Williams, Hywel C. and Naldi, Luigi and Paul, Carle and Vahlquist, Anders and Schroter, Sara and Jobling, Ray (2006) Conflicts of interest in dermatology. Acta Dermato-Venereologica, 86 (6). pp. 485-497. ISSN 0001-5555

Acta Derm Venereol 2006; 86: 485–497

SPECIAL REPORT

# Conflicts of Interest in Dermatology[1]

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**Conflicts of interest exist in dermatology when professional judgement concerning a primary interest, such as research validity, may be influenced by a secondary interest, such as financial gain from a for-profit organization. Conflict of interest is a condition and not a behaviour, although there is clear evidence that gifts influence behaviour. Little has been written about conflicts of interest in dermatology. This series of papers raises awareness of the subject by exploring it in greater depth from the perspective of a dermatology researcher, an industry researcher, a dermatology journal editor, a health services researcher and a patient representative. Collectively, they illustrate the many ways in which conflicts can pervade the world of dermatology publications and patient support group activities.** ***Key words: conflicts of interest; dermatology; disease mongering; disease awareness campaigns; ghost authorship.***

(Accepted September 26, 2006)

Acta Derm Venereol 2006; 86: 485–497.

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## 1. DEFINITIONS AND SCOPE OF THIS ARTICLE
*Hywel Williams*

*Where did it all come from?*

The basis of this article arose from a workshop led by the European Dermato-Epidemiology Network (EDEN) on the topic of conflict of interest (COI) in dermatology held at the Spring 2006 European Academy of Dermato-Venereology meeting in Finland. It might strike the reader that the topic of COI was an odd one for a meeting that relies so heavily on sponsorship from the pharmaceutical industry. Nevertheless, the session was well attended and received by a wide range of colleagues from academia, clinical practice and industry. It was clear from the discussion that ensued from the potentially difficult areas surrounding COI in dermatology, that some themes relating to COI and dermatology research output needed to be shared more widely amongst the dermatology community through a journal article. This article therefore represents a compilation of those talks, plus an additional contribution about COI and patient support groups from Ray Jobling, who has psoriasis and who has worked with patient support groups for many years.

The compilation is not intended to be a comprehensive or systematic review of the extent and effects of COI in dermatology. Instead, the article aims to raise awareness of the existence of COI in dermatology, as the topic appears to be very rarely, if ever, mentioned at dermatology meetings. Even in the dermatological literature, I could find only eight relevant publications when searching PubMed using the terms {"conflict" AND "dermatology"} as of 29th August 2006 (1–8). Indeed, I might even go so far as to suggest that COI is a taboo subject in dermatology – possibly because nobody wants to upset, what may seem to some, a cosy relationship.

The article simply makes some points about the topic of COI from a variety of perspectives. Many of the examples developed refer to psoriasis, which is perhaps unsurprising given the current substantial resources being put into launching a new range of interesting, but also very expensive, new biological treatments for this disease. Luigi Naldi, a dermato-epidemiologist from Italy, begins by lamenting the demise of curiosity-driven as opposed to financially-driven research. He then develops examples of COI from the EDEN psoriasis survey, opening our eyes to some of the subtle ways in which drugs can be promoted favourably. Carle Paul, a dermatologist with many years of experience in the

[1]**Roles and responsibilities:**

This material is taken from work that was presented in part at a workshop at the European Academy of Dermato-Venereology held at Saariselka in February 2006.

The opinions expressed in this series of articles are those of the contributing authors. Each author is guarantor of their respective section. Hywel C. Williams reviewed and edited the various contributions and all contributors have agreed on the final version.

 ISSN 0001-5555
DOI: 10.2340/00015555-0191

pharmaceutical industry, elaborates on the importance of full disclosure and how COI is not just an industry problem. He talks about selective publication and the dangers of Bodenheimer's "non-writing author/non-author writing syndrome", as well as ways of reducing such behaviour in the future. Anders Vahlquist, editor of this journal, shares his concerns about COI and comments on the extent to which dermatology journal editors can and should attempt to tackle the problem. The question remains as to whether all this concern and intrigue makes any difference to you as the reader? Sara Schroter from the *British Medical Journal* presents two key randomized controlled trials that show that the presence and type of COI as well as the type of article in which it is contained, makes a profound difference on the validity that readers place on that article. Finally, Ray Jobling talks from the perspective of patient support groups who are often desperate for funding. He points out how such groups sometimes have to wrestle in an unequal partnership with big pharmaceutical companies, who may view such groups as excellent vehicles for disease awareness campaigns and as legitimate substrates for disease mongering.

Although the article raises some uncomfortable revelations at times, its overall tenor is one of raising awareness of an issue that faces dermatologists on an almost daily basis. All contributors have been encouraged to look to the future for developing solutions and for getting the balance right.

### *What is a conflict of interest?*

It is important to start by defining the theme on which this article is based. Many definitions of COI exist, but there is reasonable similarity between those used on medical journal websites. I like the definition suggested by the *British Medical Journal* (9): "A competing interest exists when professional judgement concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry)". They later qualify the definition by restricting requests for competing interests to financial ones, based on their experience that authors often do not disclose them.

Two important points emerge from this definition. The first is that COI is a condition and not necessarily a behaviour. It may be said for instance, that dogs generally chase cats, yet there are plenty of examples of the two living together in harmony (Fig. 1). Merely being a dog does not necessarily mean that a type of behaviour (chasing cats) has occurred – it simply means that on average a dog will chase (*behaviour*) a cat because of the *condition* of "being a dog". In other words, COI is a set of circumstances, interests or conditions that place the affected person in a position of *potentially* being influenced by those circumstances. It does not mean, for example, that if I was paid to fly to Mauritius and was lavishly entertained there in order to give a talk about the new biologicals for psoriasis, that I would necessarily give a talk that portrayed these new treatments in a positive light. Sometimes, people with conflicts deliberately overcompensate for potentially biased behaviour – for example, the teacher who happens to have his own son in his class might give his son an extra hard time in order to avoid accusations of favouritism. The second point to note is that the degree to which behaviour has been influenced in relation to the declared conflict can only be judged by those in the audience. It is not for me, for example, to rationalize internally that the trip to Mauritius would not influence my portrayal of a new drug developed by those who have looked after me so well – the process requires me first to declare all possible conflicts at the start of any talk and then allow the audience to make a judgement about whether my subsequent behaviour was influenced by those conflicts. We can rationalize as much as we like that we are all above the financial or other temptations arising from conflicts, but conflicts are conflicts. Declaring them does not necessarily imply that you are "behaving badly", but they are a set of conditions that are known profoundly to affect human behaviour, and as such they must be declared (10–13).

*Fig. 1.* Conflict of interest is a condition, not necessarily a behaviour. Dogs generally chase cats, but there are plenty of examples of them living together harmoniously.

A final point that needs to be emphasized is that COI is not just concerned with a polarized debate about clinicians and the pharmaceutical industry. As Carle Paul later comments, COI can arise from the need to publish for the advancement of careers. Human characteristics such as jealousy, arrogance and favouritism can pervade processes such as peer review, especially if these are done anonymously. So COI is all around us – the key is to declare it if in doubt and let others decide if it is important. As Wazana's systematic review shows, there is now overwhelming evidence that seemingly trivial conflicts, such as receiving gifts, affect prescribing behaviour (13). I suspect that this article will confirm the

suspicions of many readers, surprise others, and even anger some who might have a lot on their conscience, but I hope that, most of all, it will stimulate colleagues to think more about COI in the field of dermatology and to ensure that checks are in place to keep the balance at the right level.

## 2. MORE ON CONFLICTS OF INTEREST IN DERMATOLOGY

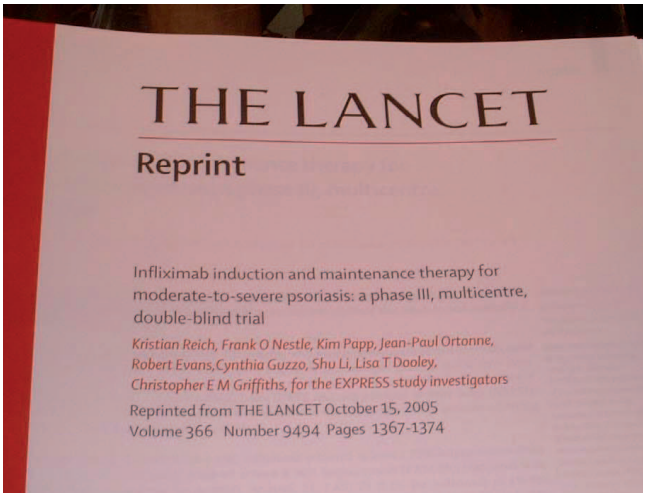
*Luigi Naldi*

### *Economic rather than curiosity-driven research*

"The most important scientific development of the 20th century is that economic interests have replaced curiosity as a driving force of research activities." This statement from the Nobel Prize winner Kary Mullis, underlines a central issue when discussing conflict of interest (COI) in medicine: a shift in research support from that provided by independent sources to that provided by the pharmaceutical industry (14). The influence of the pharmaceutical industry on medical research has increased enormously in the last decades. This has been paralleled by heavy marketing competition. Alarms have been raised repeatedly concerning the consequences of the critical dependence of clinical research on economic interests. Marcia Angell, former editor of the *New England Journal of Medicine*, was concerned about the industry becoming "primarily a marketing machine" and co-opting "every institution that might stand in its way" (15). Richard Horton, editor of the Lancet, outlined how journals "devolved into information laundering operations for the pharmaceutical industry" (16). Jerry Kassirer, another former editor of the *New England Journal of Medicine*, argued that the industry has deflected the moral compasses of many physicians (17). There is a cycle of dependency between physicians, academic opinion leaders, patient's organizations, researchers, and industrial interests (18).

### *Dermatology does not appear to be an exception*

As indicated by the European Dermato-Epidemiology Network (EDEN) psoriasis project, only a quarter of all randomized clinical trials published on psoriasis from 1977 to 2000 have been conducted independently from direct pharmaceutical company sponsorship, and the proportion of sponsored trials is increasing dramatically in more recent years (19). Randomized clinical trials are considered one of the highest forms of evidence. A large trial published in a major journal has the journal's stamp of approval (unlike advertising material), will be distributed around the world and may well receive global media coverage. For a drug company, a favourable trial published in a good journal is worth thousands of pages of advertising (Fig. 2). Quite remarkably, sponsored trials rarely produce results that are unfavourable to the companies' products. There is evidence from systematic reviews that published studies funded by pharmaceutical companies are several times more likely to show results favourable to the company than studies funded from other sources (20, 21). Not surprisingly, data from the EDEN psoriasis project showed that the large majority of sponsored trials provided positive results.


THE LANCET

Reprint

Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial

*Kristian Reich, Frank O Nestle, Kim Papp, Jean-Paul Ortonne, Robert Evans, Cynthia Guzzo, Shu Li, Lisa T Dooley, Christopher E M Griffiths, for the EXPRESS study investigators*

Reprinted from THE LANCET October 15, 2005
Volume 366 Number 9494 Pages 1367-1374

*Fig. 2.* For a drug company, a favourable trial published in a good journal is worth thousands of pages of advertising.

There are several ways to obtain the data you want from clinical research. Table I presents some examples (18). Placebo-controlled randomized trials, the use of surrogate outcome measures over a short period of time, rather than clinically relevant outcomes over a significant time-span, and duplicate publications, are all means of enhancing spin on a product, as evidenced in the EDEN psoriasis project. These factors may combine with selective reporting (22). In spite of the enthusiasm

Table I. *Examples of techniques for pharmaceutical companies to obtain the results they want from clinical trials (from R. Smith, modified (18)*

- Conduct a trial of your drug against a treatment known to be inferior (typically placebo even in the presence of active competitors).
- Compare your drugs against too low a dose of a competitor drug.
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs.
- Use multiple end-points in the trial and select for publication those that give favourable results.
- Do multicentre trials and select for publication results from centres that are favourable.
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress – for example, reduction in relative rather than absolute risk.

demonstrated by opinion leaders and the public, the development of new biological agents for psoriasis is no exception to this situation (23). To date, no long-term randomized trials that include active comparators are available on these drugs. On the other hand, promotional strategies for new biological agents in psoriasis offer additional teaching examples of the different modalities adopted to expand the market for new drugs using scientific data and statements by opinion leaders in sponsored symposia. Patient organizations in sponsored campaigns are also used to disseminate information on psoriasis management. The establishment of a new "World Psoriasis Day", originally sustained by a pharmaceutical company (Serono), is just one example (24).

*Understanding drug promotion*

In Italy, recognition of the problems involved with new drug registration and lack of data on effectiveness and safety in situations where alternative conventional treatments are already available, have prompted the initiation by the Italian Drug Agency (AIFA) of post-marketing surveillance programmes closely linking prescription to the provision of patient data at first drug prescription and on a regular basis subsequently during a pre-defined follow-up period. One example of such a programme on psoriasis is the Psocare programme (25). All the patients receiving a new systemic treatment for psoriasis for the first time (including the new biological agents) at a number of reference psoriasis centres are registered and followed up within the programme. During the first eight months of activity (as of 4th August 2006) 4302 patients were entered in the programme. Interestingly, a number of initiatives sponsored by pharmaceutical companies in connection with Italian scientific dermatological societies and the patient organizations, were started in Italy in an obvious attempt to use the Psocare programme as a marketing opportunity, illustrating the pervasive nature of marketing interests in medical activities. In a typical case, an initiative consisted of a drug-sponsored symposium with a presentation of the Psocare system and data, followed by several presentations of efficacy and safety data concerning the new biological agents, and only passing mention of older established conventional therapies. In many instances, the label "Psocare" was used in the context of these sponsored symposia without the permission or agreement of AIFA.

The industry perspective on drug promotion is better understood by reading a document such as the one produced by the European Federation of Pharmaceutical Companies. The document as reported by Liberati et al. (26) identifies 20 diseases and conditions, such as dementia, asthma, hepatitis C, rheumatoid arthritis and osteoporosis, where "potentially achievable benefits are not achieved because patients are denied access to important therapeutic interventions due to poor diagnosis, limited patient awareness of effective drugs, and strict cost containment by healthcare systems". Selectivity of reporting is the main theme to emerge from the document. In the section on Alzheimer's disease, for example, second generation acetyl cholinesterase agents are reported as increasing quality of life, with massive economic benefits for society. Only one reference (in German) is quoted, while systematic reviews pointing to inadequate follow-up and questionable end-points are omitted. One of the reasons why new drugs are registered despite a lack of firm evidence concerning their actual role in the disease for which they are developed, is the limited role played by regulatory agencies (27). It should be noted that the European Agency for the Evaluation of Medical Products (EMEA) is part of the Directorate for Enterprise and Industry and not Public Health, suggesting a possible COI in the regulatory process itself.

## 3. AN INDUSTRY RESEARCHER'S PERSPECTIVE

*Carle Paul*

Research studies in biomedical journals are under intense scrutiny because of proven examples of misleading reports of research findings from both industry-sponsored and academic research. Various types of conflict of interest (COI) exist for both authors and reviewers: publications play a role in career advancement, both in academia and in the pharmaceutical industry, leading potentially to financial gains. Enhanced reputation and media attention are associated with publications in reputable journals. The most obvious types of COI in industry-sponsored research are financial. Financial COI between clinical investigators and the pharmaceutical industry has been associated with a risk of under-reporting unfavourable study conclusions and with bias in reporting positive study results. One study from the field of dermatology showed that industry sponsorship was significantly associated with higher likelihood of reporting positive results, higher methodological quality and larger clinical trials (3).

*Disclosure of potential conflicts of interest*

The prerequisite in evaluating the role of a potential financial COI on how research results are reported is full disclosure of potential COI. Both authors and reviewers of biomedical journals should fully disclose potential COI. Although the presence of a potential COI does not imply that the research is of lower quality, it represents important information for the reader. Studies have shown that full disclosure of potential conflicts is rarely the rule (28). For the reader, identification of potential COI is not easy if undisclosed.

To illustrate this point, I have taken the example of a recent paper describing a potential risk of skin cancer with calcineurin inhibitors based on *in vitro* findings suggesting a reduction in DNA repair after ultraviolet (UV) radiation in keratinocytes exposed to these agents (29). No COI are disclosed in this work, which was also presented publicly at a Pediatric Advisory Committee of the Food and Drug Administration (30). However, a visit to the website of the company sponsoring the research and from which the authors are employees provides interesting results. The research sponsor is a bio-pharmaceutical company that develops and markets topical prescription and over-the-counter drugs in the field of DNA skin repair and photobiology (31). Among these is a "skin-cancer repair lotion" containing a DNA repair enzyme that is supposed to counterbalance the negative effect of UV radiation. Does this financial interest represent a true COI? The fact that the manufacturer of a DNA repair product may gain advantage from potential DNA damage properties of a drug cannot be denied. As Williams emphasizes in the introduction of the present paper, the readers should be given the opportunity to make their own judgements on the relevance of such a potential COI. This can only happen when the information is made available during the peer review process as well as in the publication.

### *Authorship, responsibility and conflicts of interests*

Originally, clinical research was performed predominantly by academic researchers with little or no support from the pharmaceutical industry. Since 1970, however, a dramatic increase in research funding from the pharmaceutical industry has occurred. Clinical research teams in the pharmaceutical sector comprise physicians specialized in clinical research, clinical scientists, methodologists and statisticians, the structure of which frequently mirrors the organization of a large academic centre. Most multicentre therapeutic studies are now the result of collaborations between researchers from the pharmaceutical industry (usually referred to as "the industry" in the medical literature) and clinical investigators (usually referred to as academic researchers or investigators). In many papers, both industry researchers and academic investigators meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship (32), having made a significant contribution to study design, analysis, interpretation of results and manuscript writing. Concerns have been made recently in writing and many times orally to me that industry researchers have an increased risk of introducing bias because of vested interests in the drug studied (33). Having spent eight years in the pharmaceutical industry and about the same amount of time in academic research, I have not seen major differences in the scientific behaviour and the desire to conduct good research between representatives from each sector. Bias does exist both in academia and in the pharmaceutical industry, as people become emotionally attached to the hypothesis they formulate. Confrontations of opinions during the writing process enrich the scientific debate and the discussion section of manuscripts.

Industry researchers should continue to co-author publications of their research and take ownership and responsibility for the scientific content of manuscripts. Excluding industry researchers from authoring publications would not be ethical if they meet authorship criteria. In addition, promoting scientific McCarthysm could enhance ghost-writing, carrying the risk of further disconnecting authorship from responsibility.

One traditional way to make up COI is what has been called the "non-writing author/non-author writing syndrome" (34). This syndrome has two main characteristics: an employee of a drug company or a professional medical writer, who will not appear as a named author, writes the manuscript of a scientific publication based on material provided by the company. The non-writing author, who is usually a well-known expert in the field ("a busy key opinion leader"), is offered authorship of the paper. This non-writing author is supposed to lend an air of scientific credibility to the work. Although medical writing support may be useful to edit manuscripts originally written by non-professional writers, full ghost-writing poses several problems: first it may be used to mask or to undermine COI, secondly, it may promote disconnection of authorship from responsibility. When the manuscript is entirely written by a "non-author writer", two patterns emerge in practice (Table II): some non-writing authors may be tempted not to check scrupulously the work against the original data. Alternatively, some non-writing authors read the manuscript carefully and make important contributions to the content. It is the responsibility of the authors to

Table II. *Authorship patterns for clinical studies sponsored by the pharmaceutical industry*

| The scientific investigator | The busy "key opinion leader" |
|---|---|
| • Participates in the major steps of the study: protocol generation, patient recruitment, data analysis and manuscript writing.<br>• Analyses the results carefully and requests to be provided with complete data sets.<br>• Participates in manuscript writing and critically reviews content versus key tables, analysis plan and protocol. | • Relies on a co-investigator who will substitute for him or her in all stages of the trial.<br>• Relies on the material provided without making any change or comment.<br>• Quickly reviews the manuscript written by a professional medical writer. Corrects his or her affiliation/title. |

be guarantors of the data presented, and when the manuscript has been written by somebody else it is a real challenge to take full responsibility for the results and to control the way they are presented.

Although the industry has been made entirely responsible for the "non-writing author/non-author writing syndrome", researchers outside the medical field have expressed different opinions: Trudo Lemens, from the Faculty of Law of Toronto, has suggested that medical researchers are accustomed to operating in a culture where authorship is not strictly determined on the basis of true contribution, making the acceptance of ghostwriting easier: "the line between adding one's name to an article written by a junior researcher and adding one's name to an article prepared by a medical writers' bureau seems narrow" (35).

### *Manuscript content versus original research*

A manuscript is usually a selection of data from a prospectively planned research project that was supported by a protocol, a statistical analysis plan and a set of results (statistical tables, listings and a study report). Data selection for manuscript preparation is a very sensitive process which is prone to major bias, especially when the results do not meet expectations. For example, the temptation may sometimes be high to overemphasize a "positive" exploratory analysis at the expense of a "negative" primary end-point. Unfortunately, most often reviewers and readers do not have access to the original study material and, as a result, they may ignore the data selection process. Even authors did not have access to the original data in the past in some instances. It is surprising to realize that sometimes the data presented in a scientific publication are different from the data presented in the original report. To illustrate this point, I have taken the example of a recently published clinical trial on a biological agent in psoriasis (36). Table III shows, in the right-hand column, the original data as presented to the Food and Drugs Administration and publicly available on the US drug label (37). Data from the same study as disclosed in the manuscript are presented in the left-hand column. It is striking to realize that there are major differences between the two sets of data. This suggests that the study was published without disclosing the results for the prospectively planned primary end-point.

### *Suggestions on how to better ensure reporting of clinical trials and scientific research*

Following the recommendations from the ICMJE and other researchers, significant efforts have been made by drug companies concerning prospective registration of drug trials and commitments to publish study results. The focus should now be on ensuring accurate publication of study results.

A system of checks and balances is required to ensure transparency both for "industry-sponsored" and "academic medical" research. Suggested principles to minimize the impact of financial COI on how study results are reported include:

- ensure adherence to standards for research conduct and reporting: a prospectively defined protocol and a statistical analysis plan should be made available to editors and reviewers, the principle of an independent data monitoring board for multicentre studies should be generalized;
- complete registration of clinical trials as recommended by the ICMJE with commitment to publish results;
- definition of authorship based on actual contribution to study design, execution, reporting and manuscript writing, possibly defined by the independent data monitoring board or an independent publication committee;
- full disclosure and discussion of COI (financial and academic) for authors and reviewers;
- submission of the core study material (protocol, statistical analysis plan, statistical tables and clinical study report) alongside the manuscript for all clinical studies (to allow trained reviewers to assess the impact of COI on how research results are reported);
- creation of international guidelines for systematic evaluation on how study results are reported in manuscripts to help reviewers. These principles should apply to both academic and industry-sponsored research. The current peer review process for manuscripts is not sufficient to prevent reporting bias and there is a need for a more stringent independent

Table III. *Reporting of efficacy data: differences between drug package insert and scientific publication (from 36, 37)*

| End-point | Scientific publication | US package insert |
|---|---|---|
| PASI 75 | "At any time during the study"<br>• Alefacept: 33%<br>• Placebo: 8% | "2 weeks post-dosing"<br>• Alefacept: 21%<br>• Placebo: 5% |
| Psoriasis Global Assessment | "Clear or almost clear"<br>• Alefacept: 24%<br>• Placebo: 8% | "Clear or almost clear"<br>• Alefacept: 14%<br>• Placebo: 5% |
| Maintenance of effect | "Of the patients who achieved at least 75% PASI reduction 2 weeks post-dosing, 71% maintained at least 50% improvement in PASI for 12 weeks." | 25 of the 166 patients randomized to Alefacept maintained at least 50% improvement in PASI for 12 weeks. |

control on how biomedical research findings are communicated.

The challenge ahead of us is certainly enormous, but there is no other option to optimally serve patients who have dedicated their time and effort to participate in clinical research.

## 4. THE EDITOR'S PERSPECTIVE

*Anders Vahlquist*

Throughout the history of science, conflicts of interest (COI) have been an inherent problem in medical research and thus for medical journals too, which, in the best of worlds, should be the guarantors of propagating correct and unbiased information in the best interest of the patients and the general public. However, it is only recently that matters of COI have become a daily priority for editors of medical journals; one reason is the emerging public interest in these issues, another is the increased awareness of how important economic decisions in the healthcare sector may be influenced by biased scientific reports originating from companies selling drugs or medical devices. For an editor the mere fact that the reputation of his or her journal may be jeopardized by one or two flawed papers is reason enough to scrutinize these matters. It is not surprising therefore that issues related to COI have been discussed in several recent editorials in general medical journals (12, 38–40) and two from the field of dermatology (2, 5).

### *The scope of conflicts*

Scientific publications reporting the results of clinical trials of drugs or medical equipment are notoriously liable to judgement bias. This necessitates strict guidelines, not only on the design of the study and how to document the results, but also on how to disclose any spurious impact of COI in the authors' interpretation of the results. Needless to say, COI may also be "hidden" in clinical studies that do not have any company support. For example, a description of a new diagnostic or therapeutic procedure may represent a COI if the new procedure is virtually impossible to perform elsewhere and that specific medical centre depends on revenues from additional patient referrals. For all these reasons it is imperative that a medical journal has clear guidelines, like those established recently by the *Journal of the American Medical Association (JAMA)* (39), on how to disclose COI in submitted papers. More subtle conflicts, such as a tendency of many investigators to favour a presentation of positive instead of negative findings, is more difficult for journals to control, and must rely on authors' integrity as well as good scientific training and ongoing ethical discussion at the various academic research institutions.

### *How to disclose conflicts*

All papers (also case reports that include a new therapy) should contain a statement about COI. It is advisable to highlight this under a separate heading, or under Acknowledgement. Such a policy should also apply when the editor submits a paper to his/her own journal (as author or co-author). In this situation it is advisable that an assistant editor is appointed, who then takes full responsibility for the review process and makes the decision about publication without any interference from the editor. This precaution against COI and self-interest can be highlighted in a footnote if the paper is subsequently published.

Some other questions that all journal editors should address in relation to COI are summarized in Table IV.

### *Conclusion*

Disclosure of COI is a *sine qua non* for a medical journal, and awareness of COI should influence all aspects of the review process. The reputation of a journal can be damaged if a published study is later brought into question on the grounds of undeclared financial COI, especially if the intervention has implications for the wellbeing of patients and for the cost of health services.

Starting with the selection of an unbiased section editor for each paper, he or she should in turn select peer reviewers without any known strings to the authors or study sponsor, and without competing financial interests. A declaration of COI is obligatory for the authors, but should also be considered for the referees. The question remains as to how an editor can be sure that self-declarations of COI are correct without

Table IV. *Key questions that journal editors need to address in relation to conflicts of interest (COI)*

- Has the journal's policy on conflicts been clearly declared?
- How do you ensure that authors with conflicts declare them?
- Should all reviewers also disclose their COI? What about "hostile" or "too friendly" reviewers who might have a COI?
- Should the determination of whether or not a conflict exists be in the hands of the potentially conflicted or should he or she simply report all potential kinds of COI that come to mind?
- Should papers on drugs or medical devices which are co-authored by industry people always be regarded as potentially biased and hence be treated differently in the review process?
- Do you suspect ghost writing by a drug company or an academic related to a certain commercial product without stating clearly that this is the case?
- In the case of drug-company sponsored supplements, is a declaration of sponsorship at the front of the supplement enough, or should it be on each included article given that single key articles are often distributed at marketing events? (5)

playing the role of a police officer. It is impossible to be completely thorough in this respect, because cross-examinations and filing of legally reliable documents are something most of us do not want to see as part of a peer review process.

If authors violate the guidelines and are later proven to have given false or incomplete statements about COI should this lead to disciplinary action by the editor? One medical journal recently decided to deny authors who violate the disclosure policy the privilege of publishing their work in that journal for up to two years (4). There will hardly be a consensus about such rules among different journals, but these matters need to be discussed thoroughly at journal editorial boards. The message is clear: editors must take disclosure of relationships that might influence article content very seriously.

Table V. *Score[a] distributions for readers' perceptions of papers with and without declaration of various types of conflict of interest (COI). Analysis of variance results: mean values and significance levels relating to competing interest*

| Conflict of interest (COI) | | | | |
|---|---|---|---|---|
| Scored variable | None declared group ($n$=174) | Financial COI group ($n$=192) | Grants COI group ($n$=156) | $p$-value |
| Interest | 3.21 | 3.06 | 3.26 | 0.12 |
| Importance | 3.29 | 3.03 | 3.16 | 0.035[b] |
| Relevance | 3.44 | 3.13 | 3.35 | 0.009[b] |
| Validity | 3.16 | 2.82 | 3.12 | <0.001[c] |
| Believability | 3.49 | 3.20 | 3.36 | 0.025[b] |

[a]Low scores indicate low interest, importance, relevance, validity, and believability.
[b]Rating for financial COI group significantly lower than that for none declared group.
[c]Rating for financial COI group significantly lower than that for none declared group and for grants COI group.
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## 5. EFFECTS OF DECLARED CONFLICTS OF INTEREST ON READERS' PERCEPTIONS

*Sara Schroter*

Despite growing evidence that authors' conclusions are influenced by conflicts of interest (COI) (3, 41, 42), little is known about how declarations of COI influence readers' perceptions. The *British Medical Journal (BMJ*) has long been interested in investigating the effects of COI, and for this reason conducted two randomized controlled trials (43, 44). The first (43) involved sending a paper to a random sample of 300 *BMJ* readers and asking them to rate the study in terms of interest, importance, relevance, validity, and believability, using a series of 5-point Likert scales. All readers received the same paper, which described the impact of pain from Herpes zoster on patients' daily functioning, and they were randomized to one of two groups. The first group (financial COI group) received the paper with a declaration that the authors were employees of a company and potentially held stock options in this company. The second group received the paper with a statement that the authors had no COI (none declared group). A total of 170 readers responded and *t*-tests showed readers in the financial COI group thought that the study was significantly less interesting, important, relevant, valid, and believable than readers in the none declared group ($p$<0.05).

The BMJ team then conducted a further randomized controlled trial using similar methods to evaluate the impact of the *type of COI* on ratings of interest, importance, relevance, validity, and believability; and to assess the influence of the *type of paper* on this effect (44). We introduced a third type of COI statement with a declaration that one of the authors was a recipient of funding for studentships and research grants from the company (grants COI group). The clinical impact paper from the first study was used again, together with a more general one describing the use of problem lists for letters between hospital doctors and general practitioners. A total of 450 readers were randomized to receive each paper, with 150 in each of the three COI groups. The analysis of variance showed that overall, importance, relevance, validity, and believability ratings were significantly lower in the financial COI group than in the none declared group (Table V). Validity ratings for the financial COI group were also significantly lower than for the grants COI group. There were significant differences in the ratings between papers for all five measures ($p$<0.001), with the paper about problem lists scoring significantly higher. A significant inter-relation was observed between COI and type of paper for the two measures interest ($p$=0.012) and believability ($p$=0.007). For these measures the lower ratings for the financial COI group were more pronounced for the paper describing the impact of pain from Herpes zoster.

These two studies show that the declaration of financial COI can have a significant effect on readers' perceptions of the scientific credibility of some published research. The disclosure of authors' conflicts of interest is important and all journals should actively enforce this. One could argue that the results of these studies might encourage the concealment of "potentially negative" COIs through authors fear of their research being discredited. However, I see these results as positive in the sense that readers are now paying attention to the actual wording of COI statements and assessing the integrity of reported research in light of these declarations. The size of the effect depended on the type of financial COI reported and the type of paper.

## 6. PATIENT SUPPORT GROUPS AND CONFLICTS OF INTEREST

*Ray Jobling*

### *Relationships between the pharmaceutical industry and patient support groups*

Patient support groups (PSGs) for people with skin disorders have a long history. For example, Psoriasis Associations have existed for decades (45). Most PSGs levy subscriptions and seek donations and legacies, and a few enjoy government support. Some have sizeable endowments, thereby securing income to finance their activities. The UK's Psoriasis Association has contributed more than £2 million towards research. Funding PSG operations, however, represents an ever-present difficulty. Paradoxically, better performance further raises expectations, with attendant higher costs. Partnerships and joint projects with pharmaceutical companies may therefore seem attractive. Many PSGs seek corporate members, sponsorship and advice (websites, meetings, travel, etc.). Such assistance is valuable: without it many organizations could not survive, let alone thrive.

There is, nonetheless, a danger of dependency and undue influence in what is a relationship of unequals (46). Theoretically, both companies and PSGs should co-operate on the basis of clear values, transparency and accountability, with explicit mutually-agreed ground rules. Many accept voluntary codes of self-regulation, beyond legal requirements protecting the public interest. The Association of the British Pharmaceutical Industry has its own Code, and PSGs and companies now commonly reach formal bilateral agreements covering the terms upon which any joint initiative is founded. Nevertheless, the relationship between the dermatological industry, health professionals and PSGs has become the subject of critical scrutiny (47). The UK codes, for example, have been criticized by a Parliamentary Committee as weak and ineffectual (48), a concern echoed in a current Consumers International Report (5) on the ABPI Code. New Codes proliferate however. One governs 10 companies and 40 or so PSGs, including skin organizations, affiliated to the Health Coalition Initiative. British skin PSGs are also members of The Skin Care Campaign, which works with dermatology professionals to advocate the needs of all skin patients, alongside closely associated political "lobbying" by a registered All-Party Parliamentary Group on Skin. Both draw principal funding from the industry, thereby attracting criticism, but argue the formal transparency of their operation and abstraction and distance from the interests of individual companies

### *Disease awareness campaigns and "disease mongering"*

One major focus has been political "lobbying", with allegations that companies pursue self-interest while deriving credibility from their associations with professionals and PSGs, both allegedly used as "fronts" (49, 50). The increasing use of *disease awareness campaigns* (DACs) has provoked rising concern among regulatory bodies, consumer organizations and politicians. Some have been condemned as *disease mongering*: the corporate construction of disease and its impact on health and well-being, in well-orchestrated strategic initiatives targeting public, patient and/or professional audiences (51). These offer credible channels of communication with relevant decision-makers, securing market rewards for the companies. Marketing/PR executives thus deploy a "third party technique" distancing company messages from themselves, who might be seen as self-interested messengers. PSGs and so-called key opinion leader (KOL) professionals are therefore crucial to the legitimization of campaigns. A company first to market a drug, wishing to sustain market leadership by differentiating their product from that of competitors', or by developing a new condition for that drug, would have good reasons for DAC involvement (52). A British Parliamentary Select Committee recently feared that DACs, and thus PSGs, had become no more than marketing tools for the pharmaceutical companies (53).

Company-prompted and sponsored "research" surveys of patient experience, and focus-group-based studies have become an increasingly common component of DACs, deriving legitimacy from representation as PSG initiated or approved projects. Authenticity can be reinforced by the involvement of KOL professionals. Sadly, the methodology involved can be questionable in design, execution, and in analysis/interpretation and selective presentation of results. Also prominent in DACs are "real patients", often "supplied" by PSGs or doctors (with consent) whose experience has allegedly included delayed diagnosis/consultation, lack of or old-fashioned treatment, or denial of innovative treatment needlessly harming quality of life. Most DACs also involve emotional appeals, mounted via carefully placed "human interest" media stories, directed towards securing public sympathy and official support and resources; and to prompt product demand and compliance from patients.

### *Regulation of the relationships between patient support groups, health professionals and industry*

The circumstances surrounding PSG/professional/company mutual imvolvement in DACs are growing in complexity; becoming increasingly cross-national, and global in their design and impact. Much of the substance of a DAC may be presented via the internet, and media events outside a given "home" market. Crossing cultures and regulatory jurisdictions, they are more difficult to influence, monitor and regulate. PSG

efforts to deal with company and marketing executives nationally can be undermined by the fact that strategy and tactics, substance and style of both messages and delivery can ultimately be determined perhaps at remotely placed international corporate levels as part of global marketing strategies. Claims to legitimacy come from the involvement of international steering groups, including both patients and doctors, but without any framework of formal accountability.

National voluntary regulatory codes are arguably inadequate in the face of such internationalization. Companies have increasingly elaborated their patient relations and patient organization liaison strategies to engage with international PSGs and/or federations. But the latter's organizational cultures and structures, and internal political dynamics do not always ensure that the subtleties of national perspectives, concerns and interests (including crucially regulatory requirements) are fully acknowledged. Anxieties have also been voiced about the absence or ineffectiveness of international (e.g. EU) safeguards, scrutiny and regulation.

Understandably, corporate approaches to PSGs concerning joint initiatives and offers of financial aid are founded upon calculation of interest and the prospect of financial returns. The principal business of businesses is naturally to do business, notwithstanding their broader concern to be "good citizens". PSGs operating in a field where there is a common chronic disease and more widespread expressions of it, do so in a sizeable market of major commercial significance. They can "enjoy" the benefits of industry interest, as can relevant professionals, applying welcome resources to positive purpose. Those speaking for rarer conditions and/or varieties affecting far fewer "consumers" are less fortunate. Offering no obvious "bottom line" financial advantage they can be deemed less worthy of corporate "investment", in funding research, awareness raising and lobbying. Here innovation is slow, and public knowledge and understanding lacking. Tellingly, company-supported DACs frequently ignore these completely. Another outcome is financial inequity in the circumstances of different PSGs (and research groups), sadly not always recognized by better-off organizations. Federal or collaborative organizations, which do seek to advocate for skin disorders in general (such as the UK's Skin Care Campaign) rather than solely concentrating on common conditions with associated large markets, are therefore important.

### *Globalization?*

International PSG federations can share experience and work to counter inequity, addressing the risk that those in poorer economies receive less and worse care. They can do so by mutual encouragement, transferring expertise and skills, building capacity, launching joint initiatives, and potentially lobbying at the level of international agencies and authorities. However, such federations have encountered financial problems, and potential COI. Recent experience with the European Federation of Psoriasis Associations (EUROPSO) has suggested that there can be major risk of dependency stemming from over-reliance on corporate support, even supposing the innocent intent of those providing funds. EUROPSO's recent efforts to agree a formal co-operative arrangement with a company stalled, according to a report to member organizations, when that company encountered regulatory "adversities" in relation to a specific new product (54). This, reportedly, radically changed the original plans and led to difficulties, further deepened by a company merger. Resumed negotiation produced sponsorship terms granting "sole" leadership for an initial year, and a position as "lead corporate sponsor" thereafter. In return, the company and EUROPSO would use each other's logo on their websites. Member associations would be advised that the company's dermatology portfolio would be developed on the basis of registration of a class of treatments. An opportunity to include information/promotional material in a EUROPSO membership mailing was mentioned. Other co-sponsors subsequently came forward. A plenary session of the Federation in 2004 heard, nonetheless, that full organizational and operational independence could not be assured, since perceived corporate perspectives, sensibilities and interests could provide the framework for the Federation's agenda, priority setting and decision-making, because the funding base rested virtually wholly on corporate support (55). It was decided that the incoming Executive must be mandated to consider first principles, address the risks of COI, and to report back on the appropriate basis for future relationships between EUROPSO and corporate partners. More than a year later, despite repeated follow-up questions, no progress had been reported.

### *World Psoriasis Day*

The launch of the World Psoriasis Day (WPD) initiative and the related Psoriasis Disease Awareness Campaign was arguably originally prompted by corporate efforts to launch and promote the virtues of the new biological agents for treating severe psoriasis. The date chosen for the first WPD coincided in England with a crucial stage in National Institute of Clinical Effectiveness (NICE) assessment of biologicals, raising questions of appropriateness for the Psoriasis Association, as well as wider concerns surrounding campaign content. The Association therefore took no part in the "Day", and came to a national agreement with the corporate sponsor (instructively without needing reference to the independent international steering committee) that the first WPD/campaign would have no direct publicity in the UK.

The planning and organization of the second WPD, and a widening of the DAC, drew the International Federation of Psoriasis Associations into official "ownership" of the campaign, conveying valuable credibility. Other companies now also participate. The WPD website directed towards securing wider industry campaign involvement promises companies the enhancement of "leverage/influence" over it. Earlier, it has listed certain advantages in company commitment: improvement towards expanding the market for psoriasis treatments; brand revitalization; monitoring competitors; ensuring visibility and extensive media reach. It has also stressed the opportunity to become a familiar name with patients either newly seeking or returning to a treatment regimen. WPD represents, it was said, an opportunity to any company seeking to make a name in psoriasis. Involvement would enable staff to establish and/or maintain a brand's name in the minds of people with psoriasis/psoriatic arthritis – with obvious corporate benefits. It was noted in justification of WPD involvement, that it could also help company products in current early phase development. By fully integrating a pre-market strategy with WPD, it could be used to create greater awareness amongst important target audiences – eventual adapters of development products. A chance to "give something back", and to thank patients has also been mentioned.

*A challenge?*

There are indisputable issues of principle at stake in the close, increasingly interdependent engagement of skin PSGs, dermatological professionals and industry. It is a potentially unequal relationship given the latter's considerable financial and organizational resources and global reach. There are good reasons for concern about dependency and its implications. It is not unreasonable to ask whose hands are strategically shaping perspectives, determining issues and priorities, and setting the terms of public debate. PSGs need to find and speak with their own distinctive *patient* voice. Even dermatologists must recognize and respect the importance of patient/PSG autonomy in their accounts of experience, expression of problems and needs and suggested solutions. As to campaigning/lobbying, PSGs rely for their effectiveness upon *trust*, particularly of those they try to serve and represent, but also of the wider public, agencies and governments they seek to influence. Interests demand acknowledgement; transparency and accountability need consideration; potential conflicts must be addressed. Unquestionably, close working relationships add value and represent significant social capital, but confidence and trust will come from collective self-awareness, openness, and the adoption of transparent principles encouraging sound practice and underpinning all joint working. Naturally, regulatory frameworks are also essential, but the globalization of financially substantial market and corporate activities in dermatology, and of organized patient support, represents a challenge. Dermatology lags behind many other specializations in attending explicitly to the essential issues.

## 7. WHERE DO WE GO FROM HERE?

*Hywel Williams*

*Some rays of hope*

The most important point to glean from these commentaries is simply to be more aware of conflicts of interest (COI) in dermatology. Awareness of what it is, how it can influence behaviour amongst clinical colleagues, academic key opinion leaders, and even amongst disease awareness campaigns "organized" by patient support groups. Terms such as "ghost-writing" and "disease mongering" should now part of the dermatologists' vocabulary, and they need to be taught and understood by those training in dermatology. Even though some of the material described by the contributors to this compilation might seem difficult to overcome, some simple steps have already been taken by the academic community to minimize financial conflicts. These steps have been especially noticeable with regards to the publishing of randomized controlled trials, which are so often the cornerstone of determining whether a new product makes it in the marketplace. In addition to clearer and more consistent dermatology journal and conference policies for dealing with and declaring COI appropriately, these measures include:

- The principle of prospective trial registration – to ensure that a protocol containing a declaration of the primary outcome measure and analysis plan is deposited in a publicly accessible trials register before publication. Many journals belonging to the International Committee of Medical Journal Editors (ICMJE) now insist that trials need to be registered before they can be even considered for publication (56, 57).
- Better reporting of clinical trials within journals by following the CONSORT (www.consort-statement.org) reporting recommendations to ensure that all essential trial data, such as how randomization was generated and concealed, how blinding was achieved, how many patients entered the study and how many were analysed etc are included, so that readers can quickly assess the validity of that published study (58).
- Systematic reviews, such as those produced by the Cochrane Collaboration, that attempt to produce unbiased summaries of trial evidence (59).

### *The need to be less coy about COI*

It is clear that the problem of COI in dermatology really does exist and that the answer to the problem belongs to us all – clinicians, researchers, industry, editors, ethics committees, academic institutions and patient support groups. Brennan and colleagues (12) state that self-regulation has not satisfactorily protected the interests of patients so far, and suggest that more stringent regulation is necessary, including the elimination or modification of common practices related to small gifts, pharmaceutical samples, continuing medical education, funds for physician travel, speakers' bureaus, ghostwriting, and consulting and research contracts. They propose an interesting idea whereby academic centres take a lead in addressing such issues – only time will tell if academic centres are up to the challenge.

I wish to emphasize that the aim of these commentaries is not to discourage a flourishing and innovative healthcare industry, but to ensure that processes are in place in proportion to need that ensure that COI are addressed fairly and openly. It is time for the taboo of COI in dermatology to be broken and for all concerned with its effects – including the public – to begin open discussions. That time is now – or else we risk losing the very foundation of values on which the dermatology profession is built (Fig. 3).

*Fig. 3.* Is this the new face of modern dermatology?

### *Conflicts of interests*

*Hywel C. Williams* has no financial conflicts with any for-profit organization.

*Luigi Naldi*: the GISED Study Centre is funded by AIFA to coordinate the Psocare project in Italy. In 2004, the GISED Study Centre received a grant from Serono to conduct a survey of psoriasis in Italy. During the last 3 years he has been a speaker at some industry-sponsored symposia on psoriasis.

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*Anders Vahlquist* is the Editor of this journal.

*Sara Schroter* works for the British Medical Journal, which supported her research into conflicts of interest. She does not have financial conflicts of interest to declare.

*Ray Jobling* does not have any financial conflicts with any for-profit organization.

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