Feb 2003). □

Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects?

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TO THE EDITOR: Keech and Gebski recently discussed some strategies for answering randomised clinical trial (RCT) questions with fewer subjects.¹ We would like to point out another alternative for addressing this important topic — adjustment for baseline characteristics.^{2–4}

Heterogeneity among patients participating in RCTs is common. Prognosis may vary according to important baseline characteristics, which are commonly recorded in RCTs. Heterogeneity may lead to imbalanced treatment arms, even after proper randomisation.³

Covariate adjustment for baseline characteristics is a statistically efficient procedure. It leads to more individualised treatment-effect estimates, corrects for imbalance and improves statistical power.^{2,3} Hence, it may potentially reduce the necessary sample size of an RCT for the same power as unadjusted analyses. Nevertheless, covariate adjustment is not commonly performed in the RCTs reported in major medical journals.⁵

We recently performed a simulation study using logistic regression models in the context of RCTs with dichotomous outcomes and one simple dichotomous baseline characteristic in addition to the

treatment indicator variable. Covariate adjustment was found to potentially reduce the sample size between 3% and 46%, in direct relation to the strength of the baseline characteristic (odds ratio, 2 to 30). Results of a simulation study in RCTs with survival outcomes, using Cox proportional hazards models, yielded similar results.

Covariate adjustment for well-known and important predictors of patient prognosis is a useful tool for potentially reducing the sample size of RCTs, and should be considered more often in their design and analysis.

1. Keech AC, GebSKI V. Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects? *Med J Aust* 2002; 177: 445-447.
2. Piantadosi S. Clinical trials: a methodologic perspective. 1st ed. New York: John Wiley and Sons Inc; 1997.
3. Steyerberg EW, Bossuyt PMM, Lee KL. Clinical trials in acute myocardial infarction: Should we adjust for baseline characteristics? *Am Heart J* 2000; 139: 745-751.
4. Maas AIR, Steyerberg EW, Murray GD, et al. Why have recent trials of neuroprotective agents in head injury failed to show convincing efficacy? A pragmatic analysis and theoretical considerations. *Neurosurgery* 1999; 44: 1286-1298.
5. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in

clinical trial reporting: Current practice and problems. *Stat Med* 2002; 21: 2917-2930. □

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IN REPLY: While we agree that covariate adjustment during analysis can be a potential mechanism for reducing sample size (even when there is no imbalance in the important covariate levels between the treatment groups), unless such analyses are prospectively planned then they will not allow valid statistical inference. This is because post-hoc adjustment is an exploratory procedure and may have involved examining any number of potential covariates.

Further, to quantify any anticipated sample-size gains would depend on specifying likely maximum covariate imbalances, overall covariate distributions and plausible effects of treatment within the covariate levels during study

design. In practice, the study would then have to meet these assumptions for the calculated sample-size gain to be achieved.

Covariate adjustment is an accepted practice for subsidiary analysis in clinical trials, and can take account of differential effects in imbalanced subgroups. For example, see the case of an apparent chance imbalance in numbers of women in the treatment arms of the HERO-2 trial, where investigators presented both unadjusted and adjusted results.¹

Where important predictors of the clinical outcomes are expected to be variable for the population under study, a particularly useful approach is to stratify the randomisation by those predictors.² Such stratification allows for valid adjusted analyses.³

1. The Hirulog and Early Reperfusion or Occlusion (HERO-2) Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001; 358: 1855-1863.



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2. Keech AC, GebSKI V. Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects? *Med J Aust* 2002; 177: 445-447.
3. GebSKI V, Keech AC. Statistical methods in clinical trials. *Med J Aust* 2003; 178: 182-184. □

Determining the sample size in a clinical trial

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TO THE EDITOR: Evidence-based medicine should be supported by randomised controlled trials (RCTs) that show the efficacy of interventions in producing clinically relevant outcomes, not by those that show statistically significant, but clinically irrelevant, differences.

RCTs are designed to investigate whether an intervention in one homogeneous group results in a different outcome compared with no intervention, or a different intervention in an otherwise identical group.

Statistical analyses are performed to estimate the probability that any difference in outcome has arisen as the result of chance alone, and sample size is determined to control the probability of a real difference in outcome being overlooked by chance alone. However, statistical analyses provide no information about the clinical relevance of any difference in outcome. There is no validated method for determining a minimum clinically relevant difference in outcome (minimum important difference).

Kirby and colleagues suggest that, wherever possible, the minimum important difference in response should be determined from Phase II or pilot studies and expert opinion from colleagues.¹ It is ironic that the clinical relevance of Level I evidence² depends on determining the minimum important difference based on Level IV or Level V evidence.

Although the original CONSORT statement recommended describing the minimum important difference and indicating how the target sample size was projected,³ the most recent statement is less specific and only recommends describing how the sample size was determined.⁴ Neither statement requires investigators to specifically

describe the method by which the minimum important difference was determined.

The minimum important difference must be justified so others can determine if the study has the power to detect a clinically relevant difference in outcome as the result of a particular intervention. Similarly, the minimum important difference must be stated so that any statistically significant difference in outcome can be judged for clinical relevance.

If the minimum important difference cannot be justified as being clinically relevant, the result of the study will be of statistical interest only, and valuable resources will have been wasted. While it is reasonable to suggest that sample size must be planned to ensure that research time, patient effort and support costs invested in any clinical trial are not wasted,⁵ manipulating the minimum important difference to allow an RCT to conform to these constraints cannot be justified unless the RCT can still detect a clinically relevant difference in outcome.

1. Kirby A, GebSKI V, Keech AC. Determining the sample size in a clinical trial. *Med J Aust* 2002; 177: 256-257.
2. Phillips R, Ball C, Sackett DL, et al. Levels of evidence and grades of recommendations. Centre for Evidence-Based Medicine, Oxford, UK. Available at http://www.indigojazz.co.uk/cebml/levels_of_evidence.asp (accessed Dec 2002).
3. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting or randomized controlled trials: The CONSORT statement. *JAMA* 1996; 276: 637-639.
4. Moher D, Schulz KF, Altman D, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; 285: 1987-1991.
5. Keech AC, GebSKI V. Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects? *Med J Aust* 2002; 177: 445-447. □

Determining the sample size in a clinical trial

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IN REPLY: A key message of our article is that the minimum possible difference that *would* render the intervention clinically worthwhile needs to be determined in the design phase of the study.¹ This potential clinical difference (net advantage over standard care) must, of necessity, incorporate the potential

trade-offs between any outcome advantages and associated toxicities and/or cost disadvantages.

In determining the minimum clinically worthwhile difference, the intention is not to ignore Level I evidence (phase III studies and meta-analyses) when such evidence exists. However, in most cases of designing a phase III study, such evidence is not available. In this instance, the use of phase II information (which can often provide good estimates of potential side effects and toxicities) can help to inform the estimated advantage in clinical outcome which would be needed to justify widespread use of the intervention. Tools have been developed to help clinicians determine worthwhile benefit against toxicity trade-offs for individual patients.²

While there are instances of study results reliably showing statistical significance without the measured effect being sufficiently large to be considered clinically relevant, this occurs rarely. Far more commonly, statistically non-significant results may obscure clinically relevant outcomes because studies have been seriously underpowered.³ For example, 17 of the first 22 small trials of thrombolytic therapy compared with placebo for acute myocardial infarction reported non-significant results, although they showed a 19% reduction in early mortality ($2P < 0.01$) in subsequent meta-analysis.⁴

Individual doctors treating their patients ultimately determine whether net differences are sufficiently worthwhile to change their clinical practice. The fundamental principle is that clinical trials should be designed with sufficient power (through having appropriate sample sizes) to detect differences that doctors would consider clinically worthwhile to improve health outcomes.

1. Kirby A, GebSKI V, Keech AC. Determining the sample size in a clinical trial. *Med J Aust* 2002; 177: 256-257.
2. Shakespeare TP, GebSKI VJ, Veness MJ, Simes J. Improving the interpretation of clinical studies using confidence levels, clinical significance curves and risk/benefit contours. *Lancet* 2001; 357: 1349-1353.
3. Frieman JA, Chalmers TC, Smith H Jr, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomised control trial: survey of 71 "negative" trials. *N Engl J Med* 1978; 299: 690-694.
4. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *J Clin Epidemiol* 1995; 48: 45-57. □

Professional monitoring and critical incident reporting using personal digital assistants

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TO THE EDITOR: The motivating article by Bent and colleagues¹ is a most welcome addition to the literature of what works in the movement for performance improvement. We can hardly overemphasise the need to share knowledge on innovations (ie, what works and what does not work) in the quest for best quality and safety practices. However, to aid efficient lesson-drawing, we are inclined to look for more contextual information and levers in any quality-of-care interventions.

For a safety research discussion, the report by Bent and others has at least three important elements: the use of a technology (personal digital assistants [PDAs]), the clinical performance of healthcare professionals (here, anaesthetists), and the permissive culture (to want to learn and improve). Nevertheless, what such innovative pilot practices should also incorporate and report are the contextual factors responsible for successful acceptance,² application and appraisal of quality interventions.

Bearing continuity and sustainability in mind, one should be interested in the "characteristics" of anaesthetists who would voluntarily engage in personal monitoring and feedback. Initial technology use is seen among the "technologically proficient few" before becoming widespread.³ The introduction of PDAs for incident monitoring calls for the evaluation of the sociotechnical meta-system⁴ in which it will ultimately exist. Therefore, it is important for us to add a qualitative assessment to such a pilot study to identify personal motivating factors, climate for action, and the personal performance effects. Failure to evaluate technology "deployment" in healthcare results in lack of commitment, slow technology adoption, and perhaps decreased patient safety.⁵

The application of PDAs in reporting adverse events will increase within and

across clinical disciplines and borders, but so must the rigorous appraisal to aid transference of knowledge. The global stage for international comparative research is widening, necessitating the need for integrated study designs, contextual analysis and robust reporting. It is often desirable to look for cost-effective means of improving patient care, with a dual learning carriage between institutions and nations. Patient safety and quality care studies will therefore continue to enjoy inputs from epidemiology, health services research, health economics, health policy, cognitive engineering, and information and communication technology. However, the main challenge remains: where is the patient in "patient safety"?

1. Bent PD, Bolton SN, Creati BJ, et al. Professional monitoring and critical incident reporting using personal digital assistants. *Med J Aust* 2002; 177: 496-499.
2. Fischer S, Lapinsky SE, Weshler J, et al. Surgical procedure logging with use of a hand-held computer. *Can J Surg* 2002; 45: 345-350.
3. More GA. Crossing the chasm: marketing and selling high-tech products to mainstream customers. New York: Harper-business, 1995.
4. Ramussen J. Risk management in a dynamic society: a modelling problem. *Saf Sci* 1997; 27: 183-213.
5. Gawande AA, Bates DW. The use of information technology in improving medical performance: Part II. Physician-support tools. *MedGenMed* 2000; Feb 14: E13. Available at <http://www.medscape.com/viewarticle/408033> (accessed Dec 2002). □

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IN REPLY: I thank Arah for pointing out the importance of the "context" into which any quality and safety program will be deployed. Success or failure of innovative pilot programs will always depend upon the willingness of the end-user to embrace change.

In the case of performance monitoring using electronic logbooks, this will first require an easily workable and reliable tool, not just for the technologically proficient few, but for all users. In addition, users must also be motivated to monitor their professional performance. In today's world, where medicolegal issues are increasingly significant, there is pressure to prove accountability and reduce one's risk exposure. In carrying out a pilot project only, we aimed to demonstrate the technological feasibility of such a tool. We believe that this has been successful, and that now is the time to embrace the use of such tools.

Ultimately, cultural change will only occur when the "early adopters" and

enthusiasts demonstrate the usefulness of a concept, leading the way and pulling the rest of the population behind them. □

Air pollution and its health impacts: the changing panorama

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TO THE EDITOR: A recent *MJA* article by Kjellstrom et al¹ correctly lists home heating using wood as a major cause of air pollution in Australia. It is therefore surprising to read in their optimistic view of "Circa 2100" that, whereas coal will be burnt in superefficient and clean-burning electric power stations, more wood will be burnt to heat houses.

When the Irish government banned the sale of coal in Dublin, there were substantial decreases in smoke pollution and mortality from respiratory and cardiovascular causes.² If any evidence is needed that similar benefits can be expected from banning domestic wood heaters, it is to be found in recent research on the emission of fine particles and a wide range of toxic compounds by wood heaters, old and modern.³

The reason given by Kjellstrom et al for regarding wood-burning for home heating as desirable is that it would cause less global warming. But this reason is not convincing, as the potential "benefit" would be outweighed by the immediate harm inflicted by wood smoke on public health. People are unlikely to agree that we have to accept death and disease now in order to save the planet a few decades hence.

It is commonly claimed that the burning of wood is "greenhouse-neutral". This is not true if the burning takes place in home heaters, which emit methane and soot particles — both powerful greenhouse agents. When global emission rates and global warming potentials are both taken into account, the probable ranking of the three most important greenhouse agents is (first) carbon dioxide, (second) soot particles, and (third) methane.⁴ As almost everything in greenhouse science is fraught with high uncertainty, it is not possible to say what percentage of the potential

greenhouse advantage of wood heaters is cancelled by their emission of soot particles and methane.

What *can* be said is that firing super-efficient and clean-burning electric power stations with plantation timber is the best way to burn wood, using the greenhouse advantage without the toxic hazard.

1. Kjellstrom TE, Neller A, Simpson RW. Air pollution and its health impacts: the changing panorama. *Med J Aust* 2002; 177: 604-608.
2. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* 2002; 360: 1210-1214.
3. Gras J. Emissions from domestic solid fuel burning appliances. Canberra: Technical Report No. 5 to Environment Australia, March 2002.
4. Jacobson MZ. Strong radiative heating due to the mixing state of black carbon in atmospheric aerosols. *Nature* 2001; 409: 695-697. □

Beware the zebra

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TO THE EDITOR: I read with interest the entry in "In other Journals" entitled "Beware the zebra".¹ It described a study in the United States (reported in *JAMA*)² which found that elderly people were more likely to be struck by a motor vehicle when crossing at a marked crossing than at an unmarked site! Personal observation after a year of living and working in the States has led me to be no longer surprised by such a report.

There is what I believe to be a culturally different attitude to road safety here. There seems to be a general belief by pedestrians that cars will stop if they walk out on to the road — often without looking. This is more so at marked crossings, where I can attest to the findings of the article that "nearly 40% of pedestrians incorrectly believed that traffic must stop for a pedestrian who is on the curb waiting to cross at a marked crosswalk."

I believe that this perception may have been ingrained from an early age — US school buses have stop signs which appear when the bus stops, so that traffic behind the bus, alongside and in the opposing lanes has to stop while children are getting on or off the bus and then crossing the road. There is little attempt by the schoolchildren to "look both ways", as we were taught when growing up. This, I think, leads to a misperception that traffic will stop for all pedestrians,



Photograph courtesy Ray Sherman

who may feel even more entitled at a marked crossing to cross without looking.

Since the report may have horrified some readers, I thought it might be worth providing a little local experience on the subject!

1. Beware the zebra [In other journals]. *Med J Aust* 2003; 178: 90.
2. Koepsell T, McCloskey L, Wolf M, et al. Crosswalk markings and the risk of pedestrian-motor vehicle collisions in older pedestrians. *JAMA* 2002; 288: 2136-2143. □

Correction

Re: "Lymphoedema in breast cancer patients", the letter to the editor by Graeme N Brodie in the 3 March issue of the Journal (*Med J Aust* 2003; 178: 244), in which washing soda, used in a simple dialysis treatment for lymphoedema, was mistakenly called crystalline calcium carbonate. Washing soda is, in fact, sodium carbonate.

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