Basile, Mark

From: Ian Haines [redacted]
Sent: Tuesday, 17 July 2012 3:31 PM
To: Basile, Mark
Cc: Cunningham, Megan; Jones, David
Subject: Submission on 17th Edition of Medicines Australia Code of conduct
Attachments: MJA Audits.pdf; MJA Editorial.pdf; MJA hai10221_fm.pdf; MJA olv10224_fm.pdf; MJA letter cole.pdf; MJA letter OH.pdf; MJA Letter.pdf; thomas 2012 DRUGS CELEBREX[1].pdf

!7th Edition of Medicines Australia Code: Individual submission to the ACCC

Dear Mr Basile and members of ACCC,
I write to urge that the ACCC insist on full disclosure of payments made to individual health practitioners in this 17th edition.

Many published studies recently have documented the risks to public health that can occur when pharmaceutical companies and doctors have hidden financial relationships. These can vary from withholding of unfavourable studies of new and expensive medicines from publication, incomplete data on efficacy and toxicity, exaggerated conclusions about efficacy of new drugs in medical publications.

The pressure for academic doctors to be coauthors on papers to further their careers has been shown to increase the probability that they will 'sign off' on studies that have been ghost-written, or the endpoints altered through the study, or the full data and its analysis not being available.

These same doctors sometimes become public advocates for these new and very expensive therapies without declaring their conflicts of interest or they help to write clinical guidelines for other doctors. The potential impacts of this have been seen in the USA where the medical evidence for treatment of ADHD and mental illness in children and adolescence has become grossly distorted. This has very large and deleterious impacts on the health of vast numbers of young people around the world as well as wasting vast amounts of finite public health funds. It has also led to continued, repeated and very large fines for many multi-national pharmaceutical companies (who say in their own defence on each occasion that the corrupt practices are ancient history and have been remedied….until the same charges are laid over a different drug a few years later)and punishment of several prominent professors of psychiatry from leading universities in the USA such as Harvard and Emory.

I acted as a witness for the ACCC and provided a large amount of evidence and a statutory declaration to the Federal Court hearing in 2006 where Medicines Australia unsuccessfully challenged the ACCC requirement for 6-monthly detailing of all monies provided to health practitioners every 6 months. The evidence provided there and Justice French's findings (he is now Chief Justice of the High Court) should be reread before the ACCC makes its final decision in this case.

I do not believe that providing publicly accessible data on individual doctors will impose any significant burden on pharmaceutical companies. I also believe that most health practitioners and the general public will welcome increased transparency and the same standards of disclosure that apply to other privileged professionals involved in public service and who are paid from the public purse or who have responsibility for publicly listed companies such as politicians and company directors. The public only becomes angry and disillusioned when important information is hidden rather than disclosed.
Those with nothing to hide will welcome the initiative. No doctor or pharmaceutical company need fear revealing and justifying a legitimate financial relationship.
I attach some recent articles by me on this topic.

Yours Sincerely,

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In Documents on Pain Drug, Signs of Doubt and Deception

Michael McElroy for The New York Times

Dr. Steven Nissen is overseeing a trial on Celebrex that is scheduled for completion in 2014, the year the drug's patent expires. He dismisses any claim that Pfizer has delayed the study.

By KATIE THOMAS Published: June 24, 2012

A research director for Pfizer was positively buoyant after reading that an important medical conference had just featured a study claiming that the new arthritis drug Celebrex was safer on the stomach than more established drugs. "They swallowed our story, hook, line and sinker," he wrote in an e-mail to a colleague.

The truth was that Celebrex was no better at protecting the stomach from serious complications than other drugs. It appeared that way only because Pfizer and its partner, Pharmacia, presented the results from the first six months of a yearlong study rather than the whole thing. The companies had a lot riding on the outcome of the study, given that Celebrex's effect on the stomach was its principal selling point. Earlier studies had shown it was no better at relieving pain than common drugs — like ibuprofen — already on the market.

The research chief's e-mail, sent in 2000, is among thousands of pages of internal documents and depositions unsealed recently by a federal judge in a long-running securities fraud case against Pfizer. While the companies' handling of the research was revealed a dozen years ago, the documents provide a vivid picture of the calculation made by Pfizer at the time and its efforts ever since to overcome doubts about the drug.

The documents suggest that officials made a strategic decision during the early trial to be less than forthcoming about the drug's safety. They show that executives considered attacking the trial's design before they even knew the results and disregarded the advice of an employee and an outside consultant who had argued the companies should disclose the fact that they were using incomplete data. In one e-mail, an associate medical director at Pharmacia (which was later bought by Pfizer) disparaged the way the study was being presented as "data massage," for "no other reason than it happens to look better."

In another, a medical director at Pfizer described it as "cherry-picking the data" even as officials were publicly boasting of the study's success. Dr. M. Michael Wolfe, a gastroenterologist who had cautiously praised the study in a medical journal at the outset, said after reviewing the new documents: "I always try to give investigators the benefit of the doubt, but these communications make it quite challenging for me."

The importance of Celebrex to Pfizer is indisputable. It is one of the company's best-selling drugs, racking up more than $2.5 billion in sales, and was prescribed to 2.4 million patients in the United States last year alone. The drug is the last of the so-called COX-2 inhibitor pain drugs, after Vioxx and Bextra were withdrawn in 2004 and 2005 because of safety concerns.

Some of the Celebrex's detractors contend that its risks are still not fully understood, and argue that Pfizer is dragging its feet on a study — now nearly six years old — evaluating the drug's heart risks. The study is scheduled to end in May 2014, the same month that Celebrex loses its patent protection and sales of the drug are expected to plunge.

Then and now, Pfizer has defended its decision to release partial results from the 2000 study and denies any intent to deceive. Company officials have said the drug has demonstrated its worth and safety. The proof, they say, is that 33 million Americans have taken it. "The bottom line is Celebrex is a very important option for many of these patients," said Dr. Steve Romano, head of the medicines development group in Pfizer's primary care unit.

The decision by Pfizer and Pharmacia to withhold crucial data became widely known in 2001, after the Food and Drug Administration released the study's full results. The revelations, along with similar reports of withheld data by other drug companies, led to calls for reforms in the way data from clinical trials is published, including in The Journal of the American Medical Association, which ran an article featuring the partial results from the study.

The withheld data also led to a lawsuit, filed in 2003, by several pension funds that charged that by handling the results the way they did, Pfizer and Pharmacia had misled investors and were responsible for a drop in Pharmacia's stock value when the full results were revealed. Lawyers for Pfizer and for the pension funds declined to comment. In a statement, company officials said they were confident they would prevail when all the evidence was heard. "The few documents handpicked by lawyers suing Pfizer and being reported by The New York Times are not a fair representation of this body of evidence," the company said.

The documents show that in February 2000, Pharmacia employees came up with a game plan on how they might present the findings once they were available. "Worse case: we have to attack

the trial design if we do not see the results we want," a memo read. It went on: "If other endpoints do not deliver, we will also need to strategize on how we provide the data." Another document, a slide, proposed explaining poor results through "statistical glitches."

Pfizer officials said the memo appears to reflect discussions by some Pharmacia employees about both the Celebrex study and a similar study of Vioxx. The slides, the company said, appeared to have been prepared before the results were known and discussed several situations.

While officials were boasting of the study's success, employees behind the scenes were questioning its value. In September 2000, Dr. Emilio Arbe, a Pharmacia associate medical director, expressed his reservations. After describing the decision to use the limited results as "data massage," Dr. Arbe wrote, "I wouldn't feel too comfortable presenting a fudged version of the facts."

In May 2001, Dr. Mona Wahba, who worked on Celebrex, sent an e-mail to colleagues describing as "cherry-picking" a new analysis that also used six months of the results. Pfizer officials said Dr. Wahba's e-mail was sent after the full study became known. In a deposition, Dr. Wahba said she did not recall what she meant.

Dr. Samuel Zwillich, who wrote the "hook, line and sinker" e-mail, testified in another deposition that his comment probably had to do with his concerns around a lesser claim that Celebrex led to less blood loss than other drugs. Through a Pfizer spokesman, he declined to comment.

Pfizer has argued that presenting the limited data was legitimate because so many people taking a comparison drug, diclofenac, dropped out, biasing the later results.

The controversy over the safety and effectiveness of Celebrex continues today. Celebrex and Vioxx, which was made by Merck, brought in billions in sales almost as soon as they were introduced in the 1990s. But the excitement skidded to a halt in 2004, when Merck withdrew Vioxx after studies linked it to an increased risk for heart attacks. Some studies indicated that Celebrex, too, carried elevated risks. In part to address those concerns, Pfizer announced in 2005 that it was starting a trial that would compare the heart risk for Celebrex with ibuprofen, the drug in Advil and Motrin, and naproxen, which is sold as Aleve. The trial is not expected to be finished until 2014 when the Celebrex patent expires. Dr. Steven Nissen, the Cleveland Clinic cardiologist who is overseeing the trial, said Pfizer has spent hundreds of millions of dollars and enrolled 18,000 patients. Recruiting has been difficult, he said, in part because European Union countries have barred patients with heart risks. Dr. Nissen dismissed claims from critics that Pfizer has been delaying the trial out of fears about its outcome. "The last thing in the world I want to do is to be sitting here twiddling my thumbs with a public health concern," he said.

Others were not so sure.

"One could draw conclusions," Dr. Alastair J. J. Wood, who was chairman of the F.D.A. advisory panel that examined COX-2 inhibitors, said recently. He is a partner at Symphony

Capital, which invests in drug development. “It clearly would have been nice to have had this information long ago.”

Despite its success, Celebrex’s place among pain drugs is not settled. According to Pfizer, 93 percent of insured patients have access to Celebrex. Some doctors said Celebrex has advantages because it can be taken once a day and studies have shown that it causes less stomach discomfort than other drugs, although some have argued those types of findings are not always reliable.

“You’re dealing with softer, subjective endpoints,” said Garret FitzGerald, chairman of pharmacology at the University of Pennsylvania.

There is still no clinical proof that Celebrex is better at preventing serious gastrointestinal injuries.

Dr. David Borenstein, who conducted some trials of Celebrex for Pharmacia, said the drug relieved pain in some patients when other drugs failed. “It’s easy to talk about theoreticals when you’re not hurting,” he said.

A version of this article appeared in print on June 25, 2012, on page A1 of the New York edition with the headline: Signs of Doubt and Deception In Documents on a Pain Drug.

What changes are needed to the current direction and interpretation of clinical cancer research to meet the needs of the 21st century?

Ian N Olver and Ian E Haines

ABSTRACT

- In this 21st century, we will need to better analyse the outcomes of our spending on newer and more expensive anticancer drugs, particularly through postmarketing assessment, to ensure that these investments are justified.
- Evidence-based medicine is only as good as the evidence available, and we advocate for more independently designed and funded trials that concentrate on the minimum effective dose and duration of therapies to reduce toxicity to patients and to control costs. There is a place for governments to provide funding for these studies in the public good.
- Although improving survival over standard care is the gold standard for proving the efficacy of a new therapy, surrogate endpoints such as early biological marker changes, functional imaging changes or earlier measures such as progression-free survival must be investigated to enable drug therapies to be discontinued earlier if they are ineffective.
- Studies searching for the presence of biological targets must be funded to exploit the potential advantage of targeted therapies.
- Treatment guidelines are best written by experts who are independent of the pharmaceutical industry.
- Existing databases should be linked to better monitor the outcomes of new therapies. Privacy safeguards are important, but privacy legislation may need to be modified to serve the greater public good from the information gained from linking databases.

MJA 2009; 190: 74–77

Australia's ageing population has led to an increase in the nation's cancer incidence. The enormous costs of new treatments and medical interventions for cancer, and other diseases, continue to drive up health spending as a proportion of gross domestic product, rising from 8.5% in the 1997–98 financial year to 9.2% in the 2001–02 financial year.[1] If we are to continue to provide the best possible care for all cancer patients in Australia in the 21st century, we believe there needs to be a system to follow up and evaluate the outcomes of all treatments, particularly new and expensive treatments, more systematically than we currently do.

We are all impatient for cures for more cancers, and directing resources to clinical research is to be encouraged. However, our ongoing routine clinical use of increasing doses of varying combinations of current toxic and expensive cancer therapies, which will not result in cure or substantial remission in many cancers, consumes enormous amounts of finite financial resources that could perhaps be better spent in other areas.[2-6] Do we currently have enough information about the outcomes of new and often very expensive treatments, particularly after they are approved by the Therapeutic Goods Administration and listed on the Pharmaceutical Benefits Scheme (PBS)? These approvals are often based on data from very carefully selected subgroups of patients in studies that are often designed, funded and interpreted and written by the pharmaceutical company seeking the PBS listing. Conversely, do we know that important evidence-based clinical advances are reaching the communities for whom they were designed and approved?[7]

It is not being nihilistic to suggest that we need continuous assessment of the goals and outcomes of our research to justify continuing to fund high-cost cancer treatments. We maintain that the global management and funding of cancer therapy should be conducted by adhering to good governance principles. These principles include regular review, strict corporate governance of budgets and "profit and loss statements" (ie, comprehensive outcome assessments), careful strategic planning and the setting of realistic goals.

If we are to achieve the best possible balance in the future between improving overall outcomes for all cancer patients and maintaining affordable treatment, then we need changes. Improved outcomes data will help us to set realistic treatment goals for all patients. High-quality data can help patients and their health advisors to achieve the appropriate balance between efficacy and toxicity of the treatments for each individual patient. This high-quality data will also allow us to maximise the outcomes that we achieve from our investment into cancer treatment and research.

Evidence-based medicine is only as good as the evidence that is available. For example, a recent large randomised study using a new, expensive targeted therapy, panitumumab, in metastatic colorectal cancer, sponsored by panitumumab's manufacturer, reported an improvement in progression-free survival of only 0.7 weeks compared with best supportive care. The manuscript's conclusion presented it as an important and positive study.[8] The five authors who conceived and designed the study, analysed and interpreted the data, and wrote the manuscript included two employees and stockholders of the company and two physicians who declared significant potential conflicts of interest because they had accepted consultancy fees with or without honoraria from the same sponsoring pharmaceutical company. There was no difference in overall survival, although this assessment was impaired by the cross-over design.

Another large, randomised phase III study added the targeted agent erlotinib to gemcitabine in advanced pancreatic cancer. The manuscript concluded that this was the first study to demonstrate a statistically significant improved survival in advanced pancreatic cancer for any agent added to gemcitabine.[9] Seven of the study's authors declared a significant financial conflict of interest involving the manufacturer of erlotinib, the part sponsor of the study; two of the authors were employees of that company. However, the conclusion was based on an improved median survival of only

0.33 months (10 days), which would not be considered clinically significant, especially as it was achieved with considerable toxicity, including diarrhoea, infection, rash and stomatitis. A subsequent independent conservative analysis of costs showed that the incremental cost-effectiveness ratio of adding erlotinib to gemcitabine was US$410 000–US$510 000 per year of life saved.[10] Very few, if any, health systems can afford those costs.

A third recent, large, randomised non-crossover study added the expensive agent bevacizumab to paclitaxel for the treatment of advanced breast cancer. It showed no improvement in overall survival or in quality of life with the addition of bevacizumab, but was presented as a positive study because the combination improved progression-free survival.[11] This is a meaningless benefit if it doesn't help patients feel better or live longer, as progression-free survival has not been shown to be a surrogate endpoint for overall survival. Five of the authors declared potential financial conflicts of interest involving a company that makes or distributes bevacizumab.

In addition, we believe that the decline in independent studies in the past decade has seen a significant change in the design of clinical trials in cancer. There has been a shift away from using new drugs until maximum response and then stopping to avoid toxicity and re-treating at relapse, to studies that continue very expensive and toxic treatments until relapse, as long as they are tolerated, often requiring a 25% increase in measurable disease until the treatment is discontinued. There are no survival or quality-of-life data to support this increase in treatment duration, which adds enormous costs if this design becomes the "evidence base". An Italian study has been reported to show that phase III trials, multicentre trials, and international trials are less likely to be independent. As its author states: "It is ironic that our health systems risk bankruptcy for the skyrocketing costs of drugs that were developed on their own patients using strategies that ignore the patients' needs and priorities."[12]

The independence of guidelines

We need independent advice from some of the key advisory and policy-setting groups such as is provided by the independent Early Breast Cancer Trialists' Collaborative Group overviews from Oxford and the European Clinical Trials Directive,[13-15] and we need more independent Australian oversight of foreign clinical guidelines and industry-sponsored research.

Recent large and influential studies in breast cancer had designs and results that fitted "much better with the expectations of their sponsors than those of the patients and of the health systems that must sustain the costs of the new treatments".[12] We currently rely significantly on the interpretation of clinical studies and their incorporation into clinical guidelines by foreign clinical organisations, particularly those in the United States. However, many of these US guidelines are heavily influenced by the pharmaceutical industry and special-interest groups.[16] Questions inevitably arise when pharmaceutical companies and medical-device companies with a financial stake in the outcome provide substantial funding for their development and implementation, or when members of guideline committees also have substantial financial associations with industry.[17,18]

Databases to monitor outcomes

Australia has a system of cancer registries in each state and the Australian Institute of Health and Welfare pools data under strict guidelines to report national outcomes. It is difficult for independent research groups to obtain national data for outcomes analysis, as this currently requires individual ethics approval in each state. Ostensibly, this is because of concerns about privacy and the different data collection methods which makes aggregating the data more difficult. However, it is clear that this requirement for separate ethics approval in each state is also used as a mechanism to discourage use of national data by third parties who may make unfavourable comparisons of outcomes data between states.

Access to the best possible outcomes data will require a comprehensive national cancer database in Australia that provides data on outcomes for cancer treatments such as surgery and radiotherapy as well as drug treatments, something that is potentially more achievable here than in most countries. There are already voluntary national registries established, such as the Australian Rheumatology Association Database, which is monitoring the benefits and safety of new rheumatological drug treatments.[19] However, small individual databases for different diseases will provide only a small fraction of the information that a comprehensive national database would provide.

Potential solutions

Improving the evidence by trial design

We need more independently funded and reported research for our policy-setting groups to analyse.[20] To achieve this, the clinical research community needs to rethink the terms of its cooperation with industry in clinical trials, taking into account a wider clinical and public health perspective.[21] Resources may need to be directed to independent units. A large Danish study has shown that this approach, using stricter guidelines of good clinical practice as outlined in the 2004 European Clinical Trials Directive, led to an increase in registration of independent trials.[15] This strategy has the potential to be cost-effective in the long term and provide funds for governments to spend on pivotal clinical trials to be designed and run independently of the pharmaceutical company responsible for a product. This will improve the evidence on which treatment policy is based. Such studies would not maximise the use of a product, but discover the minimum effective dose and duration that would provide a cost-effective balance between efficacy and toxicity. An example is the use of trastuzumab in addition to chemotherapy as adjuvant therapy in breast cancer. The initial trials showed the benefit of 12 months of therapy with trastuzumab, which at the time cost A$50 000–A$60 000.[22,23] An independent Finnish study showed that 9 weeks of trastuzumab therapy in this setting was effective, but no comparison of relative efficacy could be made.[24] The next study designed by the pharmaceutical industry was to test 2 years versus 12 months of trastuzumab therapy, when a 6 months versus 12 months study was needed. Although this latter design was eventually initiated in France,[25] it stimulated debate about whether governments should fund such trials, given that the pharmaceutical industry is unlikely to do so, and there is potential benefit for the public purse.

Current infrastructure funding for cancer trials groups and a National Health and Medical Research Council (NHMRC) enabling grant through the Clinical Oncological Society of Australia is a suitable model for encouraging independent trials, but needs to be

expanded. The Australian New Zealand Clinical Trials Registry is also a useful resource for identifying the trials being performed,[26] and where the gaps exist.

Evaluation of trials

Traditionally, the strongest endpoint for a new agent in cancer therapy is a clinically meaningful survival advantage in a randomised clinical trial against the previous standard therapy, ideally with confirmation in a subsequent study. However, this endpoint can take years to achieve and is costly. The discovery of surrogate endpoints is vital to clinical investigation. These could be either (i) the observation of an early change in a biological endpoint, or an early change in findings on a functional scan, such as has been recorded with responsive gastrointestinal stromal tumours having early positron emission tomography responses;[27] or (ii) analysis of whether a progression-free survival endpoint does predict for a survival advantage in a particular tumour type. This type of research is vital to guide treatment decisions, and is beginning to be explored. However, clinicians will have to practise according to such evidence, particularly if regulatory bodies make a new drug available within a budget that is contingent on complying with early-stopping endpoints. This can be difficult if, in the absence of measurements showing early progression of the tumour, the emotive response of both the patient and clinician is to continue the use of a drug for longer.

The other essential for improving the cost-effectiveness of new targeted therapies in the 21st century is to identify the functional target before widespread use, and develop a funding mechanism to allow the target's detection, so that only patients whose tumours express that target receive the drug. This avoids the unnecessary toxicity and cost of treating patients who cannot respond. This lesson was learned in the early phase III trials of gefitinib in lung cancer, where the drug appeared ineffective in most patients because the actual genetic target had not been identified.[28]

Databases and linkage

One of the keys to more effective use of the national drug budget is better monitoring of outcomes after approval, and the ability to more easily modify the indications for use and reimbursement on the basis of emerging data from a drug's widespread use. In the US, the new Sentinel Initiative allows officials from the Food and Drug Administration to use information from Medicare claims to assess the risks of marketed drugs.[29]

In Australia, many of the data required for monitoring outcomes of drug therapies currently exist in the Medicare, PBS, Veterans' Affairs and individual state Cancer Council databases, and in state registries of births, deaths and marriages. The key is to be able to better utilise these data by linkage of databases. The potential benefits of this approach for the Australian health care system have recently been demonstrated with a large postmarketing study of trastuzumab therapy using these administrative databases.[30] A Western Australian program funded by the National Collaborative Research Infrastructure Strategy is piloting linkage of federal and state data. Other recent studies have also provided good insight into the potential benefits for our future health care of a comprehensive cancer database and the information technology capability for data linkage.[31,32]

Privacy legislation is often cited as a barrier to linking databases. The key question is whether the possibility of breaches of privacy, despite mechanisms that can be used in data linkage to protect individuals, is of such concern to the public as to outweigh the public good of using linked data for the purposes of postmarketing assessment of expensive and potentially toxic drugs. A simple survey asking patients in an Adelaide oncology clinic their views on use of their data for research did not indicate that privacy was an overwhelming concern.[33] Privacy legislation should be modified to allow linkage of population data, with the appropriate safeguards in place, if the potential public benefit is sufficiently strong.

Such a database may become partly self-funding if a "user pays" system for funding high-cost new therapies that was recently commenced in the United Kingdom is widely adopted.[20] These data will not only check that we are achieving outcomes that match the data that formed the basis of the PBS or Medicare funding approval of all treatments, but will also check the uptake of important clinical advances in the general community. Only then will we have this important part of our health service ready for the complex challenges of our ageing population and the rapidly increasing costs of new medicines in the 21st century.

Guidelines

Finally, we maintain that guidelines which translate research findings into practice and are influential on the practice of clinicians should ideally be written by experts with no potential conflicts of interest, and that transparency alone is insufficient.[34] These would be based on independent evidence as outlined above, and be updated with information from the improved outcomes surveillance made possible by linked databases. Further, the editor of *World Psychiatry*, Giovanni Fava, advocates that as well as enforcing declaration of potential conflicts of interest, we should reward those who choose to remain independent by giving them priority for public research funding, guideline panels and journal editorships.[35]

Competing interests

None identified.

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What changes are needed to the current direction and interpretation of clinical cancer research to meet the needs of the 21st century?

Matthew P Doogue and
Kathleen M Knights

To the Editor: Articles by Olver and Haines[1,2] have catalysed robust discussion about the relationship between the pharmaceutical and device industries and the medical profession.[3] These authors advocate changes in the direction of clinical cancer research and in health policy.[2] In an era in which research into medicines is dominated by industry, they argue for greater scrutiny of data in a resource-constrained environment, and for fundamental changes in the collection, interpretation and ownership of data. We find their arguments sound and equally applicable to other areas of medicines research and health policy.

Their primary recommendation is for "...a system to follow up and evaluate the outcomes of all treatments..." That is, that we exercise our duty to patients by monitoring and analysing existing clinical data to inform health care policy. There is a great deal of valuable clinical data collected that are not readily accessible because of ownership or privacy issues. For example, much business involving public health dollars is labelled "commercial in confidence", and laboratory data held in many pathology databases are not accessible at all. The likely benefits to patients and society of transparency and data linkage in health care are greater than possible benefits to individuals of secrecy and privacy.

Quality use of medicines (QUM) is one of the central objectives of Australia's national medicines policy. QUM means selecting management options wisely; choosing suitable medicines if a medicine is considered necessary; and using medicines safely and effectively.[4] Olver and Haines also identify issues relating to quality use of research. Quality use of research might include: supporting research into monitoring clinical outcomes related to drug use; supporting research into better use of existing drugs; and supporting truly independent guideline development.

There continue to be advances. For example, registration of trials in public databases, such as the Australian New Zealand Clinical Trials Registry, should reduce publication bias.[5] However, the decline of independent public sector clinical drug research and the marketing-based design of phase III and, increasingly, phase II industry-funded studies contribute additional bias to the available information.

Olver and Haines' arguments apply to all therapeutics, and particularly to all drug therapies. We strongly support their proposals for health data linkage and for quality use of research. These fit within existing health policy, and our continued failure to make full use of clinical data is an ethically compelling reason for improved political and clinical governance.

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Patients expect transparency in doctors' relationships with the pharmaceutical industry

Catherine H Cole

To the Editor: Two articles in the 19 January issue of the Journal[1,2] and an article on the involvement of pharmaceutical companies in studies of their own products published in *The Australian* on the same day[3] impel me to relate my own experience of attempting to influence my colleagues' attitudes toward transparency in relationships with the pharmaceutical industry, and my good fortune to be working in a 21st century oncology clinical trials unit.

The relationship between the science of pharmaceutical development and the science of oncology is robust and fruitful. While intending to be only mildly controversial, I caused great offence in my opening address to the Australian and New Zealand Children's Haematology and Oncology Group annual meeting in 2008 by suggesting that it is no longer acceptable for any of us at the coalface of oncology to deal directly with pharmaceutical salespeople or for medical education to be directly funded by industry.

I note the view of Tattersall and colleagues that "… sponsoring doctors to attend independent conferences is recognised as facilitating continuing medical education …".[1] In my view, financial support for medical education should come from unaffiliated sources — perhaps competitive grants from the government, who may in turn raise funds from industry.

Similarly, we must be able to deny (not just declare) a conflict of interest in our activities in clinical trials and practice, and teach the difference between clinical trials (phase III cooperative group randomised controlled trials of multidrug treatment, with wide eligibility criteria to benefit as many patients as possible) and drug trials (phase I or II single-agent trials with narrow eligibility criteria, such that adverse effects of new drugs are found quickly). Both groups of trials are essential for the benefit of patients with cancer and leukaemia, as is the need for clinicians to be — and to be seen to be — at arm's length from industry.

I have been fortunate to work in a clinical trials unit that is supported by a wise medical administration and an ethics committee devoted to the practice of clinical trials as the best evidence-based medicine for patients. Our unit has clinical research associates on staff, is an active member of the

United States-based Children's Oncology Group, and does not partake in trials directly sponsored by industry. Indeed, after 20 years in the field, I know the trade names of less than 10% of the drugs I prescribe. I decline invitations to see pharmaceutical representatives or to attend industry-sponsored events. I followed the leadership of my mentors and senior clinicians. Can I convince today's trainees to follow suit?

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Brad S Dalton and Deborah J Richards

TO THE EDITOR: We support the findings of Tattersall and colleagues relating to the disclosure of competing interests by general practitioners to their patients, and we agree that greater transparency in general is required with physician–industry relationships.[1] Such relationships have the potential to enhance patient outcomes through quality use of medicines. However, in the interests of a balanced perspective, several points regarding Tattersall et al's article warrant attention.

First, the 2007–08 BEACH (Bettering the Evaluation And Care of Health) survey suggests that the mean length of GP consultations in Australia is 15.1 minutes.[2] Considering this, an adequate discussion or disclosure of industry links to each and every patient is simply not practical. Furthermore, the frequency with which GPs see industry representatives can vary greatly. Given these complexities, perhaps clinics could consider having a simple sign in the waiting room that states "We do/do not see pharmaceutical industry representatives". Disclosures would be most valuable if interested parties agreed on definitions for categories of relationships and payments, uniform approaches to calculating amounts, and standards for information to be made public. Inconsistent practices could create the impression that some practices are being hidden.[3]

Second, we want to highlight the potential benefits of physician–industry collaborations. We recently organised a panel of Australian physicians to advise a pharmaceutical company on research initiatives that need to be undertaken in a highly specialised area of medicine. An Advisory Group Charter, describing the purpose of the group, desired outcomes, and remuneration, was developed and agreed upon by all members. In this case, physicians received remuneration for time spent reviewing documents and collecting information for the meeting, and to cover costs associated with non-attendance at clinic. The aim of the Charter and two-way confidentiality agreements was to ensure transparency. After reviewing the published literature, each physician shared information about treatment practices and outcomes. The physicians identified several areas that require further research and have the potential to enhance patient outcomes in the immediate future. However, they suggested that these initiatives could be undertaken without industry support. They advised the company to direct its research funding towards large, population-based research initiatives. This is just one example of how transparent collaborations can result in enhanced patient outcomes and a redirection of funding into areas of greatest need.

While we agree that increased transparency is important for physician–industry relationships, and improvements can be made through such avenues as disclosure, a retreat from physician–industry collaborations is not in the interests of improved patient outcomes or enhanced quality use of medicines.

Competing interests: Brad Dalton has received consultancy fees from Amgen Australia, Sanofi-Aventis, Roche Products, AstraZeneca, Actelion Pharmaceuticals, Peter MacCallum Cancer Institute, the Australasian Gastrointestinal Trials Group, Gilead Sciences, the National Stroke Foundation of Australia, and Renal Research Tasmania. He was also involved with coordination of the meeting described in this letter. Deborah Richards is employed within the pharmaceutical industry.

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Martin H N Tattersall and Aneta Dimoska

IN REPLY: We thank Cole for her suggestions. We note the Royal Australasian College of Physicians *Guidelines for ethical relationships between physicians and industry* state: "Industry sponsorship to attend conferences … should usually be restricted to those in which the professional anticipates active engagement … and when attendance without support is not possible".[1]

With regard to Dalton and Richards' first point, our survey asked patients for their views about doctors in general and not specifically about general practitioners.[2] We do agree that disclosure would be most valuable if definitions for categories of relationships and payments were agreed on. Unfortunately, the options we presented to patients in our survey did not include disclosure being presented on a website, a method that has recently been launched by the Cleveland Clinic in the United States.[3] A US Senate Bill, if enacted, would require health companies to report all their financial links with doctors on a government website.[4]

The potential benefits of physician–industry collaboration were not presented in our survey. Obviously, having doctors advise the pharmaceutical industry is likely to be beneficial, but is it appropriate to continue relationships where industry is advising or educating doctors?

Notable among the 41 recommendations of a report from a Royal College of Physicians working party in the United Kingdom, chaired by the Editor-in-Chief of the *Lancet*, are: the promotion of standards for prescribing at postgraduate level; a method for gradually ending the support of the pharmaceutical industry in the education of doctors in training; and any honorarium and fee, commercial or otherwise, paid to a doctor should be declared on a publicly accessible website.[5]

We strongly support any interventions that enhance the quality use of medicines.

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Doctors and the pharmaceutical industry: time for a national policy?

Jennifer H Martin, Christopher Beer, Raymond G Morris and Matthew P Doogue

TO THE EDITOR: We share Millar's concerns about the conflicts of interest that influence the genesis and adoption of clinical guidelines[1] specifically, and the lack of independent assessment regarding information provided by the pharmaceutical industry generally. Iain Chalmers puts it succinctly:

> I do not blame industry for trying to get away with anything that is normally considered to be its primary purpose, which is to make profits and look after its shareholders' interests. It is our profession that has colluded in all of this and been prepared to go along with it — we are the people to blame because we need not have stood for it.[2]

We believe the reasons behind this acquiescence are complex, but worthy of discussion.

A strong and viable pharmaceutical industry is essential for clinical improvement. Similarly, clinical involvement in industry research is necessary. We would not debate either of these statements, but we are concerned about the failure of our profession to stand back and exercise careful scrutiny of data. Classic examples are thalidomide in the 1960s and, more recently, the cyclooxygenase-2 (COX-2) inhibitors, but many less dramatic examples can be

found, such as gatifloxacin or rosiglitazone. This failure on our part harms both patients and the standing of our profession. A recent article in this Journal suggested this failure of physician leadership may in part be due to the comfortable position we cultivate with industry,[3] relationships that go beyond the business transaction of providing independent medical advice for a consulting fee.

Further, the role of "key opinion leaders", cultivated by industry, is reinforced by criteria for hospital accreditation and university promotion, leading to disproportionate value being placed on service to company boards (which is often paid and of modest time commitment) compared with service on hospital, state and national regulatory and quality committees (which is usually time-consuming and unpaid). The presupposition in this discrepancy is that physicians on the company circuit are better physicians than those who are not.

We should all support the recommendations of Millar,[1] Olver and Haines,[3] and Van Der Weyden,[4] including those for true independence and transparency of guideline development and dissemination, strengthening ethical administrative structures and placing appropriate value on public service. Upskilling of clinicians in epidemiology and critical analysis is thus urgently needed so the incremental benefit and costs of new therapies can be objectively examined.

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Are self-regulation and declaration of conflict of interest still the benchmark for relationships between physicians and industry?

Ian E Haines and Ian N Olver

ABSTRACT

- Potential conflicts of interest do not imply wrongdoing, but can create bias, distort decision making, and create a perception that practitioners are being "bought "or "bribed" by industry.
- Transparency alone may not be sufficient to erase the doubts created when authors of clinical practice guidelines or editorials declare potential conflicts of interest. Can the subconscious obligation for reciprocation that exists when gifts are offered and accepted be fully negated?
- Analyses of published clinical cancer research studies have found a positive association between pharmaceutical industry sponsorship and reporting of positive outcomes, manipulation of clinical trials, and hiding of "preliminary data sets". More problematic is the issue of clinical researchers leaking preliminary results to the investment industry.
- Influential literature reviews and treatment guidelines have been associated with widespread declarations of conflict of interest.
- Some potential solutions are: regulating pharmaceutical companies to declare all gifts to clinicians, or ban such gifts; for clinicians to carefully declare potential conflicts of interest or to provide pro bono advice without accepting industry sponsorship; and for all gifts and payments from industry to academic physicians to be coordinated by an independent review committee.
- Journals should only allow reviews, editorials, guidelines and opinion pieces to be written by those without significant conflicts of interest.

MJA 2008; 189: 263–266

In an editorial in 2001, the Editor of the *Medical Journal of Australia* (*MJA*) found "a pressing need for an open inquiry and the formulation of national guidelines" to confront conflicts of interest in research organisations.[1] A subsequent editorial in 2002 tackled the issue of conflicts of interest in the formulation of clinical practice guidelines.[2] Articles by others echoed the Editor's concerns.[3,4]

Despite reaffirming many of the same concerns, another editorial in 2004 concluded that the aim of the *MJA* was "not to exclude anyone with a potential conflict of interest from publishing or reviewing — to do so would disqualify virtually everyone (including editors)".[5] In the light of increasing public and professional scrutiny of these issues, does this response still meet the "ultimate goal … to promote transparency, reduce bias, and maintain public trust in what we publish"?[5]

The impact of duality of interest

When clinical opinion leaders declare the receipt of financial or professional benefits in exchange for providing advice to a pharmaceutical company, but are then expected to give objective, unbiased interpretations of their industry-sponsored research or area of expertise in reviews, editorials or treatment guidelines, then a potential conflict, or duality, of interest exists. This does not imply wrongdoing, but it does create serious doubts.

We contend that leaving the interpretation of these declarations of potential conflicts of interest to consumers of these articles may be unnecessarily difficult, and that such transparency alone may not erase the doubts that are inevitably created. Others go further in suggesting that transparency may facilitate the creation of biased information because people may not sufficiently discount the influence of the declaration, and advisors may therefore feel licensed to exaggerate their position.[6] Does our diverse medical community[7] just "trust" the integrity and judgement of all authors or, conversely, should we dismiss all research findings and conclusions as biased when potential conflict of interest exists? As objective as authors with potential conflicts of interest try to be, can they fully negate the subconscious obligation for reciprocation that exists when gifts or other benefits are offered and accepted?[8] Self-regulation has rarely been shown to work effectively in any enterprise, be it politics or business reporting, as shown by Enron, HIH and many other examples.

Potential conflicts of interest are common in our field of clinical cancer research,[9,10] with complex financial relationships and conflicts of interest that may exist between the pharmaceutical industry and individual physicians,[9,11-14] academic institutions[7-9,11-15] and consumers,[16-18] and the potentially adverse effect that these relationships can have on individual patient care and public health. One author has gone as far as saying that, "We are compromising our integrity and the safety of research subjects, while engaging in unethical research practices and undermining ethical standards of research".[19]

Several studies in oncology have found a positive association between pharmaceutical industry sponsorship and the reporting of positive outcomes (even if not clinically significant),[20,21] manipulation of clinical trials,[22] hiding of "preliminary data sets"[19] and leaking of preliminary results to the investment industry by clinical researchers.[23] All such activities cast doubt on the trial results and the judgements involved in producing guidelines, when potential conflicts of interest are declared.[24] The best evidence-based guidelines are only as good as the quality of both the evidence and the evaluators.

The extent of the problem

In an editorial published in the *MJA* in 2006, Tattersall and Kerridge observed:

> The moral core of medicine and the therapeutic relationship has always been expressed in terms of the possession and expression of values such as honesty, integrity, benevolence, respect, compassion, courage and trustworthiness … Of those things that may damage trust in doctors, much of the attention in recent years has been on recognising and managing conflict of interest.[25]

However, does this always occur? For example, in the annually published analysis of significant clinical advances in oncology — as expert and ethical as each author of this document no doubt is, are there no alternative authors without conflicts of interest to take the place of the 10 authors (of the 20 overall) with declared potential financial conflicts, involving up to 13 different companies for one of them, and including ownership of shares of companies whose products they are charged with independently analysing?[26] Are there no alternatives for the expert Committee on Safety of Medicines, which advises the regulatory agency on new drug approvals in the United Kingdom, than 23 of the 29 committee members with potential financial conflicts of interest, including an association with at least five companies for 13 members, at least 10 companies for another four, and at least 20 companies for three?[27]

Regardless of the integrity of clinicians, such payments may be perceived as bribes or payments for favours received or expected.[28] The head of the Australian Competition and Consumer Commission (ACCC) views financial conflicts of interest as "grubby issues that act as an unpleasant stain on the professionalism and good name of Australia's medical practitioners …"[29] Professor Martin Tattersall, a leading Australian oncologist, has been quoted as saying that the "issue of buying the key opinion leaders is so overt these days".[30] In addition, concern about the profound influence of pharmaceutical companies on doctors is no longer confined to the developed world, as an alarming report from British organisation Consumers International reveals.[31] A former Editor of the *New England Journal of Medicine* (*NEJM*), Dr Jerome Kassirer, believes that these problems reflect the values of a rapacious society and a widespread decline in ethical standards, and are creating a fully justified loss of trust in the medical profession.[32]

Evidence-based data on the extent and impact on many integral parts of public health of potential conflicts of interest, particularly financial ones, have reached a new high point in 2008. As far back as 1970, the UK Department of Health first proposed that expert advisers to regulatory agencies suspend all conflicts of interest during their time in office.[33] However, over 30 years later, the industry's scientific experts continue to have extensive conflicts of interest while providing their advice.[27] We are conscious of the disturbing fact that the *NEJM*, which can currently claim to have the most stringent policy of the general medical journals for restricting and declaring potential conflicts of interest of authors, had to reverse its 12-year policy of precluding anyone with financial ties to industry from writing editorials or review articles in 2002 — simply because it couldn't find enough authors with no financial ties. As the Editor of the *BMJ* commented in a recent editorial:

> On the face of it, this is a pragmatic response to the world we live in. But looked at another way it's an indictment of medicine's culture. The evidence that industry funding biases the design and reporting of clinical research is overwhelming. So too is the evidence that paid opinion leaders increase prescription of the sponsor's drug. Why else would industry pay them?[34]

With recent increased public scrutiny, it is timely to review editorial and other policies.

Potential solutions

Increased transparency

We already have regulatory procedures, such as registers of clinical trials and ethics committees to approve and monitor research. In addition, in an effort to create more transparency and accountability in the often hidden relationships between physicians and the pharmaceutical industry in Australia, the federal government, through the ACCC, has recently ruled that Medicines Australia, representing pharmaceutical[35] companies in Australia, must publicly detail all gifts to physicians (updated regularly). After initially opposing this ruling, Medicines Australia has subsequently conceded that transparency alone may not be sufficient to maintain public trust in the important interface between physicians and their industry, and has appointed an external auditor to monitor these disclosures.[36]

This requirement for transparency should go further and, as with device makers and orthopaedic surgeons in the United States,[37] individual gifts to specific recipients should be publicly listed. Tight regulations on complete declaration and total transparency, with strict auditing by independent administrators, is the standard used in most sectors of society to try to counteract the effect of potential conflicts of interest. Doctors are paid from the public purse and should meet the same level of public disclosure and accountability as politicians and company directors.

Requirements by journals for opinion leaders to be free of dualities of interest

If we cannot control the design and seemingly over-enthusiastic conclusions of clinical trials by physicians with potential conflicts of interest that could conceivably be interpreted as slanted towards the interests of the product of the sponsoring company,[38-44] or find alternative sources to industry for the funding, design, data interpretation and reporting of clinical trials, then perhaps professional organisations and leading journals could retry a bold initiative and only use editorial writers, clinical guidelines committee members and reviewers with no potential conflicts of interest to declare. This still allows authors with potential conflicts of interest to publish their research, but requires others to make independent judgements of its impact.

Opinion leaders providing their expertise pro bono

Close collaboration and dialogue between industry and physicians are vital for the continued development of improvements in health care. However, many authors and reviewers demonstrate that this can occur very effectively without direct payments needing to be made from industry to individual clinicians. Some prominent clinicians have recently decided to stop accepting payments from industry and instead provide their expertise pro bono.[45] Would more clinicians consider this approach, or could industry be discouraged or prevented from offering such payments in the first place?[46]

Better medical student education

While better educating medical students about conflicts of interest and the sophisticated marketing techniques being used on them may help avert the problem at its genesis, as advocated by another former Editor of the *NEJM*, Arnold Relman,[47] much more is needed. Will our learned colleges, leading journals and academic

medical centres also help to provide the educational leadership required for practising physicians?

New guidelines for academic medical centres and opinion leaders

Now seems an ideal time to create a new set of guidelines to try to arrest the perception that some of the world's leading research organisations, journals and opinion leaders are becoming part of the marketing arm of the pharmaceutical industry.[48] The detailed recommendations of a 2-year study by the Association of American Medical Colleges taskforce on industry funding of medical education form a landmark document that should be read by all doctors, medical students and staff of academic medical centres in Australia.[49] It recommends bans on gifts, food and travel and strongly advises doctors against being on industry-sponsored speakers' bureaus to promote drug and device benefits. It advises medical schools to audit all medical education seminars given by faculty members for any "inappropriate influence". Most importantly, it advocates the establishment of a central continuing medical education office to coordinate and oversee all requests for — and offers of — industry funding, and to receive and distribute these funds. All educational scholarships and travel funding should also be coordinated through this independent office, which would evaluate and choose recipients.[49] The time has come to debate these ideas in Australia, as many of them directly affect all members of the medical profession.

The proliferating connections between physicians and the pharmaceutical industry have brought the credibility of clinical medicine to an unprecedented crisis.[50] Opinion leaders in cancer and medical treatment in general, such as the *MJA*, must continue to strive for "best practice". It is time to counteract the view that any "research deck is stacked".[51] This effort requires a bold shift from the current, largely inadequate strategies.[51] Medical care is a vocation, but it is now also a business. As with most businesses, it is essential to find the correct balance between an environment that fosters the creation, development and implementation of innovative ideas that benefit the public and the application of strict and independent oversight to protect the public.

The *MJA* threw down the gauntlet on this vital issue in 2001 and 2002. We urge that it now pick it back up. Consideration of these five strategies can help lead us forward.

Competing interests

None identified.

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Managing patients with advanced cancer: the benefits of early referral for palliative care

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Palliative care is becoming fundamental in the starting line-up of care choices

For Australian patients with advanced, incurable illness, particularly cancer, the option of referral to specialist palliative care services can seem to be a random and discretionary default option that is sometimes called on when all possibilities for life-extending treatment have been exhausted or cannot easily be accessed. Palliative care services (distinct from palliative chemotherapy) provide a broad range of inputs to patients and their carers and loved ones, including specialised medical and nursing management and advice on symptom control; psychological, emotional and spiritual support; practical nursing care; advice and assistance with goal setting and end-of-life care; and bereavement counselling and support. Despite offering these and other unique strategies in the field of cancer management, these specialist palliative care services sometimes stay on the substitute's bench until called on late, when all else has failed.

In Australia, despite having had principles of goal setting and broad palliative care education as part of the medical curriculum for over 20 years,[1-3] and despite evidence of the benefits of referral to specialist palliative care services,[4] only 42% of patients who die of advanced cancer and other terminal illnesses in the country's busiest acute hospital are referred to a specialist palliative care service.[5] Patients with haematological malignancies are referred less frequently than patients with solid tumours.[6] Although oncologists in Australia report that they favour early referral for specialist palliative care, with a concurrent rather than sequential model of care,[7] patients are usually referred late. In one large, integrated Australian palliative care service, patients had a median length of survival after referral of 54 days, representing the final 17% of their illness duration.[8]

Perceived barriers to improving palliative care referral and provision include inadequate communication about goal setting and resuscitation orders; inadequate symptom control; and lack of resources, including inadequate bereavement counselling of caregivers.[7] A Queensland senator recently called Australian palliative care services "an under-resourced shambles".[9]

In Australia and elsewhere, there have been increasing efforts to more accurately define the benefits or otherwise of early referral to palliative care services for patients with an incurable and progressive illness. However, research has been difficult, and randomised controlled trials have not been of high impact.

Now, the results of two recent prospective, randomised studies from the United States[10,11] will help to broaden Australian clinicians' and the public's understanding of the role of specialist palliative care services in the care of patients with advanced, incurable cancer and the advantages of early referral. Although the evidence from these studies has limited application in Australia because of differences in the US and Australian health care systems, the models of care being tested are similar to current Australian models, and the results have the potential to significantly shape practice and policy in this increasingly important part of health care.[9]

A non-blinded randomised controlled trial reported by Temel and colleagues[10] provides a watershed moment in oncology and palliative care. One hundred and fifty-one ambulatory patients referred to an outpatient thoracic oncology clinic for newly diagnosed non-small cell metastatic lung cancer were randomly allocated to standard oncology care with or without referral to a palliative care team. The primary outcome was change in health-related quality of life at 12 weeks. Patients in the early palliative care group had better quality of life and fewer depressive symptoms compared with those receiving only standard care (Box).

The various goals of new interventions in cancer treatment include improving survival; reducing treatment toxicity; improving quality-of-life scores (eg, mood); and reducing the financial costs of treatment. This study achieved all these goals with just the modest intervention of an average of four visits from the specialist palliative care team in the first 12 weeks.

Importantly, the median survival time of 8.9 months was at least as good as would be predicted and expected for the control group. The improvement in overall survival of 2.7 months (30%) for the intervention group who were referred for early palliative care was equal to or greater than that achieved for comparable patient groups with chemotherapy versus best supportive care[12] or the addition of the new and very expensive targeted agents cetuximab or bevacizumab to chemotherapy.[13,14] It was achieved despite significantly fewer patients receiving aggressive end-of-life care. The size of the survival benefit may have been reduced because 14% of the control group also received early referral to a specialist palliative care service for symptom control and had 1–2 palliative care visits during the 12 weeks. A survival advantage from early palliative care referral has been suggested previously,[15] but will need to be replicated by studies in other care settings and in patients with other types of cancer.

Possible weaknesses of this study are the lack of blinding and lack of patient comorbidity data. Extra time spent with health care professionals, rather than any specific palliative care intervention, may have contributed to the improvements seen. But if this were so, this effect would also have been expected in studies showing benefits of chemotherapy plus best supportive care versus best supportive care alone, whereas no difference was shown in survival advantage between these groups.[12] Also, even though the patient groups were balanced for types of chemotherapy and other treatments at enrolment and for the number of courses of chemotherapy during the study, more detailed data on specific chemotherapy regimens are lacking.

Wright and colleagues[11] followed 333 patients with advanced cancer from their enrolment until their death. Those referred to specialist palliative care services had better outcomes when treated outside an acute hospital (Box). Assessment of their carers at enrolment and after the death of the patient showed that those who were assisted in providing care at home until the patient's death had significantly less risk of developing post-traumatic stress disorder or prolonged grief disorder.

In the future, as we seek to confirm and understand more about how these improvements were achieved in patients receiving specialist palliative care, early referral for palliative care should

Two recent US studies showing benefits of early specialist palliative care in patients with advanced cancer: overview

Temel et al[10]

Research question: Does early referral of ambulatory patients with newly diagnosed metastatic non-small cell lung cancer to a specialist palliative care service affect patient-reported outcomes, use of health services and quality of end-of-life care?

Design

- Non-blinded randomised controlled trial; 151 lung cancer patients referred to an outpatient clinic
- Standard oncology care versus standard care with referral to a palliative care team (seen within 3 weeks, and at least monthly until death)
- Groups well balanced for all known prognostic factors, initial cancer therapy, and baseline quality of life and mood
- Quality of life and mood assessed at baseline and 12 weeks
- Data on end-of-life care derived from medical records

Findings

- Patients assigned to early palliative care received an average of four palliative care visits in 12 weeks (range, 0–8 visits)
- Patients in the intervention group had better quality of life than patients assigned to standard care
- Proportion of patients with clinical depression decreased in the intervention group from 22% to 16% and increased in the control group from 25% to 38% ($P = 0.01$)
- Fewer patients with early palliative care compared with standard care received aggressive end-of-life care (33% v 54% of those who had died by time of analysis; $P = 0.05$). Median survival was significantly longer among patients receiving early palliative care (11.6 v 8.9 months; $P = 0.02$)

Wright et al[11]

Research question: Is the place of death for patients with cancer associated with patients' quality of life at the end of life and psychiatric disorders in bereaved caregivers?

Design

- Prospective, longitudinal multisite study; 333 patients with advanced cancer and their caregivers
- Patients followed from enrolment to death (median, 4.5 months)
- Quality of life at end of life assessed by caregiver report within 2 weeks of death
- Caregivers' mental health assessed at baseline, and 6 months after patient's death

Findings

- Patients who died in an intensive care unit or hospital experienced more physical and emotional distress and worse quality of life at the end of life compared with patients who died at home with palliative care
- Death in an intensive care unit was associated with a greater risk of post-traumatic stress disorder in carers compared with death at home with palliative care (21.1% v 4.4%; $P = 0.02$)
- Death in hospital was associated with heightened risk for prolonged grief disorder in carers compared with death at home with palliative care (21.6% v 5.2%; $P = 0.02$) ◆

become part of all arms of any randomised trial of advanced cancer treatment, particularly when a new treatment is being compared with best supportive care or current best treatment.

The results of the two studies discussed here provide the best evidence yet for the multiple benefits of early referral to palliative care services in the care of patients with advanced, incurable cancer. They show that early referral can improve all measurable outcomes for patients by as much as, or more than, new and expensive treatments. Further, they show that early referral can help patients and carers better understand and choose between their treatment options near the end of life, reducing futile use of finite medical resources, debilitating treatments such as continuing cycles of chemotherapy in very advanced stages of illness, and acute in-hospital interventions at the end of life. The incidence of subsequent emotionally and financially debilitating psychological and psychiatric sequelae in the carers of these patients can be reduced. Because of new high-quality evidence, palliative care is rapidly moving from being an ancillary and sometimes discretionary medical treatment option to being fundamental in the starting line-up of care choices for patients with advanced cancer. If early referral for specialist palliative care were an expensive new drug, it would quite appropriately be marketed as a major advance in improving the care of patients with incurable cancer.

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Time to mandate data release and independent audits for all clinical trials

As a condition of publication of phase III clinical trials, medical journals should insist on the release of all raw data and a written independent clinical audit

Editorials and commentaries in some high-profile journals herald an upcoming revolution in personalised oncology.[1] However, any new treatment can only be considered an advance if it:

- extends the life of the patient;
- improves quality of life;
- reduces the toxicity of the current best treatment; and/or
- reduces costs.

Definitive proof of therapeutic benefit relies on freely accessible, high-quality data and their independent evaluation. Unfortunately, open access to de-identified patient data and statistical analyses remains unavailable, so only limited verification of claims emanating from commercially sponsored clinical trials is possible. This restriction reinforces concerns about reporting of trials in general, as "overestimation of the clinical benefit of a drug" is well documented.[2]

Further, reliance on progression-free survival (PFS) as a surrogate for the clinical benefit of a drug is a risky undertaking. PFS is subjective, as it is based on interpretation of radiological tumour size, whereas overall survival (OS) is objective and unambiguous. Despite the inherent subjectivity of PFS, Genentech requested its use as a basis for the approval of bevacizumab (Avastin) for first-line treatment of locally recurrent or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer.[3] However, the usefulness of PFS as a surrogate for OS, therapeutic benefit and accelerated drug approval is controversial.[4-6] To understand why, it is prudent to carefully re-examine the original data, particularly as time-constrained clinicians may be unfamiliar with important details of bevacizumab's accelerated approval.

In 2007, the United States Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee evaluated data from a report of the E2100 trial,[7] in which Genentech claimed an impressive 5.5-month increase in median PFS (mPFS) as a therapeutic benefit, but showed no improvement in median OS (mOS).[3] Hence, the participating patients did not live longer with bevacizumab treatment. As no correlation existed between mPFS and mOS or quality of life, we asked: "What, then, are the benefits of this treatment?"[8]

The uncertainties regarding the strengths of Genentech's claims were exposed by the Committee's analysis,[3] which listed many "significant protocol deviations". These deviations were tabulated in the Committee's analysis and included: stratification errors and treatment beyond progression (Table 3); absent radiographs for some participants (Table 5); discordance between the independent review facility and the trial investigators in PFS determination, with incorrect dates for disease progression, including a massive discordance rate of 51% of PFS date (Table 8); and more frequent dose modifications, omissions, delays and reductions in the bevacizumab arm (Tables 10 and 11).[3] The Committee disagreed with Genentech's cause-of-death attribution in several instances (Tables 15, 16 and 17) and documented a 20% increase in the incidence of grade 3–5 adverse events (including hypertension and neutropenia) in the bevacizumab arm (Tables 13 and 14).[3]

The Committee also analysed a precursor randomised phase III trial from Genentech (denoted AVF2119g),[9] which compared bevacizumab plus capecitabine with capecitabine alone in patients with previously treated metastatic breast cancer.[3] The increase in mPFS in AVF2119g was a non-significant 3 weeks, in striking contrast to the large 5.5 month value in the E2100 trial. The Committee took cognisance of the serious adverse events (Tables 19 and 20) and concluded that this trial "failed to demonstrate a statistically significant effect on PFS and overall survival".[3]

Given these data, the Committee voted against approval of bevacizumab for first-line treatment of locally recurrent or metastatic HER2-negative breast cancer.

Despite this recommendation, which was based on independent scientific, clinical and biostatistical analyses, bevacizumab received accelerated approval with the proviso that further confirmatory trials be conducted.[4,5]

Three years later, the confirmatory trials, AVADO[10] and RIBBON-1 (Regimens in Bevacizumab for Breast Oncology),[11] were completed. Bevacizumab plus docetaxel was compared with docetaxel plus placebo in AVADO, and capecitabine, anthracyclines or taxanes plus either bevacizumab or placebo were compared in RIBBON-1. The previous stunning 5.5-month improvement in mPFS was not seen. AVADO and RIBBON-1 yielded mPFS values of 0.8, 1.2, 1.9 and 2.9 months — again, with no improvement in mOS. Patients did not live longer and both trials confirmed "the serious risks associated with bevacizumab".[4] With this new evidence, the FDA initiated proceedings to withdraw approval for bevacizumab for metastatic breast cancer,[5] a move endorsed in editorials in the *Journal of Clinical Oncology* and *Nature Biotechnology*, which concluded, respectively, that "the outcomes were arguably not clinically compelling"[12] and that "if lack of [drug] efficacy in the face of toxicity is insufficient to reverse an accelerated approval, then what is?".[13]

It is illuminating to compare the mPFS values from the four bevacizumab breast cancer trials (0.7, 0.8, 1.2 1.9, 2.9 and 5.5 months),[7,9-11] with values from the randomised

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phase III trials of bevacizumab in prostate, ovarian, gastric, pancreatic and colorectal cancer (0.4, 0.6, 0.9, 0.9, 1.0, 1.4, 1.4, 1.7, 2.4, 3.8 and 4.4 months).[6] First, the 5.5-month value on which bevacizumab received accelerated approval is the extreme outlier. Second, statistically significant increases in mOS occurred in only two of the above 17 patient sets.[6] Clearly, statistically significant increases in mPFS were not reflected in mOS.

Thus, irrespective of whether tumour size is increasing, decreasing, or remaining stable under drug treatment, tumour size changes are extremely poor predictors of how long a patient will live. The above data show that PFS is not a surrogate for OS.

Evaluating the therapeutic benefit of other anti-cancer drugs requires similar in-depth data analyses. In the case of cetuximab for first-line treatment of metastatic colorectal cancer and the use of *KRAS* mutations as biomarkers in tumour samples, the increase in mPFS was only 0.9 months, with no increase in mOS.[14] As with bevacizumab, some physicians with no ties to the study concluded that this small difference is "clinically irrelevant".[15]

Similarly, claims of therapeutic benefit for rituximab in treatment of chronic lymphocytic leukaemia[16] and chemotherapy-sensitive low-grade follicular lymphoma[17] have been questioned, particularly as these claims were based on PFS, a largely clinically irrelevant end point in these usually indolent diseases.[18-20]

In breast cancer, claims for the superior efficacy and safety of anastrozole, an expensive, often toxic aromatase inhibitor, evaluated in postmenopausal women with early-stage breast cancer,[21] have been challenged.[22] The data failed to show a survival advantage over tamoxifen, which is cheaper and well tolerated.[21]

We further contend that claims of therapeutic benefit based on PFS — from the recent trials of sunitinib and everolimus in low-grade and indolent pancreatic neuroendocrine tumours,[23,24] zalutumumab in recurrent or metastatic squamous cell carcinoma of the head and neck[25] and vandetanib in advanced non-small cell lung cancer[26] — all require additional trials before they can be considered therapeutically robust.

Most of the above drugs, all with questionable therapeutic benefits, are very expensive. For example, approximate costs per month for an average patient for bevacizumab, everolimus, sunitinib or cetuximab are AUD $3400, $5700, $5800 and $7000, respectively.[27] Some newer drugs, recently approved in the US and already in use in trials in Australia, are even costlier (ipilimumab for metastatic melanoma sells at US$120 000 wholesale for a four-dose course of treatment given over 3 months).[28]

In summary, many drugs will add a significant burden to the Australian health care system, and hence all claims based on PFS by authors of pharmaceutical-company- or academic-sponsored trials need to be carefully scrutinised by independent experts before regulatory approval.

How can the evaluation of therapeutic benefit be improved?

A pragmatic example has been set by the molecular, neurobiological and physical sciences communities. First, all de-identified raw data should be lodged in approved, publicly accessible databases where the data conform to minimum information standards and are in a form suitable for independent statistical scrutiny, as exemplified by the US National Center for Biotechnology Information Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo). Second, an independent evaluation of the data conducted by professionals with no ties to, or financial compensation from, the sponsor or its surrogates should accompany the published abstract in medical journals. This "accompanying abstract" constitutes an independent clinical audit. Public companies cannot audit their own financial returns, and it is even more important that companies whose activities involve billions of public dollars in health care expenditure should abide by standards of transparency that can be independently verified using the highest standards of scientific excellence.

> "Medical journals and their editors [should] be beacons of transparent data processes"

As a recent *MJA* commentary stated:

> Facilitating data sharing among researchers, allowing other researchers and peer reviewers to test published conclusions, testing of secondary hypotheses, simplifying data acquisition for meta-analyses, and preventing selective reporting are all important advantages.[29]

Medical journals and their editors have a choice — to be viewed as "an extension of the marketing arm of pharmaceutical companies",[30] or to be beacons of transparent data processes that inform clinicians, improve patient treatment, and provide high standards on which governments, health care providers and patients can have confidence.

Medical journals should demonstrate strong leadership by mandating open access to detailed clinical trial protocols and de-identified raw study data. They should insist on independent audits of data, concomitant publication of an "accompanying abstract", and lodgement of the data in independent databases; these three actions should be a precondition for publication.

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