



INDEPENDENT THERAPEUTIC ADVICE

How achievable is it?

Independence Forum



Therapeutic Guidelines

This supplement summarises the proceedings of the Independence Forum hosted by Therapeutic Guidelines Limited in Melbourne on 29 October 2012

The supplement was prepared by:

Dr Sue Phillips, Chief Executive Officer
Therapeutic Guidelines Limited

Professor Paul Komesaroff, Director
Monash Centre for the Study of Ethics in Medicine and Society

Associate Professor Ian Kerridge, Director
Centre for Values, Ethics and the Law in Medicine, University of Sydney

Ms Mary Hemming, Consultant
Therapeutic Guidelines Limited

This supplement is published by *Australian Prescriber* and is available online in HTML and PDF at www.australianprescriber.com/supplement/36/2/1/48

Printed copies are available from

Therapeutic Guidelines Limited, Ground Floor, 473 Victoria Street, West Melbourne, Victoria, 3003.

Photos courtesy of Therapeutic Guidelines Limited

Citation: Phillips S, Komesaroff P, Kerridge I, Hemming M. Independent therapeutic advice: how achievable is it? *Aust Prescr* 2013;36 Suppl 2:S1-48.

Visit the Therapeutic Guidelines website www.tg.org.au for the full content of the Independence Forum:

- Podcasts of presentations
- PowerPoint slides
- Image gallery

**Therapeutic
Guidelines**

Contents

Acknowledgements	4
Introduction	5
Program	8
Rationale for the Forum	9
Therapeutic independence: A global problem	12
Evidence-based medicine: Strengths and limitations	17
Panel discussion Therapeutic independence and evidence-based medicine	22
Interpreting the evidence: Balancing truth, facts, values and interests	24
Experts and competing interests	28
Panel discussion Identifying and managing competing interests	32
GROUP DISCUSSIONS	35
How should the quality of evidence be improved?	
How should the evidence be interpreted?	
How should the interests that influence decision making be described and interpreted?	
How should declared interests be managed?	
How do end users interpret disclosures of interest?	
Should the role of guideline developers be extended?	
RECOMMENDATIONS	37
Strategies to manage interests	
Improvement of critical appraisal skills	
Reform of regulatory requirements relating to new drugs	
Public funding of clinical trials	
APPENDICES	
Appendix 1: Speaker profiles	38
Appendix 2: Speaker disclosures	40
Appendix 3: Participants	41
Appendix 4: Further reading	45

Acknowledgements

Therapeutic Guidelines Limited would like to thank the following individuals for their support, advice and time they so generously donated to ensure the success of this initiative:

Professor Chris Baggoley
Professor Rachelle Buchbinder
Professor Terry Campbell
Ms Susan Daskalakis
Professor Silvio Garattini
Associate Professor Peter Greenberg
Dr Suzanne Hill
Ms Siân Hughes

Mr Richard Kneebone
Ms Catherine Marshall
Associate Professor David Menkes
Assistant Professor Barbara Mintzes
Professor Robert Moulds
Dr Philipa Rothfield
Associate Professor Ian Scott
Professor Martin Tattersall
Ms Paulette Trevena
Dr Janet Wale
The staff of Therapeutic Guidelines Limited



Professor Paul Komesaroff addresses the Forum

Introduction

This supplement is likely to be of interest to anyone involved in the development of clinical guidelines and clinical research, including:

- health professionals, trainees and students who use guidelines as a basis for their decision making
- policy makers and others working to improve the quality of health care
- people involved in university, college and hospital education.

The supplement outlines the issues discussed at an Independence Forum hosted by Therapeutic Guidelines Limited in Melbourne, Australia, on 29 October 2012. It puts forward recommendations to overcome limitations of the evidence base and improve the trustworthiness of guidelines.

Therapeutic Guidelines is an independent, not-for-profit organisation that was established to promote the quality use of medicines through the publication of clear, concise and ready to use guidelines.

Therapeutic Guidelines convened the Independence Forum to discuss issues of independence and conflicts of interest in the context of the development of therapeutic guidelines for health professionals.

Two eminent overseas speakers, Professor Silvio Garattini from the Mario Negri Institute, Italy, and Assistant Professor Barbara Mintzes from the University of British Columbia, Canada, gave keynote presentations on the complexity of the therapeutic environment and clinical evidence base. Key Australian commentators and health ethicists – Professor Paul Komesaroff from the Centre for the Study of Ethics in Medicine and Society at Monash University, and Associate Professor Ian Kerridge from the Centre for Values, Ethics and the Law in Medicine at the University of Sydney – focused on the influence of vested interests in clinical research trials and guideline development, citing high profile examples such as the case of hormone therapy after menopause. Panel discussions provided insights on these issues from a range of perspectives, including government, evidence-based medicine, clinical research, health professionals and community. During the last session, speakers and participants worked in small groups to formulate recommendations and strategies to improve the suitability of the evidence base and trustworthiness of therapeutic recommendations and guidelines.

Independence: a global problem

Around the world it is commonly assumed that clinical practice guidelines, systematic reviews and the scientific literature are dependable and credible sources of information about the efficacy and effectiveness of therapeutic products. Health practitioners and consumers expect that these are reliable sources of up-to-date information about treatment options, and policy makers rely on them to guide important healthcare decisions. Yet all these publications are subject to many influences that can threaten their independence¹, including:

- the suitability of clinical research funding
- the limitations of conventional clinical trials
- the reliability of the evidence base
- the competing interests of guideline developers and other experts involved in guideline development.

Suitability of clinical research funding

Being situated in the private sector, the pharmaceutical industry is driven by commercial principles. It responds to incentives to develop new drugs, which are often more expensive than established therapies. Because of its size and financial power, the industry has a major influence on the nature of the research agenda. Companies decide which questions will be researched and then they design and fund trials to ensure their new drugs are seen in the best possible light. As a result, the pharmaceutical industry is exerting considerable influence over the development of clinical practice.

In recent years, there has been a trend in the industry to modify society's perception of disease. It actively campaigns for expanded definitions of diseases, which often results in normal processes being labelled as pathological ones. Despite limited evidence, this is happening in many areas, notably for menopause, blood glucose, blood cholesterol and other lipids, blood pressure and bone density. By expanding indications for treatment, the prescribing rate for the newest drugs increases, as does the likelihood of adverse effects.

Appropriate treatment often involves non-drug therapies or the use of more established drugs. Because there are very few sources of funding for research on either non-drug therapies or therapies that are unlikely to produce an economic benefit

for pharmaceutical companies, the evidence base is becoming increasingly biased towards the use of new drug therapies.

Limitations of clinical trials and reliability of the evidence base

Flaws in the design of randomised controlled trials can magnify benefits and obscure the adverse reactions of a drug. Common deficiencies and biases identified in the literature include:

- **abuse of placebo** – new drugs tend to be compared with placebo rather than an established comparator, which would discern whether the new drug offers an advantage over standard treatment
- **non-inferiority trials** – such trials are designed to show a drug is not worse than standard therapy. There is usually no requirement to demonstrate the superiority of a new drug.
- **selection of a comparator** – ideally a new drug should be tested against the best standard, at the best dose and duration of treatment. There is no requirement to assess the drug's safety and effectiveness against the current gold standard treatment.
- **surrogate endpoints** – it is common for the efficacy of a drug to be measured using an indicator that may (or may not) reflect an advantage, rather than measuring a clinical effect relevant to the patient
- **composite endpoints** – the trend for different endpoints to be grouped and analysed together makes it difficult to determine clinical significance
- **exclusion of relevant populations** – new drugs are frequently tested on men rather than the population that will be using the drug (e.g. women, older people, children, people with comorbid conditions). Consequently, there is often little or no information about which groups of people do better or worse with treatment, and little research on the impact of drugs on patients' function and lived experiences.

Analysis of trial data shows a direct link between the funding source and outcomes of a study, with industry-sponsored trials being approximately two-and-a-half times more likely to favour a drug than publicly funded trials.

Publication bias is another important barrier to independence. Positive results that show an intervention works are more likely to be published than negative results. Trials that fail to show benefit may never be published and seem to be under-represented in the published literature. In some cases trial results are published selectively, with positive

results prioritised, rather than the full set of measured outcomes. These systematic biases are a challenge for all those engaged in health, and in particular to groups producing evidence-based guidelines, evidence reviews and health policy.

Conflicts of interest

In recent years questions have been raised in the international therapeutic community about both the reliability of clinical drug trial data and the management of real or perceived conflicts of interest in guideline development groups. An editorial in the British Medical Journal, for example, indicates that the pharmaceutical industry has repeatedly withheld and misreported data on the safety and efficacy of a range of widely used drugs, limiting treatment benefits, endangering lives and wasting public money.²

Scientific data are always interpreted in the context of existing societal views and influences. People relying on trial results as a basis for developing guidelines need to be aware of the spectrum of influences that can bias the collection, analysis and interpretation of data. Conflicts of interest can occur when a commitment, goal or value that arises from a professional or social role is perceived to unduly influence the independence of data or their interpretation. Such conflicts include:

- pecuniary interests
- academic or professional interests that might accrue from publications, awards, media, professional attention or kudos
- personal or religious beliefs, or experience of a health-related condition (either personally or a close family member or friend affected).

International concern

Guideline developers around the world understand the need to create reliable and trustworthy guidelines according to the highest standards and they are becoming increasingly mindful of threats to independence.

Tools have been developed to appraise guidelines and to establish whether the views of the funding body have influenced the content of guidelines and whether the competing interests of guideline development group members have been appropriately managed.³

In the USA, the Institute of Medicine published a report outlining concerns about the quality of the processes used to develop clinical practice guidelines, the limitations in the scientific evidence base on which clinical practice guidelines rely, the lack of transparency in development groups' methodologies, and the management of conflicts of interest among guideline development group members and funders.¹

In 2012 the Guidelines International Network published recommendations for minimum standards for quality guidelines⁴ and in the same year the National Health and Medical Research Council published a report on managing conflicts of interest in the development of guidelines.

Despite the introduction of standards promoting conflict of interest policies, a growing number of reviews of clinical practice guidelines conducted in the last 10 years have revealed that the majority of guideline developers do not in fact publicly disclose any of their authors' conflicts of interest. In 2009 the Medical Journal of Australia published a review⁵ that analysed 313 Australian clinical practice guidelines. The review found that almost 80% of the guidelines analysed included no information on the conflicts of interest of the members of their development groups. Similar findings have been published in relation to US and European guidelines.

The Independence Forum

The central aim of Therapeutic Guidelines is to promote the quality use of medicines through the development, publication and distribution of independent therapeutic guidelines. Independence is a critical issue for Therapeutic Guidelines so a number of strategies and policies have been implemented throughout the organisation and its operations to ensure the independence of the guidelines it develops.

The Independence Forum brought together national and international experts, ethicists, guideline developers, health professionals, clinical researchers and medical writers to identify threats to independence and discuss measures that could be taken to identify and counteract them.

REFERENCES

1. Institute of Medicine (US). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Washington, DC: National Academies Press; 2011.
2. Godlee F. Clinical trial data for all drugs in current use. *BMJ* 2012;345:e7304.
3. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. *CMAJ* 2010;182:1045-52.
4. Gaseem A, Forland F, Macbeth F, Ollenschlager G, Phillips S, van der Wees P. Guidelines-International-Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:525-31.
5. Buchan HA, Currie KC, Lourey EJ, Duggan GR. Australian clinical practice guidelines - a national study. *Med J Aust* 2010;192:490-4.



Speakers group: Professor Silvio Garattini, Associate Professor Barbara Mintzes, Associate Professor Ian Kerridge, Mr Richard Kneebone, Dr Sue Phillips, Professor Paul Komesaroff, Ms Mary Hemming

Program

Monday 29 October 2012
Melbourne

Time	Topic	Speaker/Moderator
0900–0910	Welcome	Mr Richard Kneebone Chairman, Board of Directors Therapeutic Guidelines Limited
0910–0930	Setting the scene: Rationale for the forum and its aims	Dr Sue Phillips Chief Executive Officer, Therapeutic Guidelines Limited
0930–1010	Therapeutic independence: An international view of a global problem	Professor Silvio Garattini Director, Mario Negri Institute for Pharmacological Research, Milan, Italy
1010–1030	Moderated discussion	Professor Paul Komesaroff Director of the Monash Centre for the Study of Ethics in Medicine and Society, Melbourne
1030–1100	Morning tea	
1100–1130	Evidence-based medicine: Strengths and limitations	Assistant Professor Barbara Mintzes School of Population and Public Health, University of British Columbia, Vancouver, Canada
1130–1230	Discussion by panel of experts selected to represent a range of viewpoints	Professor Paul Komesaroff
1230–1330	Lunch	
1330–1350	Cautionary tales about how we make decisions: Balancing truth, facts, values and interests	Professor Paul Komesaroff
1350–1410	Experts, guideline development and competing interests	Associate Professor Ian Kerridge Centre for Values, Ethics and Law in Medicine, University of Sydney
1410–1500	Discussion by panel of experts selected to represent a range of viewpoints	Professor Paul Komesaroff
1500–1530	Afternoon tea	
1530–1615	Informal small group discussions to develop draft recommendations	Professor Paul Komesaroff
1615–1655	Moderated discussion of proposed recommendations	Professor Paul Komesaroff
1655–1700	Thank you and farewell	Mr Richard Kneebone

Rationale for the Forum

Therapeutic Guidelines Limited is a not-for-profit company. Its reputation is staked not only on its publications, but also on its independence of government and pharmaceutical interests. It is financially self-sufficient and does not receive any form of government or industry funding. This is a very satisfactory position to be in, both intellectually and administratively, but it also means that Therapeutic Guidelines needs to carefully manage its resources, relationships with other organisations and the clinical community, and the decisions it makes about the use of its products.

Therapeutic Guidelines evolved out of activities dating back to the 1970s, when a group of health professionals formed to develop antibiotic guidelines in response to the worrying and emerging problem of antibiotic resistance. The guidelines are now widely respected and are an accepted part of the Australian medical culture. They are characterised by their comprehensiveness, authority, convenience, currency and reputation for being a trustworthy source of independent therapeutic advice.

The Therapeutic Guidelines collection currently includes around 3000 topics, which are regularly revised and published. Experts work in multidisciplinary groups to consider feedback, assess and evaluate the evidence and develop the content. The finalised content is reviewed by external experts if required, endorsed by professional organisations and vetted through internal quality control processes.

The Therapeutic Guidelines website (www.tg.org.au) provides detailed information about the history and activities of Therapeutic Guidelines, including a description of the process used to develop the content, and our activities to support the quality use of medicines in developing countries.

Preparing guidelines is a complex process involving a large number of players. There are several areas where independence and bias need to be considered, and several factors that can threaten the reliability of the advice Therapeutic Guidelines provides. Every step needs careful thought and planning to maintain the integrity of the process. In some areas, such as managing conflict of interest, Therapeutic Guidelines can institute measures that allow it to control the integrity of the process. In other areas, such as the limitations of the available evidence, Therapeutic Guidelines has much less control.

Reliable research is an integral component of Therapeutic Guidelines. To ensure that the evidence is appropriately assessed, Therapeutic Guidelines works with people who have both critical appraisal skills and the relevant clinical experience to provide guidance about the treatments most likely to be beneficial and least likely to cause harm to patients.

The issue of conflict of interest has been the focus of much discussion in the guideline community and in other contexts and a number of organisations have developed conflict of interest policies as a result. For example, to develop the American Thoracic Society's Official Policy Statement on the management of conflicts of interest¹, Schünemann and colleagues used existing reviews of policies that were prepared for the World Health Organization (WHO) and for an American Thoracic Society guideline methodology workshop as their evidence base. They also looked at the policies of selected organisations (American College of Physicians, American College of Chest Physicians, American Medical Association, Society of Critical Care Medicine, International Committee of Medical Journal Editors, and WHO). The resulting American Thoracic Society Policy Statement provides the following, particularly helpful definition:

Conflict of interest is defined as a divergence between an individual's private interests and his/her professional obligations such that an independent observer might reasonably question whether the individual's professional actions or decisions are motivated by personal gain, such as financial, academic advancement, clinical revenue streams, or community standing.

So, how well is conflict of interest managed in clinical practice guidelines? Research over the last 10 years shows that many guidelines do not disclose author conflict of interest statements:

- 79% in a study of 313 Australian guidelines (2009)
- 58% in 215 guidelines involving drugs on the National Guideline Clearinghouse (2004)
- 95% in 44 guidelines endorsed by North American and European societies (2002).

However, the landscape is gradually changing. The need to declare and publish conflicts of interest is now more widely accepted, and current thinking is that robust mechanisms are needed to help manage people's declared conflicts. Many organisations have

Dr Sue Phillips

Chief Executive Officer
Therapeutic Guidelines
Limited
Melbourne

published advice in this area, but the US Institute of Medicine² and the Guidelines International Network³ statements are particularly useful.

In 2008, the Institute of Medicine was directed by the US Congress to develop standards for the development of rigorous, trustworthy clinical practice guidelines. This was prompted by concerns from clinicians, methodologists and consumer groups about the quality of guideline development processes and the resulting questionable validity of guideline recommendations and guideline-based performance measures. Three years later, the Institute published a 266 page report that contained eight proposed standards covering all the elements considered to be essential to developing sound guidelines.²

The Institute of Medicine report proposes the following strategies for managing conflicts of interest:

1. Written disclosure of current and planned, commercial and noncommercial, intellectual, institutional, and patient-public activities pertinent to the scope of the guidelines before appointment.
2. Each expert group member to report and discuss all conflicts of interest with the group and explain how their conflict of interest could influence the development process or specific recommendations before starting the work.
3. Members to divest themselves of financial interests they or their family members have, and not participate in marketing activities or advisory boards of entities whose interests could be affected by the recommendations.
4. Whenever possible, expert group members should not have conflicts of interest.
5. In circumstances where expert groups are not able to perform their work without members who have conflicts of interest, such members should represent not more than a minority of the expert group.
6. The Chair or Co-Chairs should not have conflicts of interest.
7. Funders should have no role in the development process.

In response to concerns about the feasibility of implementing such a long list of criteria, Guidelines International Network developed a more succinct seven page document that proposes a minimum set of international standards for developing trustworthy guidelines.³

Both sets of standards emphasise the need for strategies to actively and transparently manage conflicts of interest.

Therapeutic Guidelines Limited's conflict of interest policy

The pharmaceutical industry and government both rely heavily on bodies outside their own spheres, such as universities and hospitals, for product development and regulation. In this context, given their experience and expertise, it is likely that Therapeutic Guidelines directors and members of expert groups have, or have had, some association with the pharmaceutical industry and government committees.

To minimise the possibility of inappropriate influences, Therapeutic Guidelines has included the following strategies in its conflict of interest policy:

- Expert group members are asked to declare any potential conflicts of interest before being appointed.
- Once appointed, a register of declared interests is maintained, circulated and updated at every expert group meeting.
- All expert group meetings are chaired by Therapeutic Guidelines' Medical Advisor, who has no conflicts of interest that could, or could be perceived to, erode the integrity of the guidelines.
- The Chair decides how to manage declared interests and discusses these with expert group members.
- Information about expert group members' declarations of interest and how these were managed are published when the guidelines are released.

The conflict of interest policy for the Board of Therapeutic Guidelines and all members of its guideline teams is available on the website. This new policy was updated in 2012 to ensure that declared conflicts of interest are also published online. It is being implemented prospectively as each guideline is updated and new expert groups are established and provide their consent.

To conclude, one of the key objectives for this forum is to consider best practice regarding the management of conflicts of interest and to identify whether there is anything further that Therapeutic Guidelines should do to manage potential sources of bias when developing its guidelines.

Equally important is the need to focus on the issue of bias in the research literature and evidence base, and to consider whether new sources of funding and regulatory changes are needed to improve the scope and design of clinical trials.

REFERENCES

1. Schunemann HJ, Osborne M, Moss J, Manthous C, Wagner G, Sicilian L, et al. An official American Thoracic Society Policy statement: managing conflict of interest in professional societies. *Am J Respir Crit Care Med* 2009;180:564-80.
2. Institute of Medicine (US). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical practice guidelines we can trust*. Washington, DC: National Academies Press; 2011.
3. Gaseem A, Forland F, Macbeth F, Ollenschlager G, Phillips S, van der Wees P. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:525-31.



Forum attendees

Therapeutic independence: A global problem

Professor Silvio Garattini
Director
Mario Negri Institute for
Pharmacological Research
Milan, Italy

The complexity of the therapeutic environment

The authorisation and the life of a drug are dictated by a number of stakeholders. If it is possible to list (in decreasing order of importance) the responsibility to provide a drug to a patient, it might be as follows:

- **Legislative bodies** – the law determines the general framework of the pharmaceutical environment. The European Medicines Agency is responsible for the regulation and approval of new drugs in Europe, and publishes three documents:
 - the leaflet for patients
 - the Summary of Product Characteristics for physicians
 - the European Public Assessment Report describing the pathway that led to approval.

National agencies usually have only a minor role in the approval of drugs (today mostly generics) but are very important for reimbursement by national health services.

- **Scientific societies** – these are generally responsible for drafting guidelines and in some cases must exert pressure to obtain rapid approval of drugs (e.g. for anticancer drugs)
- **Prescribers** – whether in hospitals or primary care, prescribers have the final decision of what to give the patient
- **Patients or consumer associations** – these groups usually have very limited influence.

All these stakeholders are influenced by two forces:

- the pharmaceutical industry, which is obviously interested in selling as many medicinal products as possible at the highest possible price
- the national health service, which funds the provision of only essential drugs to patients at the lowest possible price.

Pharmaceutical companies, either directly or through their lobby groups (e.g. the European Federation of Pharmaceutical Industries and Associations in Europe), have the ability to influence all stakeholders. Their support of scientific societies, marketing to prescribers and the financing of patients' associations, as well as the media, is pervasive and extremely effective. In contrast, information coming from

the national health service is, in general, relatively scarce. This creates an asymmetric system driven by economic interests, while the national health service has limited influence.

The imbalance between the industry-funded information and independent information has led to distortion in the conception of medicinal products, which are becoming consumer goods rather than therapeutic tools.

How drugs satisfy patients' needs

Each year the US Food and Drug Administration authorises about 60 new chemical entities to be marketed, and the European Medicines Agency authorises about 30 new entities. The importance of these new products is very limited since they are often drugs belonging to an existing therapeutic class, with only small chemical changes. In addition, in the last decade there has been an increase of biopharmaceuticals (obtained by DNA-recombinant techniques, such as monoclonal antibodies).

The analyses to date indicate that most new medicinal products are not necessary. One French study showed that out of 961 drugs approved in the period 1999–2008 about 49% brought nothing new, 11% were 'not acceptable', and the others could offer some benefits, but only 2% provided any real advantage.¹ Another study analysed the improvements in quality of life, expressed as quality-adjusted life years (QALY), induced by 281 new medicinal products. Only 12% induced more than 1 QALY, while 51% induced less than 0.1 QALY.²

Some confusion arises depending on the parameters used to establish the progressive value of therapy. A percentage can be misleading, and it is better to express the advantage in absolute terms. A clear idea about the value of a drug can be estimated from the number of patients that must be treated with a given drug in order to obtain a positive outcome in terms of reduced mortality or morbidity – the number needed to treat (NNT). The same can be done using the number needed to harm (NNH), i.e. the number of patients that must be treated to observe an important adverse event. The ratio of NNT to NNH constitutes an attempt to identify a 'therapeutic ratio'.

A fair evaluation of medicinal products should not only be quantitative, but should also address the

relation between patients' unmet needs and efforts to make drugs available to meet these needs. For instance, bacterial resistance to antibiotics has not been followed by the development of new antibiotics effective against resistant microorganisms. Similarly, there have been no truly new agents for mental disorders (psychotropic drugs) in the past 30 years, and several important multinational pharmaceutical companies have abandoned this field of research.

A recent study pointed out the discrepancy between the burden of a given disease and the number of drugs available. Epidemiological data indicate that while there has been a considerable decline in mortality due to cardiovascular diseases, in the field of cancer (namely breast and colorectal cancers) in the last decade there has been less improvement over previous decades despite the number of drugs approved.

Orphan drugs merit special mention. In the last 10 years only 63 drugs have been approved by the European Medicines Agency for the 6000 rare diseases awaiting treatment. In some cases the evidence of a favourable benefit-risk ratio is very doubtful. Similar considerations are offered for the lack of new drugs for the neglected diseases of people in developing countries.

Bias in randomised controlled clinical trials

The scientific literature has recognised a number of biases that affect randomised controlled trials. In general these tend to magnify the benefit of a drug and minimise adverse reactions. All these biases lead to poor innovation.

Abuse of placebo

It is obvious that a comparison with placebo rather than with an active comparator allows better appraisal of a drug's benefit. In this respect there is considerable disagreement between the Declaration of Helsinki and the rules issued by the US and European regulatory agencies. There are three different types of abuse of placebo:

- direct comparison with placebo (two-arm studies)
- use of placebo in an add-on design
- the three-arm design (placebo, comparator, new drug).

In all three cases not using the comparator (when available) can harm patients in the placebo group because they receive no treatment or treatment that is less than optimal. Examples of this bias include:

- the recent direct comparison of placebo with drugs developed for multiple sclerosis (e.g. cladribine, fingolimod, laquinimod)

- the combination of metformin with a new antidiabetic drug where placebo is used, despite established standard treatment combinations of two antidiabetic drugs
- the comparison of antidepressants where placebo is not necessary if the trial is designed to detect superiority.

Comparator

Selection of the comparator is very important because it can affect the evaluation of the new drug. Ideally the best standard should be used, at the best dose and duration of treatment. In practice these variables are often selected in order to favour the new drug. For instance in the case of rofecoxib, comparison with naproxen would have detected the cardiovascular adverse effects induced by rofecoxib. In another example, tacrolimus was shown to be superior to cyclosporin only because cyclosporin was used at suboptimal doses.

Non-inferiority trials

In this type of trial, investigators test the null hypothesis that a new drug is worse than the active control (standard therapy). When they can reject the null hypothesis, they accept the alternative, the new drug is not worse, but do we really need non-inferior drugs? Often the difference for acceptance of non-inferiority may be 25–50%. Patients rarely receive clear information in the informed consent form about the significance of this experimental design.

Surrogate end points

Frequently the evaluation of a drug is not based on therapeutic advantages for the patients, but on indicators that may indirectly reflect possible advantages. Examples are decreased blood cholesterol as a surrogate for reduction of myocardial infarction, decreased blood pressure as a surrogate for reduction of stroke, and decreased blood glucose as a surrogate for cardiovascular complications of diabetes. In some cases therapeutic end points are considered equivalent to surrogate end points, particularly when a group of drugs belong to a class with a similar mechanism of action.

However, since each drug has its own chemical structure, adverse reactions may in fact outweigh the benefit. Statins are an example. Rosuvastatin was approved for use on the basis of its hypocholesterolaemic effect, but simvastatin and pravastatin had already demonstrated protective effects against myocardial infarction. Cerivastatin was withdrawn because of toxicity. In another example, several anticancer drugs have been approved on the grounds that they reduce tumour volume, but with no

evidence of improvement in overall survival or quality of life.

Composite end points

Where specific events are relatively few, it has become customary to group several events together. For instance death, myocardial infarction, stroke and coronary artery occlusion may be grouped as 'cardiovascular events'. When a drug achieves a statistically significant decrease in a composite end point it is proclaimed that all the individual end points have been beneficially affected. However, the significance is usually driven by minor points that are less important therapeutically.

Fragile populations

New drugs are frequently tested on men rather than the population that will be using the drug, such as older people. Children are rarely recruited for trials, nor are women of fertile age. Furthermore, patients are selected for trials in artificial conditions, while in clinical practice patients may have multiple comorbidities and be taking several drugs already. Consequently, the trials may overestimate the drug's benefits and underestimate its harms in clinical practice.

Publication bias

This term refers to the tendency to favour publications showing positive results rather than negative ones. This has created a number of problems in drug assessment. For instance, the selective serotonin reuptake inhibitors have been considered active in mild depression even though they are not different from placebo. Reboxetine is overall an ineffective and potentially harmful antidepressant when positive and negative trials are assessed together.³ The suicidal tendencies induced by antidepressant drugs in adolescents have not been well publicised.

Adverse reactions

The risk induced by drugs can seldom be detected during trials because they recruit too few people.

Adequate postmarketing follow-up is therefore important. However, most drug withdrawals are instigated by pharmaceutical companies rather than the regulatory authority, indicating that appropriate follow-up by regulatory authorities does not occur. In addition, withdrawal is often considerably delayed, such as in the case of rofecoxib, cerivastatin, rosiglitazone, sibutramine, and rimonabant.

Some proposals for change

It is difficult to change the present system because all stakeholders have some vested interests. However, the present crisis may offer an opportunity to make some changes.

There are essentially three changes needed to the legislation:

- The approval of a new drug presently requires only evidence of quality, efficacy and safety. It would be important to also require 'added value'. This would abolish pivotal studies of non-inferiority and would require comparative studies in order to identify advantages over drugs already available on the market.
- Confidentiality should be abolished, at least for pharmacological, toxicological and clinical data. There is no reason to maintain confidentiality because, for clinical trials in particular, the data belong to the patients. Without their generosity there would be no clinical trials.
- The regulatory authorities should be funded from public sources. The European Union and its member states could recover their funding from industry in different ways.

These changes in legislation would result in stricter approval processes that allow only drugs that offer true innovation in therapeutic terms to be marketed (see Table).

To avoid bias in trials, one of the two pivotal phase III trials should be carried out by an independent non-profit organisation.

Table Regulatory evaluation of clinical trials

	Current	Ideal
Kind of comparison	None Superiority to placebo Non-inferiority to active comparator	Superiority to the best available care
Kind of comparator (and its dosage)	Not always the most appropriate	The best available treatment
Outcome measure	Surrogate outcomes	Clinically meaningful outcomes addressing significant better and/or longer life

Regarding adverse reactions, it is important to require 'active pharmacovigilance'. At present the Committee for Human Medicinal Products, a technical advisory body of the European Medicines Agency, is responsible for the approval (or rejection), appeal and withdrawal of drugs. This creates a conflict of interest, since it is hard for the same body to exert contradictory functions. A separate committee should be responsible for monitoring for adverse effects over the life of a drug and making decisions about modifying the summary of product characteristics or withdrawing a drug.

Independent research must be promoted at the preclinical and clinical levels. There is a tendency to translate the effects of a drug too fast from laboratory to humans. Although this can be done on healthy volunteers under specific conditions, thorough evaluation is essential in vitro and in several animal species and models of human diseases. The action of antivivisection groups poses a serious obstacle to the extension of laboratory tests to animals. In addition, excessive bureaucratic rules hamper the development of knowledge useful to understand drug actions. It must be recognised that the pharmacological effect in animal tests is frequently too small to suggest real therapeutic action. The example of some anticancer drugs is pertinent in this respect.

Investigator-driven clinical trials organised by non-profit organisations should be encouraged by making available funding and infrastructures, particularly for international collaboration on large clinical trials, and trials for rare and neglected diseases. For the past two years, special topics for independent trials have been supported under Framework Program 7 in Europe. In Italy a special law has established a research fund by taxation of 5% on all promotional expenses (except salaries) borne by pharmaceutical companies.

For five years there have been annual calls for investigator-driven clinical trials comparing drugs for the same indications, addressing new indications for old drugs, or testing orphan drugs. An international peer review assigns funds to the selected proposals. The independent research is not only useful for better evaluation of drug toxicity and activity, but also to optimise doses and duration of treatment. In some cases equivalence of drugs with different prices can allow savings on drug expenses. Independent trials should also aim to involve practitioners in order to evaluate drugs in current clinical practice, particularly in the elderly and children.

In order to avoid repetitive studies and delay in developing new indications or contraindications, before starting any new trial it is important to

undertake a systematic review or a meta-analysis of trials that have already been done. Unfortunately, a number of trials are still done without any preliminary review. These studies waste resources and expose people to undue risks. In Europe a six-month patent extension is offered as an incentive to carry out trials in children. In some cases it would be less expensive for the national health service to fund these trials, providing the results are recognised by the regulatory authority.

The present legislation for randomised controlled trials (through Good Clinical Practices) does not distinguish between the requirements necessary for a new medicinal product and those for independent research using drugs already on the market (e.g. for comparison, optimisation or new indications). These studies should be less burdened by official requirements. The risk of a given trial should dictate the need for insurance, the grading of monitoring and the reporting of adverse reactions.

In Europe the European Clinical Research Infrastructure Network has been created to assist international trials by providing the necessary information and helping to deal with national differences in clinical trials requirements.

Discussion

Following Professor Garattini's presentation, participants raised the following key points in discussion:

- The concept of introducing a 5% levy on drug companies to fund investigator-initiated research was seen as a good idea. This money could also be used to fund research that would provide reliable information about the effectiveness of drugs in those high-need population groups that are likely to benefit from the drugs (e.g. children, women, the elderly).
- Guideline developers must constantly assess whether the study design of a trial is applicable to their target populations.
- There is a lack of trials evaluating non-drug interventions, such as physical activity or dietary changes, which may be just as effective as drug therapy for managing disease and improving health outcomes.
- A number of complementary and alternative therapies are actively advertised and promoted as having a therapeutic benefit. While not all of these therapies may be dangerous, there is no requirement to demonstrate their efficacy in rigorous trials, so there are no data about their effectiveness. There should be consideration of introducing the same regulatory framework for

the approval of these products as there are for registered drugs.

- Off-label use of products is hard to monitor and evaluate.
- There is a need to engage more closely with the public and consumers to get input into the topics of greatest concern for them and incorporate this information into the research agenda.

Professor Garattini explained the Mario Negri Institute's policy on competing interests (see Appendix 2 for details)

REFERENCES

1. Anon. A look back at 2008: pharmaceutical quality problems. *Prescrire Int* 2009;18(100):84-8.
2. Walker A, Booth C, Brown A, Paterson K. How much good do new medicines do? *Basic Clin Pharmacol Toxicol* 2009;105(Suppl 1):29.
3. Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010;341:c4737.

FURTHER READING

Garattini S, Bertele V. Adjusting Europe's drug regulation to public health needs. *Lancet* 2001;358:64-7.

Garattini S, Bertele V. Ethics in clinical research. *J Hepatol* 2009;51:792-7.

Garattini S, Bertele V. Non-inferiority trials are unethical because they disregard patients' interests. *Lancet* 2007;370:1875-7.

Garattini S, Bertele V, Banzi R. Placebo? no thanks, it might be bad for me! *Eur J Clin Pharmacol* 2013;69:711-4.

Garattini S, Chalmers I. Patients and the public deserve big changes in evaluation of drugs. *BMJ* 2009;338:b1025.

Joppi R, Bertele V, Garattini S. Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU. *Eur J Clin Pharmacol* 2013;69:1009-24.

Evidence-based medicine: Strengths and limitations

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.¹

David Sackett (1996)

This quote, from one of the gurus of evidence-based medicine, highlights the link between the systematic evaluation of scientific evidence on effects of medical treatments, and applying this evidence to patient care decisions – taking into account both clinical expertise and patient needs. Evidence-based medicine is not simply applying scientific evidence. It requires an assessment and interpretation in light of individuals' health needs and preferences.

Although the first randomised controlled trials in medicine date from the 1950s, for many years there was no way to understand the body of information produced by drug trials and other forms of medical research. Writing in 1979, Archie Cochrane said:

It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials.²

The Cochrane Collaboration (www.cochrane.org) was subsequently formed in 1992 and started its work looking at the effectiveness of obstetric interventions, as this was an area in which some interventions with substantial evidence of benefit were underused and others with little scientific basis remained widespread. The Cochrane Collaboration is an international network of more than 28 000 researchers from over 100 countries with different review groups based on clinical specialties. It helps healthcare providers, policy-makers, patients and their advocates and carers make well-informed decisions about health care by preparing, updating, and promoting the accessibility of Cochrane systematic reviews. A strength is the focus on methodological rigour, and Cochrane reviews are often seen as the 'gold standard' in systematic review. Over 5000 reviews have been published online in the Cochrane Database of Systematic Reviews (part of The Cochrane Library). The Collaboration also prepares the largest collection of records of randomised controlled trials in the world, called CENTRAL (published as part of The Cochrane Library).

The work of the Cochrane Collaboration and other evidence-based groups has grown significantly over the last 20 years. In 1981 there were only three meta-analyses indexed on Medline, in 1986 only 26. By 2011 the number had grown to around 8000.

Has the evidence-based movement been captured by commercial interests? Despite the rapid growth in the scale of activity to develop robust systematic review processes and procedures, there is a fundamental block in terms of limitations in the clinical trial evidence on the effects of new medicines. The requirements that manufacturers must meet to bring a new drug to market differ substantially from the clinical questions that physicians and patients face in order to understand a medicine's place in therapy and decide whether or not to use it.

Studies of new pharmaceuticals are to a large degree shaped by regulatory requirements in order to obtain market approval. Currently, premarket randomised controlled trials are predominantly placebo controlled – or if not, they are non-inferiority trials. The latter are studies that are designed to test whether the drug is no worse than an existing treatment within a prespecified margin. Postmarketing surveillance data are mainly derived from observational studies. Regulators are becoming more interested in postmarketing safety surveillance, but there are no set standards for the rigour of the design of such studies.

Because most drug trials are designed and sponsored by the manufacturer, they are designed to present the drug in the best possible light and publication of all of the trial information is optional. When a drug becomes available there is usually no information on:

- the effects in vulnerable population groups (because they will have been excluded from trials)
- long-term or less frequent effects
- clinical outcome efficacy (short-term surrogate outcomes are often used)
- comparative effectiveness and safety.

There is no requirement for manufacturers to prove that their products are at least as safe as existing drugs. This has meant that some new drugs have turned out to have a worse safety profile than existing drugs. For example, the most frequent serious adverse event associated with use of combined oestrogen and progestogen-containing

Assistant Professor Barbara Mintzes

School of Population
and Public Health
University of British
Columbia
Vancouver
Canada
Michael Smith Foundation
for Health Research Scholar

oral contraceptives is venous thromboembolism. However, when a new oral contraceptive comes to market the manufacturer does not need to show that their newer pill has a lower or similar rate of venous thromboembolism to existing alternatives. Several newer oral contraceptives have been found to cause more venous thromboembolism than other oral contraceptives, including the drospirenone-containing products Yaz and Yasmin.^{3,4}

In a regulatory environment without a requirement to establish an advantage in order to get a new drug to market, many new drugs are no more effective than existing alternatives. This overview is from *La Revue Prescrire*, a French independent drug bulletin that evaluates every new approved drug for its readership of over 30 000 practitioners.

The figure covers all new drugs and indications reviewed by *La Revue Prescrire* from 2002 to 2011.⁵ Over half were judged to be 'me too' drugs – i.e. nothing new. Around 7% had solid evidence of an advantage over existing drugs (whether major or minor). In around 15% of new drug reviews there was evidence of poor effectiveness or safety compared to drugs already on the market.

Commercial influences and reporting bias

The pharmaceutical industry funds the majority of research, and therefore it also shapes the current research agenda. This leads to a bias of research focus on commercially viable interventions, where there is

an anticipated beneficial outcome rather than harmful outcomes, and on products where there is likely to be a ready market. Consequently, there is not much research funding for drugs for neglected diseases affecting populations in low-income countries, where financial returns on research investments would be limited.

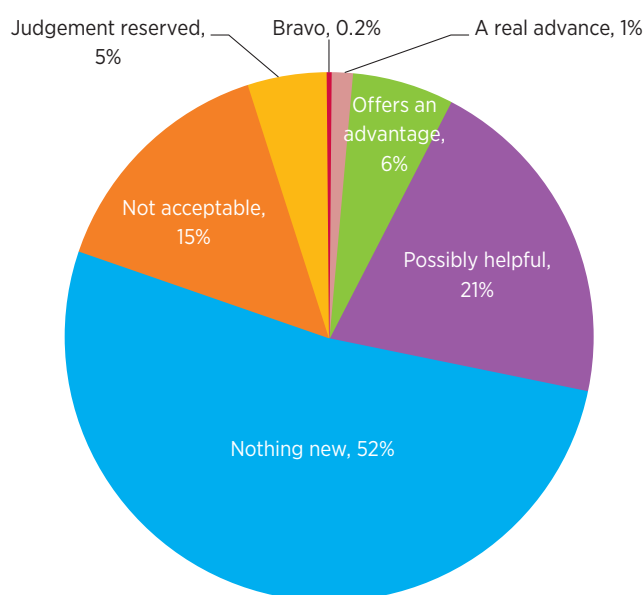
A body of research has examined the effects of industry funding on the evidence base and the types of bias it causes. A systematic review in the *British Medical Journal* in 2003⁶ looked at the results of research trials in the US based on the type of funding the researchers received and the outcome of the trial data. It found that industry-funded trials are about four times more likely (95% confidence interval 3.0–5.5) to favour the sponsor's drug than non-industry-funded trials. Another systematic review published in 2003 reported similar outcomes⁷, as have a number of more recent studies.

In late 2012, the first Cochrane systematic review on the effects of industry sponsorship was published, with a focus on studies of randomised controlled trials of drugs and devices.⁸ The authors found the same direction of effect as in previous systematic reviews but a lower magnitude: odds ratio = 2.2 (95% confidence interval 1.7–2.7) for favourable results and odds ratio = 2.7 (95% confidence interval 2.0–3.5) for conclusions as compared with non-industry-sponsored studies. The difference likely reflects the focus only on trials rather than inclusion of a broader range of research designs, including pharmacoeconomic analyses. The authors failed to find any clear trend of improvement over time.

Industry funding has also been found to influence the reporting of active-controlled trials that compare drugs in the same class (head-to-head trials). A cross-sectional study of head-to-head statin trials found a very strong association between the sponsor and the findings. Of 192 trials, 50% were sponsored by the test drug company, and these industry-funded trials were 20 times more likely to report results that favour the test drug over the competitor drug, and 35 times more likely to report favourable conclusions.⁹ Another study in 2010 looked at the outcome reporting among trials registered on the US Clinical Trials Registry covering six of the most heavily used classes of drugs (antidepressants, antipsychotics, proton pump inhibitors, lipid-lowering drugs, vasodilators). It found the proportion of favourable outcomes was high in trials funded both **directly** by industry and **indirectly** (i.e. trials conducted by non-profit organisations that receive industry funding).¹⁰

It is therefore clear from the literature that there is a direct link between funding source and outcomes

Figure Assessment of new drugs and indications by *La Revue Prescrire* 2002–2011⁵



of studies, and this leads to biased results. In a randomised controlled trial you would expect equipoise – you would not expect a situation where all trials funded by a specific source are two to three times more likely to be favourable than publicly funded trials.

Dissemination of information

The influence of the pharmaceutical industry extends beyond research. The other area where drug company influence is significant is the dissemination of information about the effectiveness of the drug and the trial results.

The pharmaceutical industry plays a dominant role in dissemination of information about drug products. It was estimated that US\$57.5 billion was spent on drug promotion in the USA in 2004. This included the provision of samples, funding sales representatives, direct-to-consumer advertising, scientific meetings, promotions, advertisements and other unmonitored promotions.¹¹ This is a massive investment – it would be great if 5% of this money went into a fund for independent research. It significantly outweighs the amount spent by public funders on the promotion and dissemination of health information, even in settings where there is a commitment to providing independent information. In the UK in 2005, the public sector spent only an estimated 0.3% of what industry spent on funding information dissemination, although the UK has more publicly provided health information than many other industrialised countries. Globally, Australia is one of the world leaders in having a larger commitment to publicly funded information.

This domination by industry poses a problem not only in terms of positively biased promotional information, but also the under-reporting of evidence about negative effects or harms.

There is also a lot of concern internationally about how the press represents or misrepresents research findings and how influential they are in creating public impressions of what drugs do or do not do. A review of press releases in *EurekAlert* (an online science news service) looked at the way journalists reported the results of a study and compared the reports with the study findings.¹² It looked at different factors that were associated with ‘spin’ in the press release, i.e. misrepresentation of the study findings as more favourable and positive than they were. There was no association with the funding source of the study and the reporting of findings. Rather, the most significant factor was spin in the study itself (i.e. if the abstract represented the study findings as being more positive than the data would indicate).

The British Medical Journal has recently begun to provide a link to press releases on its website when it publishes a new article about a drug. A recent example of biased reporting in a press release was the 2012 reporting of the Heart and Estrogen/ Progestogen Study (HERS) on the effects of hormone replacement therapy (HRT) in women.¹³ The press release was titled ‘HRT taken for 10 years significantly reduces the risk of heart failure and heart attack’. This implies the findings contradict the Women’s Health Initiative study, but important details were not mentioned:

- this was a post hoc secondary analysis of a trial that was developed to test HRT for osteoporosis and published 10 years earlier
- the post hoc analysis had an odd mix of primary outcomes (i.e. they included heart failure and heart attack as outcome measures even though heart failure was never considered to be a negative or positive effect of HRT)
- the study was open label and used a questionable method of randomisation
- the control group was on average a half year older and in poorer health.

Another area of potential bias that is sometimes difficult to detect is conflict of interest. A recent study looked at the disclosures of medical experts who had been named as illegally promoting off-label use of products in court cases in the USA.¹⁴ Ninety-two people were named, 39 of them were authors of articles in the clinical area in which the off-label promotion occurred, and conflict of interest was adequately disclosed in only 15% of these articles.

Who and what is **not** being researched is another potential source of bias. When the COX-2 inhibitors (e.g. celecoxib, rofecoxib) were introduced they were marketed as being much safer than traditional non-steroidal anti-inflammatory drugs (NSAIDs) in terms of gastrointestinal bleeding. However, they had not been tested at all in people who were at high risk of bleeding (e.g. people who had previous gastrointestinal bleeds, the elderly). In an Ontario study of hospitalisations for the elderly for gastrointestinal bleeds, more bleeds occurred after these drugs began to be widely used, most likely because they were given to people who would not have otherwise been prescribed NSAIDs.¹⁵

Selective publication

Another source of bias in evidence-based medicine is the selective publication of research results. Erythropoietin and oseltamivir are two examples of publication bias leading to a distortion of the true therapeutic value of a drug.

Erythropoietin is useful for people with very low haemoglobin. It stimulates red cell production and reduces the need for blood transfusions in people having cancer chemotherapy or kidney dialysis. Erythropoietin was in one of the 10 classes of medicines most heavily promoted to the US public in 2005¹⁶, with strong messages that the drug would increase energy levels, improve quality of life and allow patients to live as normally as possible. Problems arose when the use of the drug was extended well beyond the areas where it was proven beneficial, and there has since been evidence of higher mortality in patients who did not have very low haemoglobin before starting erythropoietin therapy. Another problem is that erythropoietin has the ability to promote the growth of tumours, which is concerning if it is prescribed for people with existing cancers (one of the approved indications). There is a strong association between the funding source and basic science studies that did and did not find this potentially harmful effect.¹⁷ The major study that led to clinical guidelines recommending the use of erythropoietin for kidney dialysis patients has been republished 14 years after the original publication (after the full trial data were accessed through the Freedom of Information Act).¹⁸ It shows that the original authors omitted very important information about serious adverse effects and potential for harm, and overstated the benefits in terms of improved quality of life.

The international stockpiling of oseltamivir highlights the worldwide impact of biased reporting. Stockpiling has occurred on two occasions – first in 2006 with the threat of bird flu, and more recently with the H1N1 pandemic in 2009. Billions of dollars were spent by governments all around the world to purchase bulk supplies of oseltamivir, believing that it would prevent the transmission of the H1N1 virus and flu complications in their populations.

In a Therapeutics Initiative review published in 2000, analysis of the clinical trial data showed that oseltamivir would only decrease the impact/duration of the flu by 0.7–0.8 of a day at best (about 18 hours) and that the effects on symptom severity were not able to be determined from the data. It found that the drug increased nausea and vomiting, and that there was no evidence that it prevented complications, hospitalisations or death. The trials excluded the elderly and chronically ill – the people who are at greatest risk from the virus.¹⁹

At the time Therapeutics Initiative did not realise how incomplete the evidence was, as this analysis was based on two published trials (one of which has subsequently been found to have been mainly ghostwritten). The US Food and Drug Administration approval of oseltamivir did not include publication on its website of the information submitted by the drug company until three years after the drug was approved for the market. For most drugs approved in the US, the Food and Drug Administration publishes a 'review report' on its website soon after approval, including a list of clinical trials submitted in the application, trial reports, and reviewer assessments. The first Cochrane systematic review of oseltamivir in 2006 included a claim that it prevents flu complications.²⁰ The review was based on one study report summarising the results of 10 pooled trials, 8 of which were unpublished, with most included patients in the unpublished trials.²¹

One of the positive aspects of a Cochrane review is that authors are required to routinely update their reviews and must commit to responding to any comments posted about the review. A Japanese researcher queried the findings of the 2006 pooled analysis of these 10 trials and asked whether the Cochrane reviewers had access to the full trial data for the 8 unpublished trials, and if not, how could the information supplied in the pooled analysis be trusted? As a result of this query, the Cochrane reviewers tried to obtain full reports of the unpublished trials. In the 2009 update of the Cochrane review, the claim that oseltamivir reduced flu complications was removed, as the data had not been disclosed. By 2012, when an updated Cochrane review was published, regulatory data had been disclosed. The authors found no effect on hospitalisation and could not pronounce on flu complications, due to incomplete and inconsistent reporting in the trials.

We found a high risk of publication and reporting biases ... we are unable to draw conclusions about its effect on complications or transmission. We expect full clinical study reports ... to clarify outstanding issues.

These full clinical study reports are currently unavailable to us.²²

This experience demonstrates the discrepancy that can exist between published reports and the full reports of clinical trials submitted to regulators, and the importance of full disclosure.

Conclusions

Key evidence needed to support patient care decisions is often lacking. In particular this can mean there is no information about:

- whether the benefits of a new drug outweigh its harms
- which groups of people do better or worse using the drug
- how the new drug compares with existing alternatives
- what the population-level outcomes are
- patients' lived experiences and priorities for the drug and the disease.

Is the dream of evidence-based medicine sinking like the Titanic? No – but there are key areas for policy change, including:

- priority-setting for research
- introducing changes to manage industry sponsorship of clinical trials and the publication of results, reporting and dissemination
- ensuring a transparent link between what regulators know and publicly available clinical evidence
- promoting public access to research protocols and results, especially through the use of clinical trial registries
- ensuring that advisory committees considering the use of new drugs meet in public

- enabling consumer groups to access data and have processes for involvement in all decisions
- posting of regulatory review reports on the internet, after approval of all new drugs
- development of alternate funding mechanisms for premarket trials so that these trials are not dominated by the pharmaceutical industry.

There is an important and stronger role for funders, payers and providers in research and resource allocation and managing the use of medicines through the provision of independent evidence-based information. One example of this is the approach taken by the non-profit health insurance plan, Kaiser Permanente, in the USA. They have developed an 'in-house' research team to assess the effectiveness of resource allocation, including outcomes from spending on new drugs. The team also provides the organisation with its own physician and patient information services on health conditions and drug and non-drug treatments. Kaiser Permanente physicians do not see sales representatives.

There is also a need to encourage reform of the regulatory landscape. This could include introducing limits to some forms of promotion of new drugs by the industry, promoting active pharmacosurveillance, and also promoting the design of pragmatic randomised controlled trials, systematic observational research and comparative effectiveness research through public funding.

Assistant Professor Mintzes provided a detailed declaration of her interests (see Appendix 2 for details)

REFERENCES

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312:71-2.
2. Cochrane AL. 1931-1971: a critical review, with particular reference to the medical profession. In: *Medicines for the year 2000*. London: Office of Health Economics; 1979.
3. Lidegaard O, Nielsen LH, Skovlund CW, Skjeldestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ* 2011;343:d6423.
4. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 2011;342:d2151.
5. Anon. New drugs and indications in 2011: France is better focused on patients' interests after the Mediator scandal, but stagnation elsewhere. *Prescrire Int* 2012;21:107-10.
6. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70.
7. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289:454-65.
8. Lundh A, Sismondo S, Lexchin J, Busuioac OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2012;12:MR000033.
9. Bero L, Oostvogel F, Bacchetti P, Lee K. Factors associated with findings of published trials of drug-drug comparisons: why some statins appear more efficacious than others. *PLoS Med* 2007;4:e184.
10. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med* 2010;153:158-66.
11. Gagnon MA, Lexchin J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Med* 2008;5:e1.
12. Yavchitz A, Boutron I, Bafeta A, Marroun I, Charles P, Mantz J, et al. Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study. *PLoS Med* 2012;9:e1001308.
13. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ* 2012;345:e6409.
14. Kesselheim AS, Wang B, Studdert DM, Avorn J. Conflict of interest reporting by authors involved in promotion of off-label drug use: an analysis of journal disclosures. *PLoS Med* 2012;9:e1001280.
15. Mamdani M, Juurlink DN, Kopp A, Naglie G, Austin PC, Laupacis A. Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. *BMJ* 2004;328:1415-6.
16. Donohue JM, Cevasco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. *N Engl J Med* 2007;357:673-81.
17. Bennett CL, Lai SY, Henke M, Barnato SE, Armitage JO, Sartor O. Association between pharmaceutical support and basic science research on erythropoiesis-stimulating agents. *Arch Intern Med* 2010;170:1490-8.
18. Coyne DW. The health-related quality of life was not improved by targeting higher hemoglobin in the Normal Hematocrit Trial. *Kidney Int* 2012;82:235-41.
19. Therapeutics Initiative. Prevention and Treatment of Influenza A and B. *Therapeutics Letter* 2000;38:1-2.
20. Doshi P. Neuraminidase inhibitors – the story behind the Cochrane review. *BMJ* 2009;339:b5164.
21. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003;163:1667-72.
22. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965.

Therapeutic independence and evidence-based medicine

Panel discussion

Panel members

Professor Rachelle Buchbinder
Professor Terry Campbell
Professor Silvio Garattini
Associate Professor David Menkes
Assistant Professor Barbara Mintzes
Dr Philipa Rothfield
Associate Professor Ian Scott

Moderator

Professor Paul Komesaroff

Each panellist was invited to comment on the issues raised by Professor Silvio Garattini and Assistant Professor Barbara Mintzes in their earlier presentations, and comments from the forum participants were also invited.

Quality of data used in guidelines

To what extent are there sufficient mechanisms to discern between biased and independent data?

In the area of psychiatric medicine there has been considerable concern about the influence of commercial interests on the data used to register new medications, especially for 'atypical' (second- and third-generation) antipsychotics, as well as selective serotonin reuptake inhibitors and related antidepressants.

There are also widespread concerns about the lack of follow-up data on the long-term effects of newly registered therapeutic products. Regulators need to have ways to follow up effectiveness and safety data on a routine basis. Some of the mechanisms for assessing the quality of the data include consideration of the comparative effectiveness of the new drugs, but often this information is not available because of the trial design used, deficient ascertainment and incomplete reporting.

Allocation of research grants

Does the process used to allocate research grants and funding naturally encourage researchers to 'talk up' their study and the results?

There is considerable support for finding ways to fund investigator-initiated trials. Full disclosure of all drug company links and funding should be required. Fines and other penalties should be imposed if drug companies falsify data. Some of the fines could be used to fund investigator-initiated trials.

Identifying conflicts of interest

There are persisting issues of real and perceived conflicts of interest. Some people will not be able to easily identify whether they have conflicts, or will have interests they are not aware of (e.g. they may not know where their university gets its funding sources). People funded by government may also be influenced by the government's current policy imperatives. These

issues, including definitions of 'independence', are often complex.

There is a need to ensure that guideline development groups include wide representation from different health disciplines and people with different backgrounds and skills, and it should be clear where there are contrasts between sets of norms, values and ideals. This will allow members of guideline development groups and committees to get a wider picture of each contributor's influences.

The issue of conflict of interest is not a solely medical/health issue. For example, it is important that all influences and interests are known when members of a jury are selected. Directors and businesses also have formalised processes for declaring and managing conflicts. People submitting journal articles are also required to make declarations in accordance with the statements on conflicts of interest in medical journals by the World Association of Medical Editors and the International Committee of Medical Journal Editors. Medical journals need to be checked to ensure they follow their own code of ethics and actively enforce their policies with contributors.

There is a need to educate clinicians and consumers in critical appraisal of intervention studies and other types of studies, in part to enable awareness of the pervasive risk of bias from diverse sources.

Driving the research agenda

There are opportunities for guideline developers such as Therapeutic Guidelines in Australia to identify areas where further research is needed to fully cover the spectrum of information required in each therapeutic area. There could also be opportunities for guideline developers to have a role in setting the research agenda and in actively promoting changes in healthcare practice.

Role of ethics committees in research design

Is there a need to reinforce the critical capacities of the people on ethics committees? Do the ethics committees and researchers actively work within the framework of ethical principles for medical research described in the Helsinki Declaration?

Ethics committees have the ability to change or seek modifications to protocols or the design of studies they are considering. However, this can be difficult, especially when multicentre approvals are being considered. There was discussion about whether the ethics committees could introduce a process of independent scientific review of study design before considering proposals. NPS MedicineWise has recently been working with ethics committees to help them access high quality information about medications. There are also plans to change the structure of ethics committees around Australia. This might include the opportunity to provide training and information to committee members to ensure they understand issues associated with study design and the need for transparency and independence.

Addressing the problem of overdiagnosis

The problem of overdiagnosis must be addressed by guideline developers. The British Medical Journal¹ and the Cochrane Collaboration are actively discussing and debating the growth of new diseases and the medicalisation of normal human development and ageing being promoted by the pharmaceutical industry and other vested interests.

Influence of consumers

The influence of consumers is seen as vital in all parts of the guideline development process. If there is going to be real change, it is important to recognise that patients and consumers are at the heart of the system and that they matter the most. Consumers must be given credit for being able to understand and digest information about their health. They want to know what treatments are going to do, how they work, how long they will take to work and what the risks and benefits are.

The Cochrane Colloquium works actively and effectively with consumers. It is useful to involve consumers in the design of every trial so that researchers and funders know that the right questions are being asked. For example, in the area of musculoskeletal medicine many consumers want to know basic information that will help them in their daily lives, such as 'what is the best kind of mattress to help reduce or manage back pain?', but this topic is not well covered by research.

The important issue is how to improve the quality of science and to take the focus away from the product and instead to focus on the needs of the person.

Publishing clinical trial data

How can we introduce greater transparency into the data relating to drugs? Who should be the agent for change? Who are the critical players/partners/stakeholders to lead the call for change? What are the preconditions for change? What are the barriers to introducing these changes?

The government has some awareness of these issues and has recently established a website for registering clinical trials (www.anzctr.org.au). At this stage there is no requirement to publish the results of all registered trials.

There are three main areas where change is needed:

1. Regulators should make publicly available all of the information they have access to when approving a drug.
2. Regulators should require applicants seeking approval for their drugs to demonstrate that the new drug has a proven therapeutic benefit compared to existing treatments.
3. Governments should take steps to increase the number of investigator-driven clinical trials.

A wider role for Therapeutic Guidelines Limited

Is there a wider role for Therapeutic Guidelines in progressing these discussions? For example:

- Would it be possible for Therapeutic Guidelines to take a leadership role in establishing gold standards of behaviour and good governance in clinical research and to provide advice to other Australian guideline developers on ways to manage conflicts of interest?
- Is there a wider global role for Therapeutic Guidelines and its products?
- Can Therapeutic Guidelines extend its purely scientific approach to include wider contextual issues such as social determinants?
- Can Therapeutic Guidelines take on a role promoting a wider understanding of the value of guidelines and also teaching critical appraisal skills?
- Does Therapeutic Guidelines have a role in improving the uptake of guidelines?
- Can Therapeutic Guidelines begin to develop guidelines that address comorbidities?

REFERENCE

1. Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. *BMJ* 2012;344:e3502.

Interpreting the evidence: Balancing truth, facts, values and interests

Professor Paul Komesaroff
Professor of Medicine and
Director of the Centre for
Ethics in Medicine and
Society
Monash University
Melbourne

Decisions taken in scientific and clinical settings are subject to complex influences. The ethos of science as a disinterested pursuit of objective truth is at best imperfectly realised in practice. As a starting point, clinicians are not scientists; there is always a major contribution of clinical judgement to all health encounters. Ethical and social values, and personal, context-dependent characteristics are all taken into account in any interaction.

Two examples will be used to illustrate these points – the case of Galileo and that of hormone ‘replacement’ therapy (HRT) after menopause.

The concept of evidence has been discussed widely. It can be taken for granted that there are two levels of evidence, which are associated with very different logical processes:

- **Large-scale population data** – where epidemiological studies, laboratory studies, in vivo experiments and randomised controlled trials are conducted
- **Local, individual clinical decision making** – these considerations draw on large-scale evidence and on local clinical experience and wisdom.

Both approaches are associated with a mix of facts and interpretations. Local, individual clinical decision making is where actual decisions are made and actions are taken in consultation with the patient.

There are separate activities and concepts of knowledge with different standards for ‘truth’. Clinical decision relies on two sets of transitions to make sense of (or convert) the data that are relevant. This is complicated. The clinician must move between the data and their interpretations, and between the level of scientific evidence and the local, individual decisions that are made every day in the clinic.

Clearly, clinical decisions are influenced by the interpretation of the data collected in the controlled setting of scientific experimentation. These interpretations are not, as they are often presented to be, objective, disinterested, a pure and simple reflection of the facts, unbiased or unaffected by personal or local cultural beliefs or prejudices. Rather, the process of scientific interpretation is always deeply affected by such factors. Scientific facts always exist in a social context and their validity depends on this context.

The case of Galileo

Galileo Galilei lived from 1564 to 1642. A great Italian scientist, he was the originator of modern physics. Many scientists believe that Galileo’s work was plainly ‘true’, and that through the power of his intellect and logic he was able to supplant the erstwhile Aristotelian view of the world with a new, mathematical one. The view of succeeding generations was to seek **objective truth**, but this is not how it happened.

Galileo was a great innovator and truly one of the great imaginative heroes of human history. However, his theories came to be accepted not primarily on the basis of the strength of his thought and observation, but on abstraction, a new language, the question of empirical validation. Galileo published a number of articles in the early 17th century strongly supporting the Copernican theory that the earth circled the sun (heliocentrism). These ideas were seen by church authorities as profoundly disruptive of the existing intellectual status quo and the church’s teachings – and they therefore had a wide set of social implications. From the time Galileo wrote *The Starry Messenger* in 1610 the church took steps to shut him up and he was subject to harassment from the authorities (especially the ecclesiastical authorities) for the rest of his life. The authorities understood that the new ideas Galileo was writing about were dangerous, that his propositions were mere representation of objective facts, but that they carried profound, potentially uncontainable social implications for political authority.

In 1633 Galileo was tried before a formal inquisition for promoting the views of heliocentrism. He was found guilty, placed under house arrest for the rest of his life, and made to recant. They showed him the instruments of torture and told him to imagine what would happen if he did not recant. They knew their man and this was all they needed to do. Galileo recanted, even though he continued writing in secret and was able to arrange for his manuscripts to be smuggled to safety, where they were subsequently published.

Today’s school students are taught that the strength of Galileo’s theory lay purely in the fact that, compared to the Aristotelian orthodoxy, it carried greater empirical validity and was more closely in

accord with objective reality. In reality, the opposite was the case. Galileo's theory – at least in its early stages – was actually empirically inferior to the Aristotelian system. Everyone knows, after all, that the first law of motion – that a body in motion tends to remain in motion – is never borne out in fact. Rather, the Aristotelian idea of inertia – that if you push a body it will stop – is what we observe on earth in every real instance. In reality, Galileo's theory was not empirically valid. It was abstract and contrary to the facts. Indeed, this was its great innovation. Galileo discovered not the concept of empirical science, but a new idealised language, the language of mathematics, in which the empirical questions could be formulated. The success of the theory was dependent not on its 'objective' validity, but on other factors related to knowledge, philosophy, society and politics.

Galileo was attacked, but he fought back in his writings. He took the struggle to the streets, writing popular works, not just in Latin, but also in Italian, the language of the common people. In a book on the arguments for and against heliocentrism (*Dialogue Concerning the Two Chief World Systems*) he sought to obtain the support not of the effete intelligentsia, but of the common people. There are two main characters in the book: Sagredo, who is Galileo himself, and a second person called Simplicius in Latin or Simplicio in Italian, who represents the Aristotelian view (that the sun revolved around the earth) and speaks in phrases used by the Pope. The name Simplicio in Italian has the connotation of a simpleton, and the portrayal of this character served to cast greater doubt on the established ideas amongst the local readers of the book and ensured readers were on Galileo's side.

Galileo's struggles to get his ideas accepted show how science, culture and society are intertwined. They draw attention to the fact that the success of a scientific theory – its acceptance or rejection, its capacity to generate approval or hostility – is not determined merely by its philosophical or empirical value, but also crucially by the complex social and political frame within which it is embedded.

Scientific meanings are subject to and dependent on social attitudes, prejudices and belief systems. People can find ways to convince themselves that a particular view is true depending on their personal attitudes. It is not the case that the process of understanding science, data and the world, is detached and objective. It is always rooted in local vested interests. Science and medicine cannot be separated from the contemporary cultural debates. This is the essence of what Galileo discovered. The success of a theory depends on social struggles,

which can be ruthless and even violent. In Galileo's case, he fought hard and, despite the setbacks, was eventually victorious, even if in his case the full victory came only posthumously.

The case of hormone therapy after menopause

In the 1930s scientific studies showed that administering oestrogen to mice could promote the development of breast cancer. Despite this, there was a strong interest in promoting oestrogens for women, starting in the 1960s. The American psychologist Robert Wilson initiated the modern emphasis on the use of hormone therapy in his book *Feminine Forever*. In today's terms this book is misogynistic, but at the time it was very popular, selling more than 100 000 copies, with the claim that menopause was 'preventable':

Every woman alive today has the option of remaining feminine forever... No longer need she fret about the cruel irony of women aging faster than men. It is simply no longer true that the sexuality of a woman past forty necessarily declines more rapidly than that of her husband.

All postmenopausal women are castrates... [but with HRT] a woman's breasts and genital organs will not shrivel. She will be much more pleasant to live with and will not become dull and unattractive.

An oestrogen-rich woman capable of being physically and emotionally fulfilled by her husband ... is least likely to go afield in search of casual encounters.

Robert Wilson, *Feminine Forever* (1966)

In the 1970s the word 'replacement' was inserted in the expression 'hormone replacement therapy' as an industry marketing strategy to make menopause appear as a pathological condition that required drugs to correct it. The pharmaceutical companies wanted HRT use to seem more acceptable and natural and to create the impression that older women needed to restore their hormones to premenopausal levels. The addition of this word turned out to be a very good investment, ultimately generating countless billions of dollars in sales of HRT.

Over the succeeding decades a great deal of scientific evidence has emerged about the actions of oestrogens and their effects on bones, the cardiovascular system, the neurological system, breast and uterus. We now know a lot about the way these hormones work.

During the 1990s HRT became widely accepted as a key treatment for menopause. The number

INTERPRETING THE EVIDENCE

of prescriptions for oestrogen-based therapies skyrocketed in the industrialised world. Guidelines issued by menopause societies in Australia, North America and Europe actively promoted HRT.

Examples of clinical recommendations from the 1990s

June 1990: 'The cardiovascular benefits of Premarin may outweigh the risks depending on the individual patient's risk profile for various oestrogen-related diseases and conditions.'¹

1991: 'Epidemiological evidence is accumulating that postmenopausal oestrogen therapy reduces the risk of cardiovascular disease and stroke by between 30 and 70% even in the presence of established risk factors.'²

1992: 'Oestrogen is cardioprotective for women. Not only does it have a beneficial effect on the circulating blood lipid fractions, but it is now established that oestrogen has a positive influence in preventing the deposit of cholesterol in the arterial endothelium. It also induces vasodilation, increases peripheral blood flow and leads to a fall in blood pressure. The use of oestrogen to reduce cardiovascular disease far outweighs any potential adverse changes.'³

1992: 'All women...should consider preventive hormone therapy.' 10 to 20 years of therapy were recommended for 'maximum benefit'.⁴

1993: 'All postmenopausal women, barring a medical contraindication like breast cancer, should take HRT for life.'⁵

1994: 'HRT can reduce the incidence of CHD in postmenopausal women by 50%... HRT reverses the increased fat distribution that results from loss of ovarian function at the menopause. HRT may also (result) in a reduction in arterial thrombosis.'⁶

1996: 'There is now good population-based evidence that HRT in postmenopausal women reduces the incidence of CHD, perhaps by up to 50%. HRT should therefore now be considered for use in postmenopausal women with established CHD risk.'⁷

2000: 'Today, HRT may be used for the primary prevention of CVD. (T)here is no compelling evidence for discontinuing – or indeed not initiating – HRT in women without CVD because of concern about cardiovascular risk.'⁸

The comfortable consensus was exploded in 2002 with the publication of the first results of the Women's Health Initiative (WHI). The WHI was, in its time, the largest and most expensive clinical trial ever, involving a total of 160 000 participants and running for more than 10 years. It began in the early 1990s as a response to rising discomfort about the lack of clinical data and concern that some of the benefits of HRT were exaggerated. The WHI evoked considerable opposition when it started, with some advocates for hormone therapies even arguing that it was 'unethical' to continue testing these treatments because so much was already known about them and the agreement about their effectiveness and safety was so strong.

The WHI hormone therapy study had two arms – an oestrogen plus progestogen arm that ceased in July 2002, and an oestrogen-only arm that ceased in February 2004. The oestrogen plus progestogen arm was stopped because the trial showed an increased risk of invasive breast cancer and an increase in

coronary heart disease, stroke and pulmonary embolism in the study participants. Two years later the oestrogen only arm was also stopped because it increased the risk of stroke, decreased the risk of hip fracture and did not affect coronary heart disease incidence. By this time several other large trials had been published that suggested the assumptions about the benefits and risks of hormone therapy may have been misplaced.

The conclusions of the WHI generated a remarkable situation. Guidelines produced by experts had been widely propagated supporting the use of hormone therapies. However, now data were available that called into question the basic assumptions on which those guidelines had been founded. The experts, of course, were scientists so one would expect that they would respond to the new knowledge by revising the guidelines to incorporate the current insights and introduce appropriate notes of uncertainty and caution. Correct? Unfortunately, no. This did not happen. The guideline developers mostly did not change their attitudes. Instead, they mounted a vigorous campaign – which even continues today – to attack and refute the study conclusions.

To avoid misunderstanding, it is important to emphasise that debates about the validity of clinical studies and the interpretation of their results are part of the legitimate discourse of science. However, in this case what is remarkable is that despite the significant size and rigour of the WHI trial and the clarity of its outcomes, and the subsequent accumulation of a great deal of supporting data, many of the committed advocates of hormone therapy refused to alter their positions to any significant degree. Instead their response was not to question their own prior assumptions, but to find arguments to support why the WHI had to be wrong. For example, it was argued that the wrong population was used (e.g. the study participants were too old, only North American, and included smokers), that the wrong hormonal preparation was administered, that the interpretation of the data was wrong, and that the wrong methods were used in the design of the trial.

In a 10-year review of the WHI results published in 2012, the original view about breast cancer in the oestrogen plus progestogen arm was validated by the long-term follow-up. In the oestrogen-only arm the breast cancer outcomes are reported as equivocal, the cardiovascular outcomes were negative, and oestrogen was shown to be harmful in Alzheimer's disease prevention.

However, even now, few of the original proponents of hormone therapy have changed their minds. Instead, they promote arguments not based on

evidence, or based on studies that provide limited (often flawed) data that appear to support their case. For example, a recent Danish study⁹ (which included 1000 people with questionable recruitment strategies and an idiosyncratic end point) suggested possible cardiovascular benefits in a particular population and was widely promoted as refuting the results of the entire WHI program. At the same time, the popular media – the same media that actively supported and encouraged the use of HRT – have continued to cast doubt on the conclusions of the WHI and a large number of other studies that now support its broad conclusions, and to promote new studies of lower quality or study design in order to demonstrate to the public that there is positive news for the use of HRT. Headlines abound, such as ‘Flaws in Major US Study on HRT’, ‘HRT gets another chance’, ‘Doctors to rethink benefits of HRT after study shows that oestrogen may protect women against breast cancer’, ‘Call for NIH to revise recommendations on HRT’, ‘A wasted decade: how one HRT scare has caused countless women ten years of needless suffering’ and ‘Expert calls for inquiry into the NIH’.

I do not want to suggest that the evidence, one way or the other, about hormone therapy is clear-cut. On the contrary, there is much that remains uncertain and there are key issues that await clarification from future scientific studies, involving both laboratory experiments and clinical studies. However, the point I want to make is that the original uncritical support for hormone therapy was not based on evidence, and the appearance of new evidence was insufficient in many cases to change this support. Many of the most zealous advocates of the therapy have retained their commitment, even in the face of considerable – if not completely conclusive – data to the contrary.

Conclusion

I hope that the parallel with the case of Galileo is clear. Even today, the informed opinion of experts and the debates around contending theories are not subject

purely to the careful, dispassionate and disinterested assessment of the facts. Rather, they are dependent on other factors operating outside of scientific discourse. They are subject to the influences of culture and ideology, of personal beliefs and reputation, of the vested interests of the pharmaceutical industry and medical practitioners, of prevailing social prejudices, and of politics and power. Of course, these arguments apply to both sides. The debates about hormone therapy after menopause – just like the debates about the two world systems four hundred years earlier – are not fought out merely in the domain of science.

These are culture wars. The battle, as in the case of Galileo, has been – and is still being – contested not just in the halls of academia, but also in the streets, in the newspapers, on television, through the internet. Every new finding is accompanied by a press release, often tendentious.

As with Galileo, with hormone therapy there are many interests and influences at play. The field is not one of pure science in the idealised sense. The ‘ethos’ of science is imperfectly realised in practice. Despite the proclaimed commitment to evidence and an open scepticism, the reality is very different.

This is the sad and sobering moral of my story, but it should not be a cause for despair. Rather, those who work (through guidelines or other means) to improve clinical practice and to effect changes in policy merely need to recognise the complexity of the environment within which they are operating and to add the factors I have been discussing as additional variables to be taken into account. There is no pure science. There is no simple, incontestable objective truth, the facts never speak for themselves. Rather, we always have to make judgments from interest-laden points of view. Whether we like it or not, the process of responsible decision making – ours and everyone else’s – always involves the establishment of a careful balance between truth, facts, values and interests.

Professor Komesaroff provided a detailed declaration of his interests (see Appendix 2 for details)

REFERENCES

1. Wyeth advertisement.
2. Hillard TC, Whitcroft S, Ellerington MC, Whitehead MI. The long-term risks and benefits of hormone replacement therapy. *J Clin Pharm Ther* 1991;16:231-45.
3. Wren BG. HRT and the cardiovascular system. *Aust Fam Physician* 1992;21:226-9.
4. American of College of Physicians leaflet.
5. The American College of Obstetrics and Gynecology recommendation.
6. Stevenson JC, Crook D, Godsland IF, Collins P, Whitehead MI. Hormone replacement therapy and the cardiovascular system. Nonlipid effects. *Drugs* 1994;47 Suppl 2:35-41.
7. Stevenson JC. Mechanisms whereby oestrogens influence arterial health. *Eur J Obstet Gynecol Reprod Biol* 1996;65:39-42.
8. Genazzani AR, Gambacciani M; International Menopause Society. Controversial issues in climacteric medicine I. Cardiovascular disease and hormone replacement therapy. International Menopause Society Expert Workshop. 13-16 October 2000, Royal Society of Medicine, London, UK. *Climacteric* 2000;3:233-40.
9. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ* 2012;345:e6409.

Experts and competing interests

Associate Professor Ian Kerridge

Director and Associate Professor in Bioethics at the Centre for Values, Ethics and the Law in Medicine University of Sydney
Staff Haematologist/
Bone Marrow Transplant Physician
Royal North Shore Hospital Sydney

What do people understand about the issues that influence their judgment and decision making? What point is served by declarations of interest? There are a wide range of people with different interests, ranging from professionals, patient organisations, medical students and the public. How much information is needed and what needs to be done beyond the 'declaration' to manage the interests?

Contacts with industry are vast and multidirectional (i.e. clinicians and researchers approach industry as much as industry approaches clinicians and researchers). There is much less data in Australia about the extent of interactions between the health sector and the pharmaceutical industry than in the USA. A US study showed that:

- 85% of professional organisations are sponsored by, or receive advertising revenue from, the pharmaceutical industry.
- More than 80% of patient/consumer groups receive support from the pharmaceutical industry.
- Many medical students have accepted gifts from industry and had extensive contact with industry-sponsored education, promotional materials and data before graduation.
- The public also engage with industry through direct-to-consumer activity – despite this being prohibited in Australia.

In 2009 an American Medical Student Association PharmFree Scorecard survey asked US universities if they had conflict of interest policies. The domains of interest included gifts, consulting relationships, industry-funded speaking relationships, disclosure, on-site educational activities, medical school curriculum, and compensation for attendance at meetings. One-third of the universities refused to answer the question. The American Medical Student Association gave permission for their methodology to be used to assess conflict of interest policies in Australian medical schools. The results were published in 2011¹ and showed that the majority of Australian universities, as with those in the USA, scored very poorly.

Another recent study looked more broadly. The Australian University Conflict of Interest Survey² showed that nearly 30% (n=12) of universities declined to provide any information. Of those that did provide information, most (n=27) had policies on staff's competing interests:

- 15 universities did not require regular declarations from staff and only four required annual declarations
- Only eight universities maintained a central register of staff declarations
- Only six universities had some mechanism in place that allowed members of the public to access information from their register
- None required that staff place their declarations on their website profiles and none had policies that indicated staff should declare conflicts when making public comment. These can be recovered through Freedom of Information processes, but it is hard work.

Recent National Health and Medical Research Council-funded studies (NHMRC 457497 and 141772) have been conducted to seek more detail on the relationships and interactions between industry and Australian specialists. The study involved 1500 clinicians and showed that:

- 96% had accepted gifts (the value of gifts was higher if the physician was in an active research relationship with that company or was on the advisory panel of that company)
- 84% had attended a sponsored symposium or product launch (as distinct from a conference)
- 52% had accepted travel sponsorship and 30% had accepted travel support for their partner
- 23% had been a member of an industry advisory panel
- 7% owned shares in pharmaceutical companies that produced drugs that they prescribed
- 6% had acted as a paid consultant.

The study also investigated the concerns of respondents about industry-funded research. These concerns, by percentage of respondents, included:

- premature termination of trials (most of these appeared justifiable e.g. adverse events) – 14% (114)
- first draft of paper written by sponsor or ghostwritten – 12% (100)
- unreasonable delay in publication – 6.7% (55)
- failure to publish negative findings – 5.2% (41)
- draft of paper editing to make the drug look better – 2.7% (22)
- concealment of results – 2.2% (18)
- inappropriate alteration of data – 0.9% (7).

The potential adverse consequences of pharmaceutical-industry sponsorship of research have been extensively described. They include:

- increased costs of care
- distortion of care, erosion of rational prescribing and quality use of medicines
- distortion of research agenda (creation of the '90/10 divide' whereby 90% of research is conducted in diseases that affect 10% of the world's population – those able to afford pharmacotherapies)
- distortion of evidence (with the results of sponsored studies consistently being more often favourable towards the sponsored therapy under investigation)
- distortion of research question (reduction in 'head-to-head' studies, particularly of competitor drugs)
- distortion of research methods (move from superiority to non-inferiority trials)
- selective reporting of data favourable to product
- loss of researchers' independence and integrity
- creation of multiple ties and conflicts of interest
- creation of gift relationships
- increase in secrecy in medicine and research
- delay or non-publication of key findings for commercial reasons (such as has been documented with studies of COX-2 inhibitors and selective serotonin reuptake inhibitors)
- erosion of public trust in research, medicine and health professionals.

While these harms work in different ways in different contexts, ultimately they all have the capacity to subvert the (proper) goals of medicine, health education and biomedical research.

This level of systematic bias in medicine is a challenge for all those engaged in health, but it is a particular problem for evidence-based practice, which emphasises and relies on published evidence. If the data on which evidence-based practice is founded are corrupted, then so is practice itself.

Concern about this level of pharmaceutical industry involvement in research, education and clinical care is not limited to liberal critics of medicine, but is shared by many of those who have an interest in the quality of medicine and biomedical science. It is noteworthy that past and present editors of many of the world's major medical journals have noted the adverse impact that industry sponsorship has had (and continues to have) on the scientific record and on the integrity of the profession.

Journals have evolved into laundering operations for the pharmaceutical industry.

Richard Horton, Lancet

Journals have been co-opted by industry.

Marcia Angell
New England Journal of Medicine

Medical journals are an extension of the pharmaceutical industry.

Richard Smith, British Medical Journal

There is a cycle of dependency between journals and the pharmaceutical industry.

PLoS Editors

Assessing and managing interests in medicine

There is now a huge amount written about conflicts of interest. Many professional bodies, colleges, universities, research institutes and industry organisations and networks now have codes of ethics and conflict of interest policies, although these are of variable quality and most remain in the private rather than the public sphere.

Three of my own experiences illustrate both the importance of having some means for thinking through conflicts of interest and the difficulties associated with assessing and managing them.

Development of embryonic stem cells and human cloning legislation

In 2005 to 2006 I was involved in the Lockhardt Committee, a Legislative Review Committee established by the Commonwealth Government to review the Acts relating to human cloning and embryo research. One of our tasks was to draw up a view regarding progress or reform in this area that was consistent with 'community values'. It became clear that, on this issue (and undoubtedly on others), there was no single community or single community view or values. Instead, there were many communities and many values and interests, and these were often diverse and sometimes incommensurable. Also, there was not a single person in the community who was not concurrently a member of many different 'communities', each of which had its own norms, values and language. A person was simultaneously a research scientist, a doctor, a mother, a Catholic and a friend of someone with a disease that may, in the future, be helped by stem cell research. The task for us as a committee, and also for every person when deciding how they should act or behave or vote, was to reflect on the multiplicity of values and to identify what these interests are, how salient they are, where upon a

continuum of interests they lie, and how they should be managed – particularly when they appear to be incommensurable.

The lesson here is that one always has multiple interests simply by virtue of having different social roles, and sometimes these are problematic and sometimes they are not. The task for guideline developers is to identify the interests at play and then to consider, through open and transparent debate, whether or not these interests create a conflict or put at risk the integrity or rigour of the guideline.

Faith

In recent times I have had cause to think about the relevance of faith to medicine and health policy. Faith is important to people, their lives and families. It comes with a set of values, rituals, authorised dogma and hierarchies of decision making that influence the way people of faith may approach any issue or situation. Faith, in and of itself, does not represent a conflict of interest or necessitate exclusion from discussions about health policy. Indeed, ethics committees are required to include representatives from pastoral care or faith in their membership. And faith undoubtedly contributes to thinking about values or beliefs or the impacts of health policy. However, while there is a tendency to privilege faith – to suggest that it is never appropriate to exclude people of faith from policy-making on the grounds that they have a conflict of interest – this seems not to be true. Surely a Jehovah's Witness has an unavoidable conflict when it comes to blood policy, a Scientologist has an unavoidable conflict when it comes to mental health policy, and a Catholic priest has an unavoidable conflict when it comes to determining policy on access to reproductive technology or third-trimester termination of pregnancy?

While one would not seek to exclude people of faith or be deaf to their values, for those charged with developing guidelines, the question is where relevant expertise (including representatives from industry or researchers with extensive ties to industry) should sit. Should the person have a role in the development of expert guidelines, or should they be kept distant but be invited to give an expert perspective – an interested perspective – via submission or review?

Interests and expertise: The ubiquitous nature of competing interest in contemporary healthcare and research

This year I was invited to write a commentary on the issues surrounding a well-publicised public and professional debate about conflict of interest.

In 2011 the well-known psychiatrist, mental health advocate and public intellectual Professor Ian Hickie co-authored a narrative review of melatonin-based therapies (agomelatine) for depression in the *Lancet*.³ In the paper both authors disclosed ties (financial and professional) with the manufacturer, Servier. This paper provoked a firestorm of criticism in the *Lancet*, lay press, and social media about the disclosure of interests. The criticism included both **empirical claims** – that the authors misrepresented the tolerability/efficacy of agomelatine – as well as **moral claims** – that the authors were conflicted or biased or that they, or Servier, may have benefited from publication.

Hickie and Rodgers penned a spirited response⁴ defending their findings, their professional ethics and their compliance with the *Lancet's* disclosure policies.

This is not the first time that psychiatry has featured in discussions around the links between the pharmaceutical industry and the medical profession. Over the past two decades there have been innumerable occasions where concerns have been raised about the links between psychiatry and industry (likely a consequence of the nature and prevalence of mental illness and the vagaries surrounding psychiatric diagnosis). In recent times, for example, concerns have been raised about the impact of commercial interest on the revisions to the DSM-5. These concerns have included questions over the definition and diagnosis of illness, issues of overdiagnosis, overt drug promotion and non-disclosure of pecuniary conflicts of interest. For the Working Groups revising DSM-5, 67% of the Mood Disorders Work Group, 83% of the Psychotic Disorders Work Group, and 100% of the Sleep-Wake Disorders Work Group had ties to manufacturers of medications used to treat these disorders.⁵

There is no doubt that Professor Hickie is entangled in a web of interests, but in this regard he is likely no different to any other major researcher or director of a research institute. As an academic researcher, well-respected clinical psychiatrist, public advocate and director of a research centre he is expected to create and sustain links with industry, forge public-private partnerships, and develop research that inevitably engages with industry.

The lesson here is that each social role carries with it a series of moral, social and professional imperatives that one assumes when one adopts that role, and these are often difficult to balance. While most of the time each of us can balance these different roles easily, in some situations conflicts may emerge – conflicts that may or may not have very serious implications for science and practice.

Conclusion

'Interests' involve a commitment, goal or value arising out of a particular social role or practice. There is nothing wrong with interests per se. So rather than speaking of conflicts of interest we should speak of multiplicities of interests and accept that just as people have many roles they also have many interests – none of which has obviously greater a priori importance or weight.

At any one time a person has a range of interests. For example, I am a clinician, teacher, director, colleague, collaborator, father and partner – all these roles have different demands and expectations attached to them and sometimes these interests collide.

The task for guideline developers and clinicians is to establish whether any one of these divergent interests constitutes a genuine conflict of interest (such that one's primary commitment at that time or in a particular context – e.g. research or design of guidelines/policy – is subverted or distorted) and to consider what should be done. This may be a function of the importance of the task and the necessity to separate interests. While this must be a matter for personal reflection and humble introspection, it must also be a public matter for discussion and discourse with relevant stakeholders.

In guideline development processes it is clear that it is not sufficient to simply disclose an interest and rely on that disclosure to resolve ethical concerns. Disclosure may obfuscate or provide moral licence and does not reduce the prevalence or impact of competing interests. Disclosure and transparency are, of course, important, but the idea that disclosure is sufficient to expunge the possibility of bias, or that responsibility for assessment lies with the public, readers and users, is naïve and morally inadequate. We need to go beyond this, and this requires that we develop a more sophisticated view of interests and that we 'de-psychopathologise' conflict of interest and remove blame or ignominy from declarations.

We must also openly establish 'interests' as a conversation and establish rigorous, transparent and professionally accepted processes for discussing, assessing and managing competing interests. These conversations will only happen, of course, if the relevant communities (be they industry, scientific or research communities) have a culture that respects discourse on these issues, and are prepared to establish guidance regarding what sort of disclosure and management of the interests is required. This guidance will need to make clear not only when and how interests should be declared and how relevant interests should be assessed, but what relationships may or may not be acceptable and how competing interests should be managed – by declaration alone, consultation, collaboration, abstention, delegation, divestment or separation.

Importantly, guidance on assessing and managing competing interests should attend both to pecuniary and non-pecuniary interests. While we have made some progress in thinking about financial conflicts of interest, much less is known about non-pecuniary interests and how we should manage them. In my view it is very likely that non-pecuniary interests (which include political influences, publication, status, professional recognition, academic progression, and belonging to a professional or academic community) are much more important 'drivers' than financial interests and rewards.

There are no clear solutions, but it is clear that we need to think differently about interests, we need to think more rigorously about interests and make the discussion about facts and values rather than personal failings or psychopathology. We also need to have these discussions in public spheres rather than purely private ones.

Acknowledgments: Professor Ross Upshur, Dr Wendy Lipworth, Professor Paul Komesaroff, Emeritus Professor Miles Little and Dr Chris Jordens

Professor Kerridge provided a detailed declaration of his interests (see Appendix 2 for details)

REFERENCES

1. Mason PR, Tattersall MH. Conflicts of interest: a review of institutional policy in Australian medical schools. *Med J Aust* 2011;194:121-5.
2. Chapman S, Morrell B, Forsyth R, Kerridge I, Stewart C. Policies and practices on competing interests of academic staff in Australian universities. *Med J Aust* 2012;196:452-6.
3. Hickie IB, Rogers NL. Novel melatonin-based therapies: potential advances in the treatment of major depression. *Lancet* 2011;378:621-31.
4. Serfaty M, Raven PW. Novel melatonin-based treatments for major depression [letter]. *Lancet* 2012;379:217-9.
5. Cosgrove L, Krinsky S. A comparison of DSM-IV and DSM-5 panel members' financial associations with industry: a pernicious problem persists. *PLoS Med* 2012;9:e1001190.

Identifying and managing competing interests

Panel discussion

Panel members

Professor Chris Baggoley
Dr Peter Greenberg
Dr Suzanne Hill
Professor Robert Moulds
Professor Martin Tattersall
Dr Janet Wale

Moderator

Professor Paul Komesaroff

Each panellist was invited to comment on the issues raised by Professor Paul Komesaroff and Associate Professor Ian Kerridge in their earlier presentations, and comments from the forum participants were also invited.

Identifying pecuniary and non-pecuniary interests

Issues of faith and religion are important to many people and are part of their make-up. Along with a number of other factors (such as their background and cultural perspectives), they contribute to each person's view of the world. It is incredibly complex, and most people are not aware of how their range of personal beliefs could influence decisions. When it comes to declaring interests, it is useful to declare faith as a possible duality of interest and to ask the group of people you are working with whether they believe it is significant enough to be a potential conflict of interest. If it is an issue, then one should disassociate oneself from the work.

By declaring the full spectrum of interests (financial, academic influence/kudos, professional or personal/family ties) early in the process, others on a group or team have a chance to consider whether it is an issue and how it can be managed. It also makes clear to others that the conflict does not create an obligation through association.

Non-industry related conflicts should also be disclosed, and there should be transparency and discussion about the effect of an interest.

Do government links and funding create potential conflicts? This is a particular consideration in cases where the government might have an established policy it wants to have upheld, or where the government may be required to consider funding activities proposed by a guideline.

Another type of conflict arises when people have gone on public record for or against a particular form of care, treatment or product and may be seen as having a fixed view that will not be swayed by evidence or other information provided to a guideline committee.

Many interests and conflicts may be hard to quantify, but it is important to strive to be as transparent as possible.

Consumers and practitioners want to trust health services and guidelines. In the past, the trust has been based on non-disclosure and placing a lot of faith in people to 'do the right thing', but there is now a strong clear call for disclosure on as many things as possible. There should also be more consumer representation and engagement on guideline teams. Where consumers represent organisations and decision-making bodies, the funding sources of those organisations should also be disclosed.

How to manage conflicts of interest

It is not possible to avoid the issues of bias in data and research. Agencies and guideline development teams need to choose people who are as independent as possible, and have transparent processes for them to follow. By having agreed processes, good people will not be discouraged from participation on guideline teams.

It might be useful to look at other sectors to see how they deal with conflict of interest issues. Does the jury system have processes that could help inform guideline processes for managing interests?

Is there a risk that disclosure could lull people into a false sense of confidence and assurance?

People with a range of values can bring a wealth of expertise to the development of a guideline. It is possible to separate out financial interests from expertise. There needs to be guidance about when people with 'interests' or expertise should be included or excluded from discussions – for example should a person involved in research about drugs or health services be part of a committee that approves that product or service? The American Thoracic Society has looked at these issues very carefully and has implemented a transparent and structured process that allows experts who have made disclosures to discuss the evidence and give their expert opinions, but excludes them from the final debate on the evidence and the formulation of recommendations. Also, the guideline panel is led by a methodologist rather than a clinical expert.

There are people with connections to industry who can nevertheless provide specialist opinions that add value and perspective to the discussion of a guideline.

To gain trust in the process, the conflicts need to be declared, managed, recorded and made publicly available. The Chair of the committee should be free from competing interests.

How to decide whether the disclosure is a conflict

A nuanced approach to identifying issues and influences that may present (or appear to present) a conflict is useful. There also needs to be consideration of whether a disclosure represents (or is perceived to represent) a high- or low-level conflict or influence, and appropriate responses are required. Or perhaps the views simply represent a valuable perspective? It will be important to ascertain whether the view or belief carries with it a real or perceived obligation to an external party.

Guidelines seek to be as reliable and credible as possible. One of the guiding principles in assessing the perception of conflict that can be used is to ask the question 'What would be the impact if this issue was reported on the front page of a major newspaper?' The answer to the question will help to judge the most appropriate ways to understand and deal with the declared interest.

The World Health Organization uses evidence juries and evidence hearings for managing conflicts of interest when the input of commercial groups or heavily sponsored groups is required.

Agencies like the Pharmaceutical Benefits Advisory Committee and Therapeutic Guidelines need to be seen to have high standards of disinterestedness because of their public roles and tasks. They provide advice on issues in the health sector that have the capacity to influence diagnosis, treatment, health outcomes and quality of life. They have an enormous amount of public credibility and integrity, and their reputations are at stake if they don't manage interests well.

Recruiting people onto guideline development groups

It is important to make every effort to find people with expertise who do not have significant ties with industry, academic conflicts or personal interests. The Pharmaceutical Benefits Advisory Committee requires members to make annual declarations of interests as well as a meeting-by-meeting declaration of interest that is recorded in the minutes. However, these declarations are not publicly disclosed, and in some cases it might be inappropriate if they were (e.g. a member of the committee declaring that a child in their family uses a drug that is being considered by the committee). Strategies such as recusal or removal from the room for the discussion of the item are used

in meetings to ensure that the Committee as a whole maintains a high level of independence.

In addition to managing the conflicts or perceived conflicts of people on guideline development teams, it is also important to ensure that the members are aware of other areas and risks of bias in assessing research findings.

Promoting trust

Guideline users want to have faith and belief in the scientific process and want to be sure that all reasonable care and scientific rigour has been applied to the guideline development. In a number of cases, guidelines are also used as training tools for new health practitioners. While there are a lot of competing kinds of information (such as activities funded by the pharmaceutical industry), there needs to be a way of assuring the users (including consumers) that guidelines have been developed using careful and independent processes. Trust and reputation of the guidelines are critical. It is important to users that the pecuniary interests, faith and beliefs of the guideline developers are clearly stated and managed, and that the evidence has been evaluated to assess the risk of bias.

Therapeutic Guidelines has a reputation for trusted, easy-to-access guidelines that are endorsed by professional colleges. Many guideline developers have a vested interest in either promoting government policy or maximising health outcomes.

The National Health and Medical Research Council has developed standards for clinical practice guidelines that require public comment on all draft guidelines so that any issues of bias can be disclosed and debated in the open. It also has conflict of interest guidelines and recently refused to approve a guideline developed by an external body (funded by taxpayers' money) because of a conflict that was not dealt with by the developers. It is not always possible for those people developing guidelines to recognise where the perceived or real conflicts exist. It is unclear how many connections with industry are too many – what is the right number or financial limit?

Creating a framework

A framework for managing conflicts is required because it is not always clear when a conflict exists. There must be a formalised process in place that everyone knows, understands and respects. This process needs to be apparent to the people on guideline teams, the groups and agencies funding, approving and endorsing the guidelines (e.g. professional societies, non-government agencies and government agencies such as the Department of Health and Ageing and the National Health and

PANEL DISCUSSION

Medical Research Council), and the users of the guidelines (e.g. health practitioners, healthcare students and health consumers). Thresholds should be agreed in advance so that it is clear how many connections with industry are too many. However, there are no absolute rules and some conflicts are hard to recognise, so there should be a process for reviewing declared conflicts as the work of the group progresses.

Declarations of conflicts are necessary but not sufficient. The time at which disclosures are made is also important. To make sure the conflicts can be managed and that the appropriate people are selected for guideline teams, disclosures should be made before inviting people to be involved. Agencies like Therapeutic Guidelines need to know the person's

background and affiliations before inviting them to participate on a guideline development group.

The overall framework of each guideline should be considered. The bigger issue beyond conflict of interest is whether the scope of the guideline is appropriate. For example, will the guideline cover a wide range of topics from diagnosis, to treatment, use of drugs and rehabilitation? It is also important to consider whether the process for considering the evidence encourages debate and provides opportunity for public consultation and comment. Guideline developers should also have a process to ensure regular updates of the guidelines so that they are relevant and provide advice on the latest most reliable evidence.



Panel discussion: Dr Peter Greenberg, Dr Suzanne Hill, Professor Chris Baggoley, Dr Janet Wale, Professor Martin Tattersall, Professor Robert Moulds

Group discussions

The forum participants were asked to spend time in small groups to discuss the issues raised during the day and make suggestions, particularly in relation to the following six key questions.

How should the quality of the evidence be improved?

It is important to make it very clear from the start of any guideline project that there are processes and tools that can be used to assess the quality of evidence and risk of bias. There should be training for the health workforce (providers and researchers) to help them understand how to use these tools. Ethics committees and guideline development team members could be trained on ethical and scientific assessment of study design.

A range of changes to the way clinical trials are designed and funded are supported, including:

- increasing the scientific appraisal of research projects before submitting proposals to ethics committees. This ensures robust design to determine the therapeutic benefit of drugs and any superiority to existing products
- encouraging researchers to involve real people in trials so that the applicability of the drugs to the appropriate populations is rigorously tested
- requiring researchers to provide full access to all trial data in a way that it can be easily and publicly accessed
- promoting the independent funding of research rather than relying on industry-funded research, such as through the introduction by government of a prescriptive 5% tax on the pharmaceutical industry to cover the funding of independent clinical research
- increasing the transparency of all clinical trial data and making this information freely available. For example, research funders/purchasers should require registration of trials and access to all trial data if industry seeks to have public reimbursement of its products
- providing feedback on the usefulness of the research undertaken so that the funders of Australian research can commission the research that is needed.

How should the evidence be interpreted?

Guideline development teams need to be seen to be independent and have a Chair without any conflicts of interest and, if required, an expert Co-chair. To ensure that guideline teams adopt processes for interpreting evidence in a way that addresses the risk of bias, the following strategies are proposed:

- provide training on a standard methodology for conducting systematic searches of databases to find the most relevant and appropriate data
- provide training on reporting on critical appraisal of the evidence (e.g. detecting bias, interpreting the trial results and reporting risk and benefit data)
- ensure that teams include the right mix of people appraising the studies. Evidence should be reviewed by multidisciplinary teams.
- introduce standards for guideline development processes, such as recording sources of funding for guideline development teams, ensuring that guidelines are peer reviewed and open for public consultation
- ensure that there is a balance of the kind of evidence that is used in the development of guidelines (e.g. looking at issues from different perspectives such as remote rural issues and also qualitative data)
- acknowledge where there are areas of disagreements between guideline team members in the published guidelines.

How should the interests that influence decision making be described and interpreted?

It is important that people involved in guideline development and the assessment of therapeutic evidence have appropriate skills and expertise in their work. However, there should be a range or balance and diversity of interests represented – they should not be dominated by one group or one approach.

Before inviting people to join a guideline team, find out about each prospective team member's interests.

Discuss the need for transparency of interests with the people invited to be part of a guideline or project team. Advise them that their declarations of interests will be shared with other members of the group and published with the guideline.

There should be full public disclosure of all pecuniary and non-pecuniary interests of the group members so that the interests can be actively managed by the Chair.

Provide the Chairs of guideline development groups with training on the range of strategies available to manage conflicts of interest.

How should declared interests be managed?

There needs to be a clear policy describing the steps that can be adopted to manage conflicts, and the process for making decisions should be agreed in advance. These processes should be reported in guidelines or other publications.

Processes for managing conflicts should include:

- being clear that full disclosure is a requirement of participation
- recording points of difference or disagreement
- recording how declared interests were managed during meetings
- ensuring that the process includes a way to keep sensitive or personal interests private and shared only with the Chair.

How do end users interpret disclosures of interest?

Clinicians and consumers want to rely on the credibility of the agency providing advice. There needs to be clear information explaining that disclosure of interests is not 'naming and blaming', but is a credible professional and ethical operating process.

End users want to be able to assess the significance of the interest, to know that a process of managing the interest has been followed, and to be given advice about how to interpret the impact of the interest.

It would be useful to research what effect disclosures have on the perception of reliability of guidelines.

Should the role of guideline developers be extended?

Should guideline developers such as Therapeutic Guidelines and other guideline development agencies include being agents for change? Should they take on an 'activist' role, promoting change in practice and addressing public health outcomes in guidelines?

Some of the activities guideline developers could consider include:

- advocating for greater access to clinical trial results
- identifying and prioritising areas of unmet patient need that require more research
- advocating for increased public funding for clinical trials
- developing strategies to help people understand how to use guidelines
- taking on a broader role with consumer information (e.g. promoting evidence-based consumer information resources to accompany guidelines)
- broadening the scope of guidelines to include diagnosis and social determinants of health. Guideline developers could actively consider a wider range of interventions (beyond drug therapy) for inclusion in guidelines and also address deprescribing issues.
- including discussion about the effectiveness of complementary and alternative therapies in guidelines and having an agreed process for assessing the evidence/effectiveness of these therapies
- extending the remit of guidelines to include implementation activities.

Recommendations

During the presentations and the discussions following them many ideas and strategies were proposed to reduce the impact of bias and competing interests in guidelines and to improve the quality and reliability of the evidence base.

Strategies to manage interests

- Organisations and working groups involved in the development of guidelines and other resources should establish clearly defined and transparent processes for declaring and managing dualities and conflicts of interests.
- All researchers, academics, committees and people involved in such development should be required to make declarations of their dualities of interests, both pecuniary and non-pecuniary, and to give consideration to the potential influence of these dualities on the emerging products. This should occur at the outset of the development process and it should be revisited at every meeting.
- Where possible, the number of participants and authors with dualities or conflicts should be limited.
- Published materials should include rigorous documentation both of the process for managing dualities and conflicts and of the actual interests of participants, sufficient to demonstrate how the independence and integrity of the final guideline or resource was safeguarded. This may entail detailed annotations in relation to each part of the discussion explaining any relevant issues relating to interests and how they were managed.

Improvement of critical appraisal skills

- Researchers, ethics committees, clinicians, consumers, and newspaper and media journalists should undergo training in techniques for critically appraising clinical trial information.

Reform of regulatory requirements relating to new drugs

- Approval of new drugs should be subject to the criterion of 'added value', in addition to present requirements for proof of quality, effectiveness and safety, to ensure a therapeutic advantage over drugs already on the market.
- It should be a requirement that at least one of the two pivotal phase III randomised controlled trials should be carried out by an independent not-for-profit organisation.
- Pharmacological, toxicological and clinical trial data (appropriately de-identified) should be made freely available for scrutiny, preferably through publicly accessible trial registration websites.
- Regulatory authorities should be fully funded from public sources, independently of the industry they are meant to regulate.

Public funding of clinical trials

- Trials to answer important clinical questions without potential commercial benefit should be publicly funded. Such research would include trials to assess drug safety and effectiveness compared to existing best therapy, drug therapy in children and the elderly, non-drug therapies and orphan drugs used for rare and neglected diseases.
- Public funding for research could be largely derived from a levy on drug companies (e.g. a percentage of their marketing budget).
- All drug trial protocols and results should be publicly available to regulators, researchers, guideline developers and the public.
- Areas of unmet patient need should be identified and should receive priority public funding.

Appendix 1

Speaker profiles

Mr Richard Kneebone



Richard Kneebone is the Chairman of the Board of Directors of Therapeutic Guidelines Limited. He is a qualified lawyer and consultant on corporate governance and compliance and was formerly employed as Company

Secretary for Orica Ltd, Company Secretary for BHP Billiton and subsidiaries, General Counsel and Company Secretary for Australian National Line, and Legal Advisor for Hong Kong Mass Transit Railway Corporation. Before that he was in private practice.

Dr Sue Phillips



Sue Phillips is the Chief Executive Officer of Therapeutic Guidelines Limited. She was awarded a Doctorate of Philosophy by the University of Oxford in 1985 for her research on cellular immune responses to developmental

tumours. She was formerly employed as Director and Interim Executive Director at the National Health and Medical Research Council's National Institute of Clinical Studies, Senior Policy Analyst at the Royal Australian College of General Practitioners, Director in various health policy positions within the Australian Government's Department of Health and Ageing, and Post Doctoral Research Fellow at the Australian National University John Curtin School of Medicine and Monash University Biochemistry Department. In 2008, Sue was awarded an Australia Day Achievement Medallion for services that have made a significant contribution to the nation. Sue is a member of the Guidelines International Network Board of Trustees.

Professor Silvio Garattini



Silvio Garattini qualified in medicine in 1954. He was appointed as lecturer in chemotherapy and pharmacology.

He was the founder of the Mario Negri Institute for Pharmacological Research and

was its director when it opened in 1961. The Institute now has a staff of more than 850 people in three locations and in its 50 years has published more than 12 000 scientific papers and more than 250 books, on topics such as cancer and its treatment, tumour immunology, neuropsychopharmacology, and cardiovascular and renal pharmacology.

Professor Garattini was a member of Commissione Unica del Farmaco (the Italian organisation that decides on the reimbursement of drugs) from 1993 to 1997, member of Committee for Medicinal Products for Human Use (European Medicines Agency) from 1997 to 2004, Chairman of the Committee for Clinical Research (Agenzia Italiana del Farmaco) from 2005 to 2010, and is currently a member of the National Committee on Bioethics. He was also a founder of the European Organisation for Research and Treatment of Cancer. He has received many awards for his work, including the French Legion d'Honneur for Scientific Merit, and the Grande Ufficiale della Repubblica Italiana, the Medaglia d'Oro al Merito della Sanità Pubblica granted by the Italian Ministry of Health.

Assistant Professor Barbara Mintzes



Barbara Mintzes is an Assistant Professor with the School of Population and Public Health at the University of British Columbia. The main focus of her research is on pharmaceutical policy, including the effects of

direct-to-consumer advertising and physician-directed promotion on prescribing and medicine use decisions. She also carries out systematic reviews of the effectiveness and safety of new drugs with the university's Therapeutics Initiative. These reviews are used as background information for provincial reimbursement decisions. Dr Mintzes has a PhD in Health Care and Epidemiology from the University of British Columbia, and holds a Michael Smith Foundation for Health Research Scholar Award.

Professor Paul Komesaroff



Paul Komesaroff is a physician, medical researcher and philosopher at Monash University in Melbourne, where he is Professor of Medicine and Director of the Centre for Ethics in Medicine and Society.

He is a practising clinician, specialising in the field of endocrinology; his scientific research work focuses on the effects of hormones on the cardiovascular system and the development of noninvasive techniques for assessment of cardiovascular risk.

Paul is the Director of the Clinical Ethics Service at the Alfred Hospital, Ethics Convener of the Royal Australasian College of Physicians and Chair of the Royal Australasian College of Physicians Expert Advisory Group on Ethics, Executive Director of Global Reconciliation and Chair of the International Health Workforce Society of Australasia.

Paul has been actively involved in numerous committees, including the Victorian Justice Health Advisory Committee, the Victorian Department of Human Service Genetics Advisory Committee, Australians Donate, the ethics committees of the US Endocrine Society and Australian Medical Association, and the Australasian Bioethics Association.

Associate Professor Ian Kerridge



Ian Kerridge is Director and Associate Professor in Bioethics at the Centre for Values, Ethics and the Law in Medicine at the University of Sydney, and Staff Haematologist/Bone Marrow Transplant physician at Royal North Shore Hospital,

Sydney. He is the author of over 150 papers in peer-reviewed journals and five textbooks of ethics, most recently *Ethics and Law for the Health Professions* (Federation Press). He is a member of the Australian Health Ethics Committee, Chair of the Australian Bone Marrow Donor Registry Research Committee, and a member of the NSW Health Department's Clinical Ethics Advisory Panel. His current research interests in ethics include public health ethics, the philosophy of medicine, stem cells, prescription drug policy, end-of-life care, synthetic biology, and organ donation and transplantation.

Appendix 2

Speaker disclosures

Sue Phillips made the following disclosure:

- Guidelines International Network board member and contributing author to the paper she quoted in her presentation:
Qaseem A, Forland F, Macbeth F, Ollenschlager G, Phillips S, van der Wees P. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:525-31.

Silvio Garattini explained the Mario Negri Policy on Independence, which includes:

- Independence from politics, industry, finance and ideology or religion
- The Institute has many funding streams with no more than 10% of the total budget from a single source
- No patent applications
- Allow collaboration with industry but require ownership of data until publication
- Insist on freedom of expression in all publications.

Barbara Mintzes made the following disclosures:

- No conflicts of interest to declare
- Associated with the Therapeutics Initiative, which hosts the Cochrane Hypertension review group
- Publicly funded (Canadian Institutes of Health Research, Michael Smith Health Research Foundation, British Columbia Ministry of Health)

Paul Komesaroff made the following disclosures:

- Clinician and researcher
- Professor of Medicine, Monash University
- Director of Centre for Ethics
- Engaged in research into menopause and the cardiovascular effects of steroid hormones
- Collaborative relationships in research projects, past and present, with pharmaceutical companies
- Ethics convener of the Royal Australasian College of Physicians
- Principal author of Royal Australasian College of Physicians 'Guidance for Ethical Relationships Between the Medical Profession and Industry' and other documents
- Member or Chair of various ethics committees
- Executive Director, Global Reconciliation

Ian Kerridge made the following disclosures:

- Not employed (or reimbursed) by the pharmaceutical industry
- Not a member of advisory group or engaged as a consultant for the pharmaceutical industry
- Receives no travel or academic support from the pharmaceutical industry
- Not a shareholder of any pharmaceutical industry
- Contributes to enrolling patients into clinical trials sponsored by Roche, Pfizer, Cellgene, CSL, Onyx and Amgen
- Chair of HPC Transplant Group and member of Haematology Group for NSW Cancer Institute
- Member of Royal Australasian College of Physicians Ethics Committee and the Australian Health Ethics Committee

Appendix 3

Participants

Name	Role	Organisation	Location
Ms Jo Allardice	Editor	Therapeutic Guidelines Limited	Melbourne
Professor Chris Baggoley	Chief Medical Officer	Department of Health and Ageing	Canberra
Mr Martin Basedow	Lecturer, Health Care Management	Flinders University	Adelaide
Dr Margaret Beavis	General practitioner		Melbourne
Dr Phil Bergen	Lecturer	Centre for Medicine Use and Safety, Monash University	Melbourne
Ms Marion Berry	Manager, Melbourne Office	NHMRC	Melbourne
Ms Alice Bhasale	Consumer Team Leader	NPS MedicineWise	Sydney
Professor Frank Bowden	Principal Medical Advisor	ACT Health Directorate	Canberra
Professor Jo-anne Brien	Professor of Clinical Pharmacy	St Vincent's Hospital, University of Sydney	Sydney
Ms Siobhan Brophy	Communications Manager	National Asthma Council Australia	
Dr Heather Buchan	Director, Implementation Support	Australian Commission on Safety and Quality in Health Care	Sydney
Professor Rachelle Buchbinder	Director Professor and NHMRC Practitioner Fellow Joint Coordinating Editor	Monash Department of Clinical Epidemiology, Cabrini Hospital Department of Epidemiology and Preventive Medicine, Monash University Cochrane Musculoskeletal Group	Melbourne
Ms Nicki Burrige	Publications Pharmacist	Society of Hospital Pharmacists of Australia	Melbourne
Professor Terry Campbell	Senior Associate Dean	Faculty of Medicine, University of New South Wales	Sydney
Dr Shane Carney	Physician	John Hunter Hospital	Newcastle, New South Wales
Professor John Condon	Professor of Psychiatry	Flinders University, Daw Park Repatriation Hospital	Adelaide
Mr Glen Cormick	Manager, Business Development	Baker IDI Heart and Diabetes Institute	Melbourne
Ms Karen Crawford	Health Professional Training Coordinator	Diabetes Australia	
Dr Marilyn Cruickshank	Healthcare Associated Infection Program Manager	Australian Commission on Safety and Quality in Health Care	Sydney
Dr Sladjana Cvetkovic	Medicines Information Manager	NPS MedicineWise	Sydney

APPENDIX 3

Name	Role	Organisation	Location
Dr Jonathan Dartnell	Executive Manager, Innovation and Learning	NPS MedicineWise	Melbourne
Ms Susan Daskalakis	Editor	Therapeutic Guidelines Limited	Melbourne
Dr Janice Davies	Consultant	Whole Systems Work	Melbourne
Ms Janette Donovan	Consumer representative		Melbourne
Dr John Dowden	Medical Editor	Australian Prescriber	Canberra
Mr Geraint Duggan	Assistant Director, Guidelines Program	National Health and Medical Research Council	Melbourne
Ms Leia Earnshaw	Acting Assistant Director	National Blood Authority	
Mr Peter Francis	Lawyer	Maddocks	Melbourne
Professor Silvio Garattini	Director	Mario Negri Institute for Pharmacological Research	Milan, Italy
Professor Alastair Goss	Professor, Oral and Maxillofacial Surgery	University of Adelaide	Adelaide
Professor Lindsay Grayson	Professor/Director, Infectious Diseases	Austin Health and University of Melbourne	Melbourne
Dr Peter Greenberg	Physician	Department of General Medicine, Royal Melbourne Hospital	Melbourne
Dr Robert Grenfell	National Director, Cardiovascular Health	Heart Foundation	Melbourne
Mr Stephan Groombridge	Program Manager	Royal Australian College of General Practitioners	Melbourne
Ms Natalie Hannaford	Research Fellow	University of South Australia	Adelaide
Dr Ken Harvey			Melbourne
Dr James Hayes	Emergency Physician	Northern Hospital	Melbourne
Ms Mary Hemming	Consultant	Therapeutic Guidelines Limited	Melbourne
Mr Kelvin Hill	National Program Manager, Clinical Issues	National Stroke Foundation	Sydney
Dr Suzanne Hill	Chair, Pharmaceutical Benefits Advisory Committee	Department of Health and Ageing	Canberra
Dr Ingrid Hopper	Clinical Pharmacologist	Alfred Hospital	Melbourne
Ms Susan Huckson	Manager, Centre for Outcome and Research Evaluation	Australian and New Zealand Intensive Care Society	Melbourne
Professor Alan Husband	Health Professional Team Leader, Medicines Information	NPS MedicineWise	Sydney
Professor Garry Jennings	Director	Baker IDI Heart and Diabetes Institute	Melbourne
Ms Melanie Jeyasingham	Editor	Therapeutic Guidelines Limited	Melbourne
Dr Jane Johnson	Research Fellow, Department of Philosophy	Macquarie University	Sydney
Mrs Jenny Johnstone	Editorial Director	Therapeutic Guidelines Limited	Melbourne
Dr Sarina Kempe	Clinical Pharmacology Registrar	Alfred Hospital	Melbourne

Name	Role	Organisation	Location
Associate Professor Ian Kerridge	Director	Centre for Values, Ethics and the Law in Medicine, University of Sydney	Sydney
Ms Benafsha Khariwala	Editor	Therapeutic Guidelines Limited	Melbourne
Miss Carol-Anne Kilkenny	Medical Writer	NPS MedicineWise	Sydney
Ms Georgina Kilroy	Editor	Therapeutic Guidelines Limited	Melbourne
Mr Richard Kneebone	Chair, Board of Directors	Therapeutic Guidelines Limited	Melbourne
Professor Paul Komesaroff	Director	Monash Centre for the Study of Ethics in Medicine and Society	Melbourne
Ms Catherine Lavars	Assistant Director, Clinical Adviser	Department of Health and Ageing	Canberra
Ms Kerry Lavery	Project Officer	Australian and New Zealand Intensive Care Society	Melbourne
Ms Rebecca Lee	Project Officer	Heart Foundation	Melbourne
Ms Anne Leversha	Senior Lecturer	Monash University	Melbourne
Ms Emma Lourey	Senior Program Officer, Health Professional Learning	NPS MedicineWise	Melbourne
Dr Liz Marles	President	Royal Australian College of General Practitioners	Sydney
Ms Catherine Marshall	Independent Guideline Adviser and Health Consultant		New Zealand
Professor Christine McDonald	Director	Department of Respiratory and Sleep Medicine, Austin Hospital	Melbourne
Dr Aidan McElduff	Endocrinologist	Northern Sydney Endocrine Centre	Sydney
Ms Angela Melder	Clinical Effectiveness Senior Consultant and Manager	Quality Unit, Monash Medical Centre	Melbourne
Associate Professor David Menkes	Associate Professor of Psychiatry	University of Auckland	New Zealand
Assistant Professor Barbara Mintzes	Assistant Professor	School of Population and Public Health, University of British Columbia	Vancouver, Canada
Ms Deborah Monk	Director, Innovation and Industry Policy	Medicines Australia	Canberra
Ms Georgia Morris	Senior Policy Advisor	Australian Medical Association	Sydney
Professor Rob Moulds	Medical Advisor	Therapeutic Guidelines Limited	Melbourne
Ms Carol Norquay	Electronic Production Editor	Therapeutic Guidelines Limited	Melbourne
Mr Mark Olszewski	Communications Project Officer	National Asthma Council Australia	Melbourne
Ms Ali Patterson	Publishing Director	Therapeutic Guidelines Limited	Melbourne
Associate Professor Christopher Pearce	Clinical Design Lead	National E-Health Transition Authority	Sydney
Dr Sue Phillips	Chief Executive Officer	Therapeutic Guidelines Limited	Melbourne
Dr Jane Robertson	Senior Lecturer, Clinical Pharmacology	University of Newcastle	Newcastle, New South Wales

APPENDIX 3

Name	Role	Organisation	Location
Dr Susie Rogers	Editor	Therapeutic Guidelines Limited	Melbourne
Dr Philipa Rothfield	Senior Lecturer, Philosophy Program	La Trobe University	Melbourne
Ms Sandy Scholes	Pharmacist		Melbourne
Dr Ian Scott	Director	Internal Medicine and Clinical Epidemiology, Princess Alexandra Hospital	Brisbane
Ms Vanessa Simpson	Medical Writer	NPS MedicineWise	Sydney
Ms Lishia Singh	Coordinator, Business Development	Baker IDI Heart and Diabetes Institute	Melbourne
Associate Professor Jane Smith	Associate Professor of General Practice	Bond University Medical School	Gold Coast, Queensland
Dr Kay Sorimachi	Director, Policy and Regulatory Affairs	Pharmaceutical Society of Australia	Melbourne
Ms Janet Struber	Coordinating Editor	Centre for Remote Health	Alice Springs, Northern Territory
Professor Martin Tattersall	Professor of Cancer Medicine	Department of Medicine, Central Clinical School, University of Sydney	Sydney
Professor John Tiller	Director	Therapeutic Guidelines Limited	Melbourne
Dr Janet Wale	Consumer representative		Melbourne
Dr Judith Walker	Senior Policy Officer, Policy and Advocacy Unit	The Royal Australasian College of Physicians	Sydney
Dr John Waterston	Consultant Neurologist	Alfred Hospital and Cabrini Medical Centre	Melbourne

Appendix 4

Further reading

The following list of background references was provided to Independence Forum participants.

Independence: what's the point? ISDB General Assembly. Melbourne; 14 September 2005. www.isdbweb.org/documents/uploads/Independence_000.pdf [cited 2013 Aug 12]

Avraham R. Clinical practice guidelines: the warped incentives in the U.S. healthcare system. *Am J Law Med* 2011;37:7-40.

Boyd EA, Bero LA. Improving the use of research evidence in guideline development: 4. Managing conflicts of interests. *Health Res Policy Syst* 2006;4:16.

Gale EA. Between two cultures: the expert clinician and the pharmaceutical industry. *Clin Med* 2003;3:538-41.

Gale EA. Conflicts of interest in guideline panel members. *BMJ* 2011;343:d5728.

Guyatt G, Akl EA, Hirsh J, Kearon C, Crowther M, Gutterman D, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med* 2010;152:738-41.

Hirsh J, Guyatt G. Clinical experts or methodologists to write clinical guidelines? *Lancet* 2009;374:273-5.

Ioannidis JPA. Why most published research findings are false. *PLoS Med* 2005;2:e124.

Johnson AJ, Rogers WA. Conflict of interest guidelines for clinical guidelines. *Med J Aust* 2012;196:244-5.

Mintzes B. New UK guidance on industry-health professional collaboration. *BMJ* 2012;344:e3952.

Norris SL, Holmer HK, Ogden LA, Burda BU. Conflict of interest in clinical practice guideline development: a systematic review. *PLoS One* 2011;6:e25153.

Robertson J, Moynihan R, Walkom E, Bero L, Henry D. Mandatory disclosure of pharmaceutical industry-funded events for health professionals. *PLoS Med* 2009;6:e1000128.

Roseman M, Turner EH, Lexchin J, Coyne JC, Bero LA, Thombs BD. Reporting of conflicts of interest from drug trials in Cochrane reviews: cross sectional study. *BMJ* 2012;345:e5155.

Roseman M, Milette K, Bero LA, Coyne JC, Lexchin J, Turner EH, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA* 2011;305:1008-17.

Williams MJ, Kevat DAS, Loff B. Conflict of interest guidelines for clinical guidelines. *Med J Aust* 2011;195:442-5.

Zuiderent-Jerak T, Forland F, Macbeth F. Guidelines should reflect all knowledge, not just clinical trials. *BMJ* 2012;345:e6702.



Panel discussion: Professor Rachelle Buchbinder, Associate Professor Ian Scott, Associate Professor David Menkes, Professor Silvio Garattini, Dr Philipa Rothfield, Professor Terry Campbell, Assistant Professor Barbara Mintzes



Associate Professor Ian Kerridge addresses the Forum

The views expressed in this supplement are not necessarily those of the Editorial Executive Committee or the Advisory Editorial Panel.

Apart from any fair dealing for the purposes of private study, research, criticism or review, as permitted under the Copyright Act 1968, or for purposes connected with teaching, material in this publication may not be reproduced without prior written permission from the publisher.

