

## Beyond conflict of interest

*Transparency is the key*

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Conflict of interest is being taken more seriously by doctors and by society at large. The *New England Journal of Medicine* has twice recently been heavily criticised for failing to declare authors' conflicts of interest—despite its declared policy of doing so.<sup>1 2</sup> Last week the BBC halted a £360 000, well reviewed television series because of a “potential conflict of interest”: the producer owned commercial property featured in the series.<sup>3</sup> Despite the rising concern, medical journals have done an indifferent job in tackling the problem.<sup>4</sup> Four years ago I wrote an editorial arguing that we had to do better,<sup>5</sup> and we began then to require all authors to sign forms declaring conflicts of interest. Unfortunately authors often fail to declare conflicts of interest. This issue of the *BMJ* contains a collection of material on the subject, and we are proposing new policies.

### A common problem

Conflict of interest has been defined as “a set of conditions in which professional judgment concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”<sup>6</sup> It is a condition not a behaviour, and there is nothing wrong with having a conflict of interest. It is common.

Some people have taken the view that conflict of interest is a lot of fuss about nothing, or, worse, that identifying people's conflicts of interest is a form of McCarthyism.<sup>7</sup> Those who argue against concerns about conflict of interest say that science is science, methods are transparent, data either support the conclusions or do not, and it is neither here nor there whether researchers have, for example, shares in a company that manufactures a drug included in a trial.

This argument is becoming steadily less tenable as evidence accumulates on the influence of conflict of interest. Several studies have shown that financial benefit will make doctors more likely to refer patients for tests, operations, or hospital admission,<sup>8–10</sup> or to ask that drugs be stocked by a hospital pharmacy.<sup>11</sup> Now we are beginning to have data on the effects of conflict of interest on publications. Original papers published in journal supplements sponsored by pharmaceutical companies are inferior to those published in the parent journal.<sup>12</sup> Reviews that acknowledge sponsorship by the pharmaceutical or tobacco industry are more likely to draw conclusions that are favourable to the industry.<sup>13–16</sup>

This year has seen the publication of two important studies that mean we must take conflict of interest more seriously. Stelfox et al showed in a paper published in the *New England Journal of Medicine* that authors were much more likely to be supportive of calcium channel antagonists for treating cardiovascular disorders if they had a financial relationship with manufacturers of the drugs.<sup>4</sup> The safety of calcium channel antagonists was a good subject to investigate because it is intensely controversial and the market for the drugs is huge and lucrative. The authors looked at 70 articles (mostly reviews or letters) published in medical journals between March 1995 and September 1996 and classified them as critical of calcium channel antagonists (23), supportive (30), or neutral (17). They then contacted all the authors and inquired about financial relationships with manufacturers: financial support to attend a symposium, speak, organise education, or perform research, and employment and consultation. Two thirds of the authors had a financial relationship with manufacturers, but (and this may be the most important result of the study for journals) “only two of the 70 articles ... disclosed the authors' potential conflicts of interest.” Almost all supportive authors (96%) had financial relationships with manufacturers, compared with 60% of neutral authors and 37% of critical authors. The study has been criticised for being more about the nature of evidence than about conflict of interest: many of the supportive authors were clinical researchers who are more likely than epidemiologists (most of the critical authors) both to receive funding from manufacturers and to give more weight to clinical judgment than to evidence from randomised controlled trials.<sup>17</sup> Nevertheless, this remains an important study, not least for its demonstration of journals' failure to disclose conflicts.

### Building a convincing case

The second study, published in *JAMA*, looked at what characteristics determined the conclusions of review articles on passive smoking.<sup>18</sup> The authors identified 106 reviews, with 37% concluding that passive smoking was not harmful and the rest that it was. A multiple regression analysis controlling for article quality, peer review status, article topic, and year of publication found that the only factor associated with the review's conclusion was whether the author was affiliated with the tobacco industry. Three quarters of the articles concluding that passive smoking was not harmful were

written by tobacco industry affiliates. The study authors suggest that “the tobacco industry may be attempting to influence scientific opinion by flooding the scientific literature with large numbers of review articles supporting its position that passive smoking is not harmful to health.” Again, only a minority of the articles (23%) disclosed the sources of funding for research. The authors had to use their own database of researchers linked with the tobacco industry to determine whether authors had such links.

These two papers and their predecessors begin to build a solid case that conflict of interest has an impact on the conclusions reached by papers in medical journals. They also show convincingly that medical journals are failing to get authors to declare conflicts of interest. Readers might want to bear these thoughts in mind as they try to unravel the accusations and counteraccusations in our large cluster of letters that feature conflict of interest (beginning on p 343), many of which are concerned with passive smoking. Look too at the three pairs of papers on whether researchers should take money from industry (starting on p 333): tobacco researchers generally don't; alcohol researchers are moving towards not taking money; and those researching infant feeding remain divided over taking money from baby milk manufacturers.

### What should the *BMJ* be doing?

The *BMJ*'s policy is disclosure of conflict of interest rather than prohibition.<sup>5</sup> We simply don't think prohibition is feasible, although we try to avoid having an editorial written by somebody with a major conflict of interest. We send authors of all original papers, editorials, and review articles and of selected letters a form in which we define what we mean by conflict of interest and ask them to sign to say whether they have one. We have gone for a broad definition that extends beyond financial interests to personal, political, academic, and religious ones. With original papers we give the source of funding and disclose what authors have told us about whether or not they have other interests. With the other articles we add a note only if authors tell us they do have a conflict of interest.

Our impression, supported by the two recent papers, is that many authors are willing to sign that they don't have a conflict of interest when by our definition they do. We have two hypotheses to explain this. Firstly, authors think that an admission of a conflict of interest implies wickedness. We don't think so. Secondly, authors are confident that they have not been influenced by a conflict of interest and so don't tell us they have one. Our response is that bias works in subtle ways and that none of us is blessed with knowledge of our own motivations and mental mechanisms. We are thus proposing some changes to see if we can do better. They will be phased in from now.

- We will replace the term “conflict of interest” with “competing interests.” This will, we hope, reduce the sense of wrongdoing and encourage people to disclose competing interests.
- We will restrict ourselves to financial interests and modify our form accordingly. The authors of the *New England Journal of Medicine* article suggest that authors should be sent a questionnaire similar to the one they used in their study, and we have adopted

this idea (see the form on our website ([www.bmj.com/guides/advice.shtml](http://www.bmj.com/guides/advice.shtml))). Restricting ourselves to financial interests is a tactical move: narrowing the range may make it more likely that authors will declare competing interests. If authors want to disclose other competing interests then we will disclose them to readers.

- Authors of all original papers, editorials, and review articles will be asked to complete our questionnaires. Competing interests will be disclosed, and if authors tell us they have none (the usual case) we will write “none declared” rather than “none.” With letters we will continue to encourage authors to disclose competing interests but will send them a questionnaire to complete only if we suspect that authors might have competing interests. Authors of letters about drugs will usually be sent a questionnaire.

- If we learn after publication that authors had competing interests that they did not disclose then we will tell readers.

Some readers will regret such moves and remember a golden age when conflict of interest was not an issue. Times have changed however, and transparency and accountability are increasingly expected in all aspects of society. I doubt that the changes we are proposing will solve the problem, but they seem to us to be a step in the right direction. Authors and readers who disagree will no doubt tell us—and we will listen.

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# Older people with schizophrenia: providing services for a neglected group

*It's the quality of their environment that matters, not where it is*

Schizophrenia is a severe psychiatric disorder affecting about 1% of the elderly population.<sup>1</sup> Symptoms include delusions and hallucinations as well as apathy, blunting or incongruity of emotional responses, and social withdrawal. Most older people with schizophrenia will have developed the illness before the age of 45. In the past many of these patients have ended up in long stay psychiatric beds, but their exact number is unknown. In Britain the drive to close long stay psychiatric hospitals is continuing at a time when the elderly population is increasing.<sup>2</sup> It is important that older people suffering from schizophrenia are not neglected as community psychiatric services are planned.

One survey of five English psychiatric hospitals due for closure reported that about 20% of the long stay population was over the age of 65 years and had a diagnosis of schizophrenia.<sup>3</sup> Few studies have specifically looked at elderly people with schizophrenia, but those who reside in long stay wards are known to suffer from significant disabilities, particularly in affect, motivation, and the ability to perform the basic functions necessary for independent living.<sup>4</sup> In the community they represent at least as high an economic burden as younger patients,<sup>5</sup> but public awareness about schizophrenia is often focused on younger sufferers who may present more floridly and are more likely to commit violent acts.<sup>6</sup>

Closures of psychiatric hospitals began in America far earlier than in Europe and information about how this process has worked has come largely from American studies. Many elderly sufferers of schizophrenia will end up in residential or nursing homes. What kind of life can they expect? In America Linn et al studied a group of older men, including 159 suffering from schizophrenia, who were long term psychiatric patients in Veterans Administration hospitals.<sup>7, 8</sup> The patients were assigned to either a nursing home in the community, a Veterans Administration nursing home, or another long stay psychiatric ward or they remained on the same ward. At 12 months outcomes were best for the group transferred to another long stay ward and worst for the group transferred to community nursing homes. The important factors affecting outcome were found to be staff characteristics and the functional ability of the other residents in each unit.<sup>8</sup> The community nursing homes had the lowest staff-patient ratios, the highest staff turnover, and also the least able residents.

A smaller retrospective study from Britain followed up a group of elderly long stay patients most of whom suffered from schizophrenia.<sup>9</sup> Half the patients remained in hospital and half were relocated to community homes. Two to three years later the patients who had been transferred to the community had declined more slowly than those who remained in hospital.

Although at first sight the findings in the British and American studies appear contradictory, the quality of the environment rather than the type determined the outcome for patients in both countries. The average size of community nursing homes in the American studies was 120 beds, which is far larger than residential homes in Britain. In the British study staff-patient contacts were found to be more frequent in community facilities than on the long stay wards. Patients with schizophrenia can benefit from deinstitutionalisation,<sup>10</sup> but community care has to be carefully planned and adequately resourced. Because a residential home is in the "community" does not mean the quality of the environment is automatically any better than that in a traditional psychiatric institution.

Those working for health or social services or for other agencies in contact with elderly people with schizophrenia need to be aware of the potential to improve their quality of life. The recently published *Handbook on the Mental Health of Older People* contains some guidelines for purchasers.<sup>2</sup> Four factors in particular should help in providing effective and seamless services for these patients.

Firstly, general practitioners have a central role in coordinating service provision,<sup>11</sup> and it is important that they assess the physical needs of these patients as well as their mental states.<sup>12</sup> Secondly, since many of these patients will be living in nursing and residential homes, the organisation of specialist mental health services should take this into account. Thirdly, purchasers need to be aware of the effect environmental factors have on the functioning of these patients when planning their residential care needs. Finally, many agencies (including psychiatric, social, and voluntary services) operate age related services. There should be clarity about which services have the responsibility for each individual's care at any one time. If patients move from one service to another this transfer should be planned in advance and coordinated. Resources should be allocated so that account is taken of this movement in and out of services.

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## How can treatment of systemic sclerosis be improved?

*By setting up a national database of all cases and entering patients into trials*

Systemic sclerosis is a rare disease (about 10 cases/1 000 000/year) with a substantially higher mortality than other autoimmune rheumatic diseases.<sup>1</sup> This, and an even greater morbidity, make it an unwelcome diagnosis for clinicians and a fearful one for patients. No cure exists, though much can be done to alleviate the organ based complications of the condition, and many different agents are used in an attempt to modify disease progression. Unfortunately, few drugs have been properly evaluated in clinical trials and even the standard treatments are not of proved efficacy.<sup>2</sup> More aggressive therapies are now being tried in some centres—for example, immunoblation with autologous peripheral stem cell rescue<sup>3</sup>—and there is an urgent need to compare these novel regimens with standard treatments. How can we improve the management of this condition and ensure that management is based on the best possible evidence?

Research over the past 20 years has led to a clearer understanding of the cellular and molecular pathology of systemic sclerosis and implicated new causal agents. Substantial advances have also been made in disease assessment and in the detection and monitoring of visceral complications, especially interstitial lung fibrosis, pulmonary hypertension, and vascular disease. Risk stratification based on autoantibody profiles and HLA typing together with the results of specialised tests such as DTPA (technetium-99<sup>m</sup> diethylene triamine pentacetate) lung scanning, high resolution computed tomography, and bronchoalveolar lavage have permitted more accurate identification of patient subgroups at increased risk of particular complications. For example, autoantibodies directed against RNA polymerase I or III have been associated with increased risk of renal crisis and antitopoisomerase antibodies with pulmonary fibrosis.<sup>4</sup> Anticentromere antibodies are associated with limited cutaneous scleroderma, the subset in which potentially fatal isolated pulmonary hypertension most often occurs. Doppler echocardiography has been shown to be an effective non-invasive technique for detecting scleroderma associated pulmonary hypertension,<sup>5</sup> provides a useful means of screening patients at risk, and allows earlier diagnosis of asymptomatic cases. Standardised methods of severity assessment have now been developed by an international committee, which should allow the comparison of cases in different centres.<sup>6</sup>

The main treatment used world wide for diffuse skin disease has for many years been D-penicillamine,

though  $\alpha$  and  $\gamma$  interferon, methotrexate, and relaxin have been trialled more recently. Options now exist for treating the main complications, such as prostacyclin (iloprost and flowlan) infusions for vascular complications such as severe Raynaud's phenomenon, skin ulceration, and pulmonary hypertension. Active fibrosing alveolitis is currently treated in most centres by either oral cyclophosphamide and corticosteroids or intravenous cyclophosphamide, with encouraging results. Less serious complications such as reflux oesophagitis can be dramatically relieved using proton pump inhibitors. However, the use of these organ based treatments is largely based on small studies or experience with other diseases, and their use may well be improved if specific trials in scleroderma were performed. Some of these issues have been addressed in multicentre trials of interferon in Britain and D-penicillamine in America, and the data from these studies are currently being analysed.

We can now define the natural history of systemic sclerosis much better, and this allows the effectiveness of established treatments as well as potential new ones to be examined. Moreover, the growing understanding of pathogenetic mechanisms at cellular, molecular, and genetic levels may eventually lead to specific targeted therapy.<sup>7</sup> This optimism must be tempered by the dismal track record of trials in systemic sclerosis. Many have been performed, but lack of statistical power and other methodological problems have often prevented reliable interpretation. The reasons include the small number of new cases, disease heterogeneity, and the variability of assessment methods between different centres. As a result there is often a downward spiral of incomplete assessment, inadequate therapy, and then crisis management when complications arise. This is often associated with a poor outcome, which serves only to increase therapeutic nihilism towards systemic sclerosis.

How can this situation be improved? One way would be to establish a central database for new cases of systemic sclerosis and to maintain a minimum data set on all cases. This would also provide the infrastructure for multicentre clinical trials. Good examples of coordinated approaches to management and research exist in several disciplines, often using a "hub and spoke" arrangement of cooperating central and regional centres with an emphasis on local supervision of patients but centralised assessment. In oncology and haematology these approaches have undoubtedly improved management as well as helping to educate those involved in the various aspects of patient care.

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We suggest, firstly, that a national registry should be established so that protocols for national and international trials can be enabled. Secondly, standardised treatment protocols should be established by consensus, based on the evidence that does exist, probably through the national and international societies for systemic sclerosis. Thirdly, both clinicians and patients must be better educated about advances in disease assessment so that individuals at risk from certain complications may be investigated appropriately. This will provide more reliable prognoses and better quality information for patients. A centralised database will provide enough numbers of motivated patients and clinicians to permit high quality clinical trials to be undertaken, which the disease and its sufferers deserve.

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## Sentinel node biopsy in breast cancer

*A promising technique, but it should not be introduced without proper trials*

The status of the axillary lymph nodes in a woman with breast cancer is the single most important prognostic factor, and important clinical decisions are based on it. In the absence of non-invasive methods, it has become routine either to perform a partial axillary dissection to stage the axilla or to remove completely all axillary lymph nodes to both stage and treat the axilla. With the development of screening, increasing numbers of women are seen who are node negative. In these patients extensive axillary surgery is difficult to justify because most women gain no significant benefit and suffer considerable morbidity from the axillary surgery. Research has focused on developing procedures that assess axillary lymph node status while minimising morbidity.

Twenty years ago Cabanas showed the existence of a specific draining lymph node, the so called "sentinel" lymph node, which could be identified after lymphangiography through the dorsal lymphatics of the penis.<sup>1</sup> He confirmed that the first node visualised, the sentinel node, was the first site of metastases and reported that it was often the only affected lymph node. Unaware of this report, in 1992 Morton and colleagues developed cutaneous lymphoscintigraphy as a method of identifying nodal areas at risk of metastases in patients with malignant melanoma.<sup>2</sup> They showed preferential drainage to one or two nodes in a particular lymph node group. Applying this concept to breast cancer, we would expect that if malignant cells spread to a regional lymph node then they should follow the same route as lymph draining from the primary carcinoma. If the draining or sentinel node from a breast cancer can be identified and is free of metastasis then theoretically the other axillary nodes should also be free of disease.

Early studies of sentinel nodes in breast cancer used a vital blue dye. The initial rate of sentinel node identification with this technique was 66%, although success has improved with experience.<sup>3,4</sup> No sentinel

nodes outside the axilla were identified with this technique. The blue colour appears in the axillary lymphatics and nodes within a few minutes of injection and can be visualised, but before surgery it is not possible to ascertain where in the axilla the sentinel node lies. Injecting a gamma emitting radiopharmaceutical around the primary tumour permits preoperative visualisation of the draining node using a gammacamera and has shown that the sentinel node is in the internal mammary chain in up to 6% of patients.<sup>5</sup> Using a hand held gamma probe, the surgeon can locate the node with the highest uptake and make an exact skin incision directly over it, which limits the dissection and associated morbidity of the axillary staging procedure. By using different pharmaceutical agents radioactivity can be identified in sentinel nodes 1-16 hours after injection. With technetium labelled albumin sentinel nodes were identified in all but three of 241 patients in one study, with an overall accuracy compared with a full axillary clearance of 97.5%, a false negative rate of 4.6%, and a sensitivity of 94.7%.<sup>6</sup>

There would be an obvious advantage if the sentinel node or nodes could be assessed intraoperatively, so that a patient with affected nodes could have the option of proceeding immediately to a full axillary dissection. Routine frozen section examination appears to miss up to 30% of metastases in sentinel nodes.<sup>6</sup> A newer, more accurate technique using multiple sections and an immunohistochemical technique to reveal epithelial cells has been described but takes up to 40 minutes to perform.<sup>7</sup> Until this technique has been refined and its accuracy confirmed in other centres, intraoperative assessment of sentinel nodes cannot be recommended.

Sentinel node biopsy is a promising technique, but before it can be introduced into routine practice the technique of node identification needs to be optimised and it needs to be compared with other surgical options for axillary node staging.<sup>8</sup> The available data

suggest that both a radioactive tracer and supravital dye are needed to provide a satisfactory rate of sentinel lymph node identification.<sup>9</sup> The best carrier agent for radioactivity, site, volume of injection, and interval between injection and surgery remain to be defined.<sup>5-7</sup> Thereafter it will be necessary to show that different surgeons with a range of skill in axillary surgery can produce a satisfactory rate of sentinel node identification. Then and only then should multicentre randomised trials comparing sentinel node biopsy with standard techniques of assessing axillary lymph node disease be performed. Introduction of this technique into clinical practice before results from these randomised trials are available cannot be supported.

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## Change at last at WHO

*But will the regions play ball?*

Dr Gro Harlem Brundtland has done what most people hoped she would. On her inauguration as director general of the World Health Organisation, she has swept away the existing secretariat (though keeping some members on as advisers), and announced her own carefully chosen cabinet to an increasingly optimistic staff. Of the 10 new appointments, eight come from outside the organisation and six are women.<sup>1</sup> There is an even split between the north and south, and all of the WHO's six regions are represented. Along with the new cast come plans for a new way of working—reducing overlap and increasing convergence between individual programmes.

The speed of the appointments has taken the organisation by surprise, and one appointment in particular is causing concern. Michael Sholtz, who is to be responsible for health technology, will be in charge of the action programme on essential drugs, the WHO's key initiative to provide poorer countries with appropriate and affordable drugs. Dr Sholtz comes from the pharmaceutical industry and has little experience of the developing world. Dr Brundtland has portrayed the appointment as providing a liaison between the industry and the WHO. Dr Sholtz will have to prove his allegiance at a tough time for world health, when the development of effective but expensive drugs for AIDS has brought to a head the north-south fight over drug patent rights.

So far the changes all relate to the WHO's headquarters in Geneva, where Dr Brundtland has executive powers to hire and fire. The more difficult and perhaps more crucial test of her ability will be in dealing with the WHO's six regions, over which she has no direct control. Regional directors are elected by their constituent countries rather than appointed by the director general, and they can hire and fire staff within their regions. Especially important is their

responsibility for appointing country representatives—the WHO's front liners, who, because of lack of training and resources, form one of the weakest links in the WHO's chain of influence.

The regions have always presented the WHO's leaders with a problem. But Dr Brundtland must take them on after 10 years of unchecked autonomy and at a time of strong support from their constituent countries. Regional meetings have become an important forum, especially for developing countries—many of whom feel that their voice at the World Health Assembly has been eroded by northern dominance and by decline in the assembly's influence.

Dr Brundtland clearly understands the need to woo the regional directors, three of whom were her rivals for the director general's post. A retreat is planned for the end of the month, which all six regional directors will attend. This seems designed to set the tone for the annual round of regional meetings in September and October and to establish a process for streamlining the currently diverse regional structures and methods of working. The fate of the country representatives is also likely to be on the agenda: Dr Brundtland is understood to want to meet them in person and to strengthen their ties with headquarters. Meanwhile, money is to be made available to install proper communications between the regional offices and headquarters. This will allow frequent video conferences so that regional directors will become actively involved in policy making. In Dr Brundtland's phrase, there will be one WHO speaking with one voice. If she can achieve this politically difficult internal alliance, the WHO may again at last become an effective advocate for world health.

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1 Mach A. Brundtland replaces top staff at the WHO. *BMJ* 1998;317:229.

*BMJ* 1998;317:296