Can you trust clinical guidelines?

A question of interest

Tim Stokes

Elaine Gurr Chair of General Practice
Dunedin School of Medicine
GP Mornington Health Centre
Declaration of interests (ICMJE)

• Tim Stokes is employed by the University of Otago and works clinically as a locum General Practitioner

• He has not received any personal funding from industry groups for research, consultancy or travel

• He has received over the last five years an honorarium from one pharmaceutical company paid into a University of Birmingham (UK) school account for speaking about NICE's work programmes in the UK in 2013
Overview

• Clinical Guidelines
Overview

• Clinical Guidelines
• Conflicts of interest (COI)
  – Financial versus Non-financial
Overview

• Clinical Guidelines
• Conflicts of interest (COI)
  – Financial versus Non-financial
• Do COI matter?
Overview

• Clinical Guidelines
• Conflicts of interest (COI)
  – Financial versus Non-financial
• Do COI matter?
• What should we do about them?
  – Self-regulation
  – External accountability
New Zealand
Primary Care Handbook 2012
Cardiovascular risk assessment and diabetes screening
Cardiovascular risk factor management
Management of type 2 diabetes

- Smoking cessation
- Weight management
- Stroke and transient ischaemic attack
- Coronary heart disease
- Heart failure
- Prevention of infective endocarditis
- Rheumatic fever
What are clinical guidelines

• **Clinical guidelines are:**
  – “recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”
  – one of the key foundations for quality improvement in health care
  – International consensus is that guidelines should be developed using a rigorous, explicit and transparent process
Cardiovascular Risk

- Drug therapy is indicated for people with CVD risk 15% (5 year risk)
  - NZ Primary Care Handbook 2012

- Statin therapy is recommended … for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD
  - NICE UK 2008 (CG67)
Cardiovascular Risk

- Drug therapy is indicated for people with CVD risk 15% (5 year risk)
  - NZ Primary Care Handbook 2012
- Statin therapy is recommended … for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD
  - NICE UK 2008 (CG67)
- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD
  - NICE UK 2014 (CG182)
Can I trust the recommendations?

• A NICE storm?
Can I trust the recommendations?

• A NICE storm?

"This has been a challenging time for the BMJ but I am very pleased the panel has taken the view that we acted appropriately," said BMJ editor in chief, Dr Fiona Godlee.

"I echo the panel’s call for the individual patient data from the statins trials be made available for independent scrutiny. Patients and their doctors need access to all relevant information to make informed decisions about their health. Extending statins to healthy people is a topical issue of wide public interest and we will continue to cover the debate from all sides."
"Under disclosure rules, I'm required to tell you I own stock in the company whose drug I'm prescribing."

CONFLICTS OF INTEREST
Conflicts of interest (COI)

• Definitions
  
  – “set of conditions in which professional judgement concerning a primary interest (such as a patient’s welfare or validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”

Conflicts of interest (COI)

• Definitions
  – “set of conditions in which professional judgement concerning a primary interest (such as a patient’s welfare or validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”

  – Financial versus non-financial
Financial versus Non-Financial COI

- **Financial COI**
  - Easier to define
    - NICE study:
      - Pecuniary interests relatively easy to identify
        - e.g., share holding or paid pharmaceutical advisory board meetings
    - Have clear evidence they bias research findings


Financial versus Non-Financial COI

• Non-Financial COI
  – More difficult to define
  • Interests related to (1) the individual through personal beliefs, (2) others through personal relationships, (3) the institution through institutional relationships, and (4) career advancement
Financial versus Non-Financial COI

• Non-Financial COI
  – More difficult to define
  – NICE study
    • seen as both widespread and also difficult to assess in terms whether or not they constituted a COI:
      – Non-pecuniary personal [interests] are most difficult because it is about anything you have been outspoken about – if they publish as most academics do or do research about it you will have been outspoken about a particular treatment. [Senior Staff NCC, I3]
      – Do not have clear evidence they bias research findings
Conflicts of interest (COI)

• Definitions
  – “set of conditions in which professional judgement concerning a primary interest (such as a patient’s welfare or validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”
  – Financial versus non-financial
  – From whom?
Big “Bad Pharma” …. 

My evidence to the Science and Tech Select Committee inquiry on missing trial data

April 26th, 2013 by Ben Goldacre in alltrials campaign, bad science, big pharma | 6 Comments »

The UK House of Commons Science and Technology Select Committee are currently looking at the problem of clinical trial results being withheld from doctors and patients (partly, the committee says, in response to Bad Pharma, which is heartening). A clear, thoughtful report and policy recommendations from this committee could be an important step towards fixing these problems.

I gave oral evidence this week on a panel with Roche, GSK, and the ABPI (who have previously tried to pretend that all the issues in Bad Pharma were “historic” and “long addressed”). I’ve posted the video below, and I’ve posted my written evidence underneath that. First is my submission addressing the specific questions posed by the Committee, and then my appendix, giving background on the problem of withheld trial results. Read the rest of this entry »

AllTrials campaign launches, please sign and spread!

January 16th, 2013 by Ben Goldacre in alltrials campaign, big pharma, publication bias | 2 Comments »

I am very pleased to announce the launch of a prominent campaign for access to all trial results, which we have launched this week at www.alltrials.net, with myself, Sense
Conflicts of interest (COI)

• Definitions
  – “set of conditions in which professional judgement concerning a primary interest (such as a patient’s welfare or validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”
  – Financial versus non-financial
  – From whom?
    • Big Pharma; Devices, Food, alcohol and tobacco groups; Health care industry and providers
Conflicts of interest (COI)

• Definitions
  – “set of conditions in which professional judgement concerning a primary interest (such as a patient’s welfare or validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”
  – Financial versus non-financial
  – From whom?
    • Big Pharma; Food, alcohol and tobacco groups; Health care industry and providers

– Where?
  • Clinical Trials; Systematic Reviews; Guidelines; Ethics Committees .... The list goes on!
DO FINANCIAL COI MATTER?
YES!

- Industry funding for research and education is sizeable
  - US data for 2014
  - 11.4 million payments totalling $US 6.49 billion

https://openpaymentsdata.cms.gov/
Data 30/6/15
YES!

- Industry funding for research and education is sizeable
  - US data for 2014
  - 11.4 million payments totalling $US 6.49 billion
- Clinicians do receive industry funding
  - 607,000 US doctors and 1,121 teaching hospitals
YES!

• Industry funding for research and education is sizeable
  – US data 30/9/14
  – 4.4 million payments totalling $US 3.5 billion
• Clinicians do have financial ties to their sponsors
  – 546,000 US doctors and 1,360 teaching hospitals
• Financial links need to be declared and can be COIs
• Financial COI is associated with bias
Why is bias important?

Figure 1.
Cycle of Bias Framework for Evaluating Health Studies

Why is bias important?

• Evidence of its effect
  – From research conduct to practice recommendations
• Findings / Recommendations are widely cited
• Weakens evidence-base for health care decisions
• We may “do no good” or “more harm that good”

Lisa Bero  Taming the Beast: Managing Conflicts of Interest in Research
Where does bias occur?

- Conduct of primary research studies (RCTs)
- Conduct of systematic reviews
- Conduct of Guideline Development Groups
Primary Research Studies

• Industry-funded studies are likely to produce findings that:
  – favour the sponsor’s intervention or that support public health policies that benefit the funder

• Cochrane review
  – pharmaceutical industry sponsored studies overestimate the efficacy and underestimate the harm of their treatments
  – even when controlling for methodological biases

## Analysis 1.1. Comparison 1 Results: Industry sponsored versus non-industry sponsored studies, Outcome 1

Number of studies with favorable efficacy results.

### Review: Industry sponsorship and research outcome.

### Comparison: 1 Results: Industry sponsored versus non-industry sponsored studies

### Outcome: 1 Number of studies with favorable efficacy results

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Industry n/N</th>
<th>Non-industry n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabali 2009</td>
<td>77/29</td>
<td>2/10</td>
<td>0.9 %</td>
<td>1.21</td>
<td>1.136 [0.30, 4.88]</td>
</tr>
<tr>
<td>Bero 2007</td>
<td>65/94</td>
<td>48/97</td>
<td>13.7 %</td>
<td>1.40</td>
<td>1.10 [1.07, 1.13]</td>
</tr>
<tr>
<td>Boeth 2008</td>
<td>49/120</td>
<td>50/165</td>
<td>12.2 %</td>
<td>1.25</td>
<td>1.09 [1.05, 1.13]</td>
</tr>
<tr>
<td>Bourgeois 2010</td>
<td>222/360</td>
<td>48/85</td>
<td>21.0 %</td>
<td>1.51</td>
<td>1.25 [1.01, 1.53]</td>
</tr>
<tr>
<td>Clifford 2002</td>
<td>46/66</td>
<td>21/34</td>
<td>8.1 %</td>
<td>1.13</td>
<td>0.83 [1.54, 1.83]</td>
</tr>
<tr>
<td>Etter 2007</td>
<td>25/49</td>
<td>9/41</td>
<td>2.8 %</td>
<td>2.32</td>
<td>1.23 [1.40, 1.40]</td>
</tr>
<tr>
<td>Kelly 2006</td>
<td>12/13</td>
<td>4/8</td>
<td>1.1 %</td>
<td>1.85</td>
<td>0.91 [1.27, 1.36]</td>
</tr>
<tr>
<td>Moomaw 2009</td>
<td>20/24</td>
<td>6/95</td>
<td>8.8 %</td>
<td>1.03</td>
<td>1.04 [0.84, 1.26]</td>
</tr>
<tr>
<td>Moncrieff 2003</td>
<td>2/2</td>
<td>2/7</td>
<td>0.4 %</td>
<td>2.67</td>
<td>0.85 [0.53, 1.39]</td>
</tr>
<tr>
<td>Perkins 2008b</td>
<td>93/113</td>
<td>37/49</td>
<td>15.0 %</td>
<td>1.09</td>
<td>0.91 [1.31, 1.31]</td>
</tr>
<tr>
<td>Rasmussen 2009</td>
<td>66/109</td>
<td>14/28</td>
<td>6.5 %</td>
<td>1.21</td>
<td>0.81 [1.81, 1.81]</td>
</tr>
<tr>
<td>Rattinger 2009</td>
<td>26/36</td>
<td>18/25</td>
<td>6.2 %</td>
<td>1.00</td>
<td>0.73 [1.38, 1.38]</td>
</tr>
<tr>
<td>Tulipan 2006</td>
<td>15/15</td>
<td>7/9</td>
<td>2.7 %</td>
<td>1.29</td>
<td>0.89 [1.87, 1.87]</td>
</tr>
<tr>
<td>Vladi 2007</td>
<td>5/11</td>
<td>0/4</td>
<td>0.2 %</td>
<td>4.58</td>
<td>0.21 [0.68, 0.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>941</strong></td>
<td><strong>647</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.32</strong></td>
<td><strong>[1.21, 1.44]</strong></td>
</tr>
</tbody>
</table>

**Total events:** 683 (Industry), 329 (Non-industry)

**Heterogeneity:** CH² = 22.26, df = 13 (P = 0.05); I² = 52%

**Test for overall effect:** Z = 6.05 (P < 0.00001)

**Test for subgroup differences:** Not applicable

---

Systematic Reviews

• The basic unit of knowledge translation
• Industry-funded systematic reviews and meta-analyses are
  – more likely than non-industry funded reviews
  – to produce findings that favour the sponsor’s intervention
• Have limited reporting of funding sources of included drug trials and author-industry financial ties

Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. BMJ2006;333:782.

Roseman et al. Reporting of conflicts of interest from drug trials in Cochrane reviews: cross sectional study BMJ 2012;345:e5155
Clinical Guideline development

• Financial COI among guideline group chairs and members:
  – are common and ? under-reported

• US and Canada (CGs 2000-2010)
  – 52% of panel members had financial COI (92% declared)
  – Panel members from government sponsored guidelines were less likely to have conflicts of interest compared with guidelines sponsored by non-government sources (15/92 (16%) v 135/196 (69%); P<0.001


• Europe (Denmark 2010-2012)
  – 53% of panel members had financial COI (2% declared)

Clinical Guideline development

• COI can directly influence the development of clinical guideline recommendations:

• Case study of two guidelines on ITP
  - One pharma funded – ICR - (16 panel members out of 22 reported associations with pharmaceutical companies)
  - One Medical Society funded (Am Soc Haematology)
    » Members: Content Expertise PLUS had to have lack of financial COI
  - Discrepancies were conspicuous when the guidelines addressed treatment
  - In contrast to the ASH guideline, the ICR gave stronger recommendations for agents manufactured by companies from which the ICR or its panel members received support

A chain of bias ...

- Conduct of primary research studies (RCTs)
- Conduct of systematic reviews
- Conduct of Guideline Development Groups
Case study

• Calcium and vitamin D supplementation and osteoporosis
  – Continues to be recommended internationally
  – Clear evidence of lack of benefit

• Changing ineffective practice
  – Made difficult by a complex web of interaction between industry, advocacy organisations and academia

Grey A, Bolland M. Web of industry, advocacy, and academia in the management of osteoporosis BMJ 2015;351:h3170
WHAT SHOULD WE DO ABOUT COI?
How should we tackle financial COI?

• **Self Regulation**
  – Self disclosure and codes of conduct
  – “internal accountability” … trust me I’m a doctor

• **Mandatory (legal) disclosure**
  – “external accountability”
Self Regulation

• **Self regulation and Clinical Guidelines**
  – development and implementation of policies that:
    • Address the disclosure of COI by guideline group members
    • give clear guidance on how such COI should be handled during guideline development
  – Such policies are in general use internationally

• **NICE has had a COI policy since 2004**

Summary of NICE COI Code of Practice as it relates to clinical guidelines (2007)

Definition of types of COI

- **Personal pecuniary interest**: involves a current (within the last 12 months) personal payment, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as 'specific' or to the industry or sector from which the product or service comes, in which case it is regarded as 'non-specific'.

- A **non-personal pecuniary interest** involves payment or other benefit that benefits a department or organisation for which an individual has managerial responsibility, but which is not received personally. This may either relate to the product or service being evaluated, in which case it is regarded as 'specific', or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as 'non-specific'.

- A **personal non-pecuniary interest** in a topic under consideration might include, but is not limited to: i) a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review; ii) a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence; iii) holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration; iv) other reputational risks in relation to an intervention under review.

- A **personal family interest** relates to the personal interests of a family member and involves a current payment to the family member of the employee or member. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as 'specific', or to the industry or sector from which the product or service comes, in which case it is regarded as 'non-specific'.

Declaration of COI

- The chair and members of the guideline development group (GDG) need to declare any COI on appointment to the GDG, annually and at each guideline development group meeting.

Action to be taken in response to COI:

**At appointment to GDG**

- The chair the GDG must divest him/herself from any personal pecuniary interest on appointment, or as soon as practicable afterwards.

**At GDG meetings**

- **Personal specific pecuniary interest**: Declare and withdraw
- **Personal non-specific pecuniary interest**: Declare and participate (unless, exceptionally, the chair rules otherwise)
- **Personal family specific interest**: Declare and withdraw
- **Personal family non-specific interest**: Declare and participate (unless, exceptionally, the chair of the advisory body rules otherwise)
- **Non-personal specific pecuniary interest**: Declare and participate, unless the individual has personal knowledge of the intervention or matter either through his or her own work, or through direct supervision of other people's work. In either of these cases he or she should declare this interest and not take part in the proceedings except to answer questions
- **Non-personal non-specific pecuniary interest**: Declare and participate (unless, exceptionally, the chair of the advisory body rules otherwise)
- **Personal specific non-pecuniary interest**: Declare – action is at discretion of the chair
Self Regulation: NICE experience

• Relies on Self Reporting
  – Both chairs and guideline developers talked about medical practitioners being unaware that their activities constituted a COI:
  – *If you give a talk at [a specialist medical society] you have to put up a slide with your COI. When I put a slide of my conflicts – others are amazed and nobody else has any declarations of interest ... most speakers had a conflict but didn’t recognise that they had one.* [NICE guideline chair, l12]
  – Several chairs highlighted the fact that the process of applying for and being appointed chair of a NICE committee made them realise how important COI were in the context of developing clinical guidelines
Self Regulation: NICE experience

• Disclosure of COI
  – relies on self reporting and staff had to take “on trust” the information they received
  – non disclosure viewed as the result of members not being aware as to what constituted a COI
  – The strategy guideline developers and chairs stated they used to deal with disclosure was one of repeatedly emphasising the policy at recruitment of members to the guideline and at each meeting and probing clinical members if they had “nothing to declare”:
    • *you can only labour the point and hope they do declare because you do not know what they get up to.* [Senior Staff NCC, I1]
Mandatory Disclosure - US

• ProPublica
  – https://www.propublica.org/
  – $2 billion in payments to doctors
  – 22 doctors earned at least $500,000
Mandatory Disclosure - US

• ProPublica
  – https://www.propublica.org/
  – $2 billion in payments

• Physician Payment Sunshine Act (PPSA) US 2010
  – Covers all manufacturers of drugs, devices, and biological and medical supplies covered by federal health care programs and require the tracking of all financial relationships with physicians and teaching hospitals
  – Easily accessible website
  • https://openpaymentsdata.cms.gov/
Open Payments

- Sometimes, doctors and hospitals have financial relationships with healthcare manufacturing companies. These relationships can include money for research activities, gifts, speaking fees, meals, or travel. The Social Security Act requires CMS to collect information from applicable manufacturers and group purchasing organizations (GPOs) in order to report information about their financial relationships with physicians and hospitals. Open Payments is the federally run program that collects the information about these financial relationships and makes it available to you. To gain a deeper understanding of data published on September 30, 2014, view our factsheet.

https://openpaymentsdata.cms.gov/
Total US Dollar Value: $6.49 Billion
Total Records Published: 11.41 Million

- Total Companies Making Payments: 1,444
- Total Physicians with Payment Records: 607,000
- Total Teaching Hospitals with Payment Records: 1,121

Show More Details
Open Payments Data in Context

Open Payments gives the public more information about the financial relationships between physicians and teaching hospitals and applicable manufacturers and GPOs. Specifically, the program:

- Encourages transparency about these financial ties
- Provides information on the nature and extent of the relationships
- Helps to identify relationships that can both lead to the development of beneficial new technologies and wasteful healthcare spending
- Helps to prevent inappropriate influence on research, education and clinical decision making

Open Payments means different things to different people and audiences.

For patients, consumers, and the public, Open Payments can be used to learn about the relationships between physicians and applicable manufacturers and GPOs. We encourage patients to discuss these relationships with their health care providers.

For physicians and teaching hospital representatives, reviewing the data reported about you in the Open Payments system can ensure that this information is accurate. You can also:
Mandatory Disclosure

• Physician Payment Sunshine Act (PPSA) US 2010
  • 2013 data:
    – 4.3 million payments totaling $3.4 billion and 470,000 US doctors and about 1,360 teaching hospitals received at least one payment (not including continuing medical education payments).
  • 2014 data:
    – 11.4 million payments totalling $US 6.49 billion with 607,000 US doctors and 1,121 teaching hospitals receiving at least one payment.
Let the sunshine in—making industry payments to New Zealand doctors transparent

Cindy Farquhar, Tim Stokes, Andrew Grey, Mark Jeffery, Peter Griffin

Whilst several countries are enacting legislation to tighten requirements for disclosure of the financial ties between pharmaceutical companies and health practitioners, the situation in New Zealand remains as murky as ever. Due to a lack of transparency in New Zealand it is impossible to know to what extent monetary benefits are flowing from industry to health practitioners in the form of sponsored...
Other jurisdictions

• UK
  – widespread professional support for industry payments to doctors to be made public
  – Association of the British Pharmaceutical Industry (ABPI) member companies have agreed to disclose payments to individually named healthcare professionals, including consultancy services such as speaking and sponsorship to attend medical education meetings.
  – This will come into effect in 2016
  – UNCLEAR if there will be any requirement to force doctors to disclose their payments if they are not willing to consent to this
New Zealand

- **Lack of transparency**
  - No mechanism for disclosure of payments to doctors from pharmaceutical and device industries
  - All pharmaceutical companies are required to limit the hospitality provided to doctors by including an educational component
  - Rate of adherence is unknown and there is no formal oversight or auditing
New Zealand

• **Is NZ exceptional?**

  • “The situation in NZ may be different from USA and or Australia as so much of what is available in the public system is purchased via PHARMAC. This double regulatory hurdle of Medsafe’s safety, quality and efficacy, and PHARMAC’s cost-effectiveness may limit the scope for industry to influence prescribing decisions in terms of one brand over another”

  (personal communication, Dr Stewart Jessamine, MEDSAFE, July 2014).
What we said

• New Zealanders should be rightfully proud of our public health system and our access to a range of drugs and procedures at competitive prices.

• BUT we can’t afford to ignore the fact that many commercial groups seek and establish relationships with health professionals that may undermine health policy development.

27th March 2015

What we said

• There is an urgent need to have this information made transparent so that our clinicians and policy-makers are seen as making independent trustworthy decisions on health care.

• We consider that New Zealand should adopt international best practice with respect to transparency over industry payments to individuals.
Drug company treats to doctor should be public - experts

By Martin Johnston
1:33 PM Friday Mar 27, 2015

Doctors receiving payment, overseas holidays and generous hospitality from medical suppliers should be under public scrutiny, say some health and science experts.
Medicines NZ chairwoman Heather Roy said it would be unlawful under the Privacy Act for companies to name doctors without their consent.

"Our preference would be industry self-regulation and we already have a rigorous code of practice."
Health Minister Jonathan Coleman said, "There are a number of existing guidelines and standards in New Zealand which cover this. There are no plans to develop legislation in this area."

- NZ Herald

Take home message

• Financial COI exist in the health sector
  – Industry Payments to doctors
  – Internationally (US) are extensive

• Financial COI bias
  – reporting of research studies, systematic reviews and guidelines

• They may be regulated by:
  – Self regulation (rest of the world)
  – Mandatory Disclosure (US …)
• Initiative of
  – Cochrane Collaboration; BMJ; others …
• Wide range of members (609)
  – NZMA
  – Royal Australian and New Zealand College of Psychiatrists
  – Pharmaceutical Industry (GSK)
Can register individual support
www.alltrials.net
The New Zealand Medical Association (NZMA) is the country’s largest voluntary pan-professional medical organisation. We aim to provide leadership of the medical profession, promote professional unity and values, and the health of New Zealanders. We welcome the opportunity to sign the AllTrials petition. The NZMA strongly supports clinical trial registration and the mandatory publishing of all results, whether positive or negative. These measures are aligned with the requirements in the Declaration of Helsinki. We believe that the AllTrials initiative should help ensure that all information from clinical trials is available so that the knowledge base for the optimal care of patients can be developed accurately and efficiently.
Thank you!

tim.stokes@otago.ac.nz